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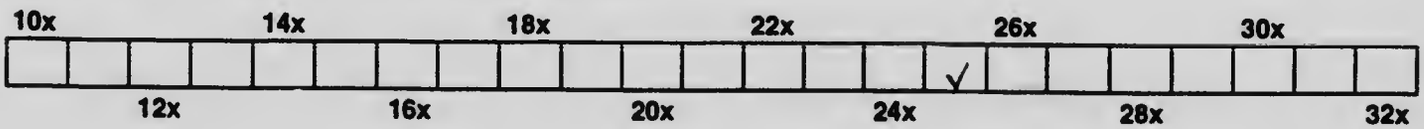

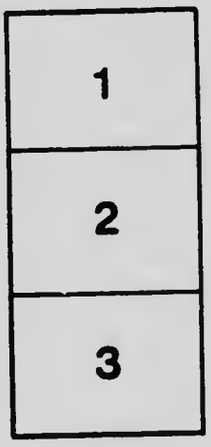

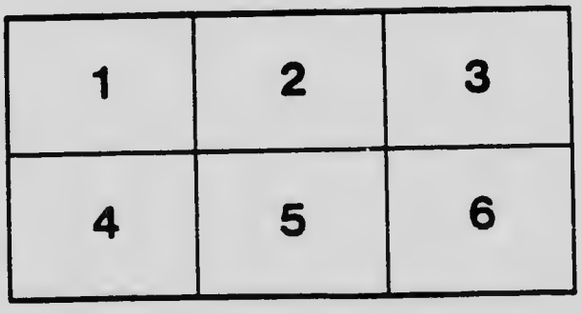

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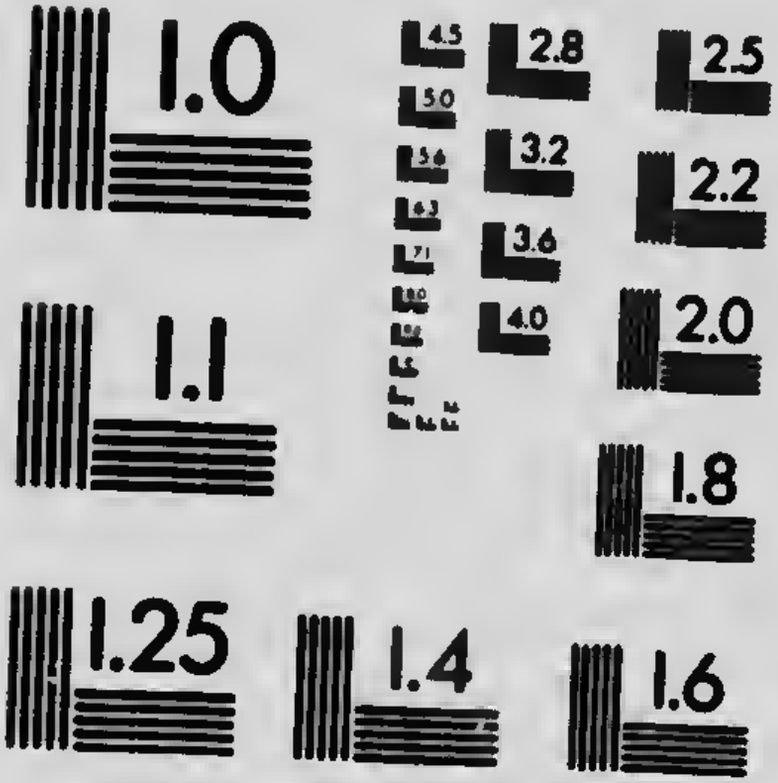

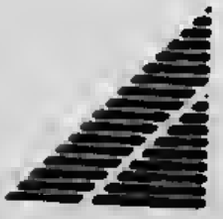

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THE PRINCIPLES OF PATHOLOGY

Volume I

GENERAL PATHOLOGY

By J. George Adami, M.A., M.D., LL.D., F.R.S.

Volume II

SYSTEMIC PATHOLOGY

By J. George Adami, M.A., M.D., LL.D., F.R.S.
and
Albert G. Nicholls, M.A., M.D., F.R.S. (Can.)

THE

PRINCIPLES OF PATHOLOGY

BY

J. GEORGE ADAMI, M.A., M.D., LL.D., F.R.S.
PROFESSOR OF PATHOLOGY IN McGILL UNIVERSITY, AND PATHOLOGIST TO THE ROYAL VICTORIA HOSPITAL, MONTREAL; LATE FELLOW OF JESUS COLLEGE, CAMBRIDGE, ENGLAND

VOLUME I

GENERAL PATHOLOGY

WITH 322 ENGRAVINGS AND 16 PLATES

PHILADELPHIA AND NEW YORK
LEA & FEBIGER

TO

A. E. S.

THE FRIEND AND COUNSELLOR OF MORE THAN
A QUARTER OF A CENTURY

IN ALL GRATITUDE

PREFACE.

When, nearly twelve years ago, I was approached by my publishers to write a text-book upon Pathology, with the added suggestion that the treatment of the subject should be along the lines adopted in an article of mine upon Inflammation, which had recently appeared in Professor Allbutt's *System of Medicine*, not knowing what was before me, I assented willingly. Little did I dream of the heavy burden of being, as it were, with child with the book through all these years; of its ever-present and ever-growing weight; of the travail of its slow delivery. Works for the student, giving a condensed presentation of pathological data, were many and excellent. But classification alone is not science, at most it is the implied recognition that like phenomena are due to like causes, whereas science, fully developed, is the discovery and study of the laws or principles governing the production of phenomena, and thus underlying and determining classification. I knew of no recent attempt in our language to place before student or physician in an orderly and reasoned manner the principles of Pathology, the science, as distinct from the practice of medicine; the science upon which that practice is, or should be, based. Preëminently it is the duty of the pathologist as teacher to train the student in the habits of medical thought, to afford those data which bear upon disease in general, to show how such data are to be weighed, and what deductions may logically be drawn therefrom, so that later the student investigating a particular case may do so armed with a sound knowledge of general principles; that he may recognize individual symptoms not as isolated facts, but as indications of definite orders of disturbance affecting one or other organ, and, knowing what in general induces those disturbances, may form a judgment regarding the causation and meaning of the sum total of symptoms in a case. As Bacon laid down, "Vere scire est per causas scire"—To know truly is to know through causes—and he is the scientific physician or surgeon who seeks and determines causes; for only when the cause is deduced can treatment be rational.

I hold, therefore, that, whatever may be the case with other subjects, what is needed in a text-book of Pathology is not the mere record and

description of phenomena, but the attempt to analyze those phenomena in an orderly manner. That text-book should be a training in medical thought. It was, however, one thing to hold these views, another thing to write a treatise embodying them. I will not state how many times most of the chapters of this work have been written and rewritten; nor how often the arrangement has been changed before the work has assumed its present shape in two volumes, this, the first of two, dealing with what is usually termed General Pathology; that to follow with Systemic (including Special) Pathology. I will only say that, constantly, in working over each section, I was forced, with Virchow, to recognize the cell and the changes undergone by it as the basis of all pathological study, and thus, eventually, to guard against constant reversion to elementary but basal and all-important matters, was compelled to write an introductory section upon the cell and its properties, more particularly in relationship to morbid changes.

The work thus assumes a novel, but what I am convinced is a logical, form. It begins not with a study of the blood and of circulatory disturbances, as has been usual with most German works in General Pathology, but with a study of the properties of living matter. The study of circulatory disturbances is not, indeed, a part of General Pathology, and, accordingly, it is treated as the introduction to Systemic Pathology, that is, to the study of the diseases affecting individual systems and the effects of those diseased states upon the organism as a whole. As such it will be treated in our second volume. It would be as appropriate, if not more so, to begin the study of General Pathology with the discussion of nervous disturbances and their effects upon the body at large.

There are different orders of minds, and no work can appeal to all. For myself, in beginning my studies, I found that I could easily remember the matter of such works as the larger Lyell's *Principles of Geology*, Foster's *Physiology*, and Fagge's *Medicine*, to cite examples in which there was a reasoned treatment of the subject, whereas, to attempt to commit to memory "cram books" laden with facts and names was mental agony. I saved time and gained knowledge by reading my subject at large. It is to those possessing a like order of mind that this work is addressed. To those readers [illegible] explanations are due. My manuscript had been completed, and all save a few chapters sent to my publishers, when, in April, 1907, the greater part of the Medical Building at McGill University was burned to the ground, and with it my library, the chapters in question, and the illustrations I had made or gradually collected over many years for the purposes of the book. It has been

impossible to reproduce most of these illustrations, and I have had to fall back upon illustrations from many sources. I am very far from uncertain as to whether the work has not greatly gained from the greater diagrammatic clearness of the selected illustrations. To the authors of these illustrations I would here express my deep sense of indebtedness, most particularly to Professors Ribbert and Schwalbe. So, also, the loss of my library has made it impossible for me to turn to the familiar shelves and from them fill in a very large number of references. For these deficiencies the indulgence of the reader is asked.

What has impressed the writer most in attempting thus to bring out a work upon General Pathology is the present hopelessness of any one man's being able adequately to master the subject in all its aspects. It is impossible for any individual to keep abreast of the manifold developments of all the sciences ancillary to medicine, physics and physical chemistry, biochemistry, biology and embryology, parasitology, histology, and physiology, and at the same time to master the literature of Pathology proper. In bacteriology alone and its one branch, the study of immunity, there is enough material being brought forth month by month to keep the reader fully engaged. Much that is of first-class importance is passed by in silence in these pages. At most, the writer has made the attempt to call attention to the intimate bearing of these other sciences upon medicine, and, in addition, to the important work now being accomplished by English-speaking workers. This last is not through Chauvinism, or as a protest against the neglect that this work has too often received at the hands of Continental writers, but primarily to encourage the student in the habit of consulting authorities at first hand, of reading original articles and making his own deductions independently of the opinion expressed by the writer of the text-book. There is no difficulty in obtaining the leading American and English medical journals, and when once the student appreciates the added strength and interest that comes from first-hand reading, he will not be content until he masters the other languages of science, German, French, and, it may be, Italian also. And, what is of like importance, it is sought to impress upon the student the opportunities that are before him in our university laboratories and well-equipped hospitals to undertake equally valuable investigations. If others, it may be of the same school or known to him, have accomplished work of high order, why should not he also undertake research and seek to add to the sum of medical knowledge?

I cannot conclude without bearing witness to the patience and constant consideration of my publishers. I can but hope that their willingness to

accede to my opinion that the development of medicine and more particularly of pathology in our midst is such that there is an opening for a work of this nature has not been mistaken. Here, also, I would express my thanks to my colleague, Dr. W. Francis, for his valuable aid in compiling the index.

The heaviest debt of all I owe to my old teachers. It has been my good fortune and my privilege as a student to come under the influence, and that intimately, of not a few men who have been masters of their particular subjects, who, diverse, it may be, in their gifts have each possessed that intangible something that we recognize as greatness; men who have inevitably moulded my thoughts: Milnes Marshall and Francis Maitland Balfour, Michael Foster and Rudolf Heidenhain, Julius Dreschfeld and Charles Smart Roy, Emile Roux and Elie Metchnikoff. To them and to their teaching and inspiration, is due whatever of virtue these pages may possess.

331 Peel Street, Montreal. J. G. A.

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SECTION I.

PROLEGOMENA.

CHAPTER I.

INTRODUCTORY.

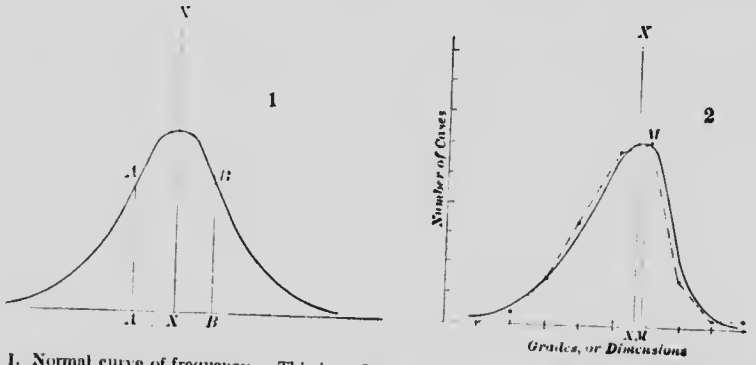
Definition.—Just as physiology is the study of the functions of the body in health, so is pathology the study of the same functions in disease. To this extent we can accurately define the scope of our subject, but a moment's thought reveals that the definition is only superficially precise; further thought shows that, strive as we may, we cannot approach nearer to perfect definition. For everything depends upon what we understand by the terms "health" and "disease," and we are forced straightway to recognize that there is no boundary line between the two conditions—they merge insensibly the one into the other.

We all, it is true, have a general understanding of what health is, but when we come to attempt to express our understanding in words we find that, like "life" itself, it eludes definition. Why this is we may here briefly indicate.

It depends primarily upon the basal fact of variability. No two living beings, although belonging to the same species and the same family, are structurally identical, nor even born identical; and if this be true of structure, it is true also of the outcome of structure—namely, function. There is thus no absolute standard of either structure or function in any one species. Every individual of the human or other species varies in every particular from every other individual; the dimensions of the different component parts, the proportional relationship between the parts, the action of the parts, present more or less evident divergence in any two individuals studied. At most, by the statistical method we can in some cases arrive at an approximate or theoretical standard. To give an example: There is no absolute standard of height for human beings; the average height varies in the different branches of our race, and differences, sometimes pronounced, occur

among the members of one and the same family. But if, as Quetelet[1] first noted, we take one thousand, or preferably ten thousand, full-grown males—the larger the number the better—belonging to the same branch of the human race, and measure accurately their height, and plot out the results obtained, we find that the majority conform to, and are included in, a relatively short range. We can speak of that particular height to which the greatest number of individuals conform as the standard, or *mode;* or again, taking the sum of the heights and dividing by the total number measured, we can obtain the arithmetical mean, or *type*. ("Mode" and "type," it may be added, do not necessarily correspond.) It will be found that the majority of individuals come within a relatively small range on either side of this mode, and we can on either side of the mean (or of the mode) determine the *median* or

Fig. 1



1. Normal curve of frequency. This is a flowing curve symmetrical about the mean (which corresponds with the mode) and without limit at either end. *X X*, ordinate of mean or type (and of mode); *A A*, *B B*, ordinates of lower and upper median deviation. 2. A *skew* curve of frequency in which *X X*, the ordinate of mean or type, does not correspond to *M M*, the ordinate of the mode. The continuous line here represents the estimated (theoretical) curve of frequency, the interrupted line joins the numbers of the different classes or grades found in a particular case.

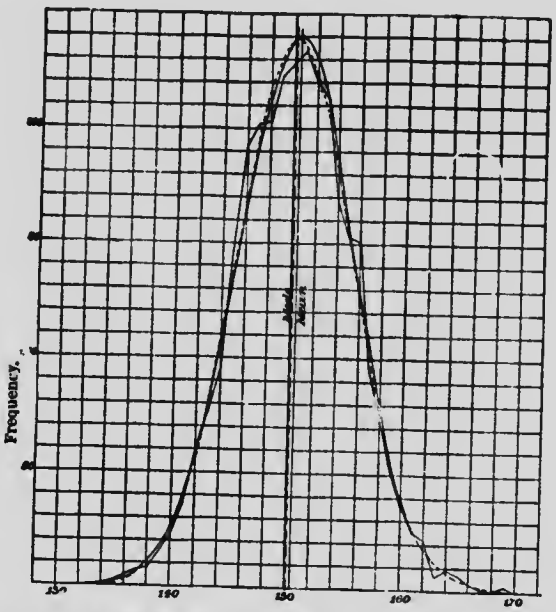
probable deviation, above and below which fall 50 per cent. of the measurements. We can go farther and *assume* that the 50 per cent. within these limits constitute the normal class, those outside the abnormal. We, in short, obtain a curve which, in an uncomplicated case, corresponds curiously with that of the law of chance (Fig. 1). To illustrate: Taking the case of twelve dice, throwing an infinite number of times and counting the sum of the numbers turned uppermost (from 12—all "ones"—up to 72—all "sixes"), it can by this "law of chance" be determined mathematically what is the probable frequency of a given number—say 25—being exposed. Plotting out these probabilities, they are found to form an exact curve. This has been tested by Weldon, who selected a somewhat simpler case. Taking twelve dice, he threw them several thousand times, and tabulated the number of dice at

[1] Anthropométrie ou Mésure des différentes Facultés de l'Homme, Brussels, 1871.

each throw which presented more than three points on their uppermost surface. Plotting out the number of dice—1, 2, 3 to 12—which fulfilled the conditions, he found that the curve giving the successive numbers followed with remarkable closeness the mathematical curve of chance.[1]

In plotting out the measurements from a series of men or of other species, we obtain a like curve presenting a regular diminution at either side of the mode, the least frequent classes being those situated further and farther away. While the majority of individuals conform to the mode, few will exactly conform either to it or to the type (Fig. 2).

FIG. 2



Curve of variation in the head breadth in millimeters of 3000 criminals. Irregular continuous line = polygon of observed frequency; darker continuous line = normal curve of frequency as estimated by law of chance; dotted line = estimated skew curve of frequency of type IV (Pearson's table). (After MacDonnell.)

But in all such tabulations it has to be realized that the results obtained are not absolute; measurements of another thousand or ten thousand individuals *might*, nay, would surely, to some extent, move the mode or type in one or other direction; we only obtain an approximate standard.

We need not here discuss *skewness*, or want of correspondence between mode and type (mean), or again, *multimodal curves*, in which two or more classes or modes are discovered grouped around certain dimensions and separated by intermediate classes containing fewer individuals.

[1] A concise and excellent account of the mathematics of variation is given by R. P. Bigelow, art. *Variation*, Buck's Ref. Handbook, second edition, 1904.

What we wish to emphasize at the present moment is that the normal gives place imperceptibly to the abnormal, every gradation being found between cases which approximate to the mode, and so may be regarded as normal, and those which show extreme departure from the same.

What is true of bodily dimensions and structure must inevitably be true also regarding function. From this it follows that, if health be regarded as the indication of perfect functional activity, and disease of imperfect function, the two merge imperceptibly the one into the other. For this must be accepted from the beginning, that conditions of disease are conditions of disturbed or imperfect function; they connote either the exaggeration or the diminution of processes which are of normal occurrence.

Local Disease, its Relationship to General Health.—If the difficulty in drawing a sharp line of distinction between the normal and the abnormal—between health and disease—obtains in connection with inherent bodily states, it obtains also in connection with those that are acquired during the course of the individual existence. Considering man in the first place—but the same is true of all multicellular organisms—it is seen that, while the organism is in one sense a complete unit, in another sense it is a compound formed of a great number of different structures, each made up of individual cells and the products of their activity. These structures and the cells composing them are at the same time—to an extent varying in the various organs—interdependent and independent. So far as they are interdependent, disturbance or disease of a given organ is liable to affect the other organs, and the body as a whole, causing constitutional disturbance; so far as they are independent, local disturbance may remain wholly local, or, in other words, the organism as a whole may be healthy while a part is diseased. For example: injury, disease, or loss of one tooth is liable to throw more work on the other teeth, and, rendering mastication not so perfect, may throw more work on the stomach; while again, through the disturbed innervation of the part there may be profound nervous irritation, sleeplessness, lack of rest, and in this and other ways marked constitutional disturbance may be set up. One knows full well, however, that any single tooth may be the seat of progressive caries or may be entirely lost, and no such train of constitutional disturbances be set up; there may be local disturbance and excellent general well-being. Thus our conception of what is health and what disease must be dependent upon whether we take into consideration the organism as a whole or the condition of the various constituent parts. To this paradoxical interdependence and independence of the cells we shall return.

In the forthcoming chapters we shall have to consider the more important features bearing upon the production of the conditions of disease, and the reaction of the organism to the same whereby a condition of health or relative health is brought about. In the meantime it will be well to afford a working definition. Bearing in mind that these terms are, and can only be, relative, it is well to consider health as a condition of metabolic equilibrium—a condition in which the organism, or the part,

is attuned, or in complete adaptation to its surroundings; disease as a condition in which equilibrium and adequate adaptation are wanting. In other words, to employ a metaphor encountered by chance in the works of a seventeenth century Italian theologian, "health is harmony, disease discord," a statement which can be applied to either general or local bodily condition, and which, to continue the metaphor, acknowledges or embraces the fact that the harmony may be in a minor key. That individual is regarded as enjoying good health, and in fact actually does enjoy good health, who nevertheless may for years have had extensive local disease of the heart valves, which in its turn has caused hypertrophy of the heart muscles in response to the increased work thrown on the organ. It is true that in such an one any sudden excitement or demand for increased work, which would have no deleterious effect upon the normal organ, suffices to bring on indications of heart failure. But within certain limits, employing ordinary caution, a subject of valvular disease of the heart may for long years enjoy life and carry out well all the ordinary duties without obvious bodily disturbance.

If, then, we take the position that for every structure and every function of the body, and for the body as a whole, there is a certain mode within the confessedly vague limits of which conditions are to be regarded as normal, it follows that anything outside the limits on either side is abnormal, and it is these conditions of excess or defect that for us must constitute disease; it is these we have to study. It follows also that constantly in our study of pathology we must base ourselves upon physiology and, so far as it throws light upon functions and functional disturbances, upon anatomy; for, obviously, pathological conditions are but extreme examples of physiological. Nay, more, it is useless to begin the study of our subject unprovided with a sound knowledge of physiology. Throughout this work, therefore, we would take for granted a knowledge of the main facts of physiology. Unfortunately, however, this is not always possible. More correctly, we should say that a knowledge of the physiology generally taught is taken for granted; certain branches of the subject must be considered with a fulness which is regrettable so far as, having regard to limitations in the size of our work, we thereby become compelled to condense our presentation of other matter, but is necessary, and in fact advantageous, so far as it tends to give the reader a more thorough comprehension of the meaning of morbid processes, and by laying down clearly the data upon which certain conclusions are based is indeed economical of space, since once laid down fully the briefest reference to general principles will suffice in later sections.

Cellular Physiology and Cellular Pathology.—Why we have to dilate upon certain matters physiological becomes evident when we call to mind that physiology and pathology have for the last seventy-five years, at least, been divorced to this extent, that they have undergone development under separate influences. Under the influence more particularly of Ludwig and his pupils, physiological research has been directed to the study of organs and tissues. The organ as a whole has been taken into account. Results have been obtained by exact

measurements—mechanical, electrical, or chemical—of the work performed by one or other organ under varying conditions, with the result that nowadays we possess a rich store of data bearing upon what may be termed *mass effects*. Nor can it be denied that these methods have very materially advanced our knowledge of function and of the bodily processes.

But the oncometer, the pendulum myograph, the recording cylinder, and Kjeldahl's apparatus cannot be applied to the study of the individual cell units of which the tissue is composed. It is under the influence of another great master (Virchow) that modern pathology has been developed. His teaching was based upon exact study of diseased organs and the correlation between gross and microscopic appearances. It was largely histological, and, as a result, mass effects were followed back to the disturbances in the individual cells composing the tissue. In place of an organ, or tissue pathology there was developed a "cellular pathology." Thus we owe it to Virchow that for now more than half a century pathology has held steadily before it the view that eventually the cell and the modifications undergone by it must be studied if we are to understand aright the disturbances affecting the tissues and the organism as a whole. The cell and not the tissue is our unit.

We admit freely that for a long period after the publication of Virchow's great work comparatively little advance was made in our comprehension of cellular pathology. As so constantly happens when a new territory in science is opened up by a master in exploration, the tendency is for the majority of workers to rush into that territory, following the route and employing the methods of the pioneer. It is in science as in gold-mining—a new "find" is announced, and workers from other fields forsake them and join in the rush. These other workers in pathology have, it is true, in the course of years contributed an enormous mass of facts, but the facts in the main have confirmed rather than advanced Virchow's observations. Virchow, indeed, employed his great influence in discouraging pathological speculation. He recognized that more facts must be accumulated before sure advance could be made. These facts preparatory to advance were in the meantime being accumulated not by the pathologists, nor, again, by the physiologists, but by the zoologists, the botanists, and the embryologists—facts, namely, bearing upon the finer structure and the functions of the normal cell. It was left to a zoologist (Metchnikoff) to realize the bearing of these facts upon the cell in disease, and, by his studies upon the leukocytes, to emphasize the importance of the study and to develop new methods.

So strong was the influence of Virchow that through the last half of the nineteenth century pathology, as usually taught, consisted of little beyond the facts of gross and minute morbid anatomy. The text-books in our subject were devoted to the data of disease—to descriptions of the appearances (more particularly under the microscope) of the tissues and their component cells under various conditions of disease, and the abundant nomenclature in connection with the same. Attempts to explain and to generalize were reduced to a minimum.

It has taken many years—Metchnikoff's studies upon the leukocyte

began in the early eighties—for a general realization of the bearing of these researches of Metchnikoff upon pathology and pathological research, and then only through the demonstration of their profound effect upon the related studies of the bacteriologist on infection and immunity. Now more than ever is pathology becoming truly cellular.

We admit freely also that the physiologists are, from other considerations, being simultaneously led back from tissue to cellular physiology. It is the natural course of events that, having established their science upon the reaction of organs and tissues as a whole, they should proceed to study the reaction of the component cells. As a matter of fact, we already possess at least one important work upon cell physiology, that, namely, of Verworn. But, excellent as it is, and suggestive, this is not yet generally read by the ordinary student; add to which, approaching the subject independently and from a different standpoint, we find ourselves not wholly in accord with Verworn over more than one matter of importance. Hence, since cell physiology is not given a proper place in the routine teaching of the student, and as this must be the basis of a cellular pathology, it is essential that we bring together and discuss in some little detail those facts bearing upon the life of the healthy cell, a knowledge of which, in our opinion, is necessary for an adequate comprehension of the changes which take place in the cell in disease. Associated with a study of the life of the cell we shall have to discuss certain phenomena—growth, adaptation, reserve force, heredity—which have an intimate bearing upon certain pathological processes, which again receive but the most summary treatment in the ordinary text-book of physiology.

Scope and Order of the Work.—These more physiological subjects we shall endeavor to deal with in an introductory section of the work. They will form the basis upon which we propose to develop our treatment of pathology proper.

As to this treatment: If, in its widest significance, pathology is the study of the functions of the body in disease (and conversely, we should add, of noxæ, or serious alterations in environment, as they bear upon the bodily functions), then clearly our subject embraces the whole field of scientific medicine, save and except therapeutics, or treatment. In other words, it has to deal with:

1. The causes of disease.
2. The course of disease (including the reactive processes on the part of the organism, whereby that course is modified).
3. The results of disease.

Each of these main divisions can be approached and treated in at least two ways. Thus, on the one hand, forming or attempting to form a classification of diseases, we can discuss the *etiology*, or cause of each in turn; similarly we can describe the course of each separate disease, giving the *symptomatology;* and thirdly, we can note the results of each separate disease. On the other hand, studying all the conditions which cause disease, we can endeavor to *classify* the etiological factors, grouping together those influences which, acting on the

organism, are seen to produce allied morbid conditions; similarly, from a knowledge of the course of various diseases, we can attempt to distinguish and describe certain morbid processes, one or more of which we recognize as underlying, and as common to, the course of individual forms of disease; and, coming to the results of the disease, instead of dealing with individual cases, we can discuss and classify the results of disturbed function upon individual organs and tissues, and attempt to gain a broad idea of how these local disturbances in one organ or tissue affect other organs and the organism in general.

The first of these methods is that of *special pathology*, so-called; it is the method employed in text-books of medicine and surgery; indeed, on the European continent, what we would term general works upon medicine and surgery are entitled text-books of internal and external pathology. Dealing, as is our purpose, with the broad principles of pathology, the second is the only possible procedure. We shall endeavor to arrange our matter in the order given—namely, to discuss first the causes, next the course (the morbid and reactive processes), and thirdly, the results of disease. As will readily be understood, it is not always easy, or indeed desirable, to discuss the causes of disease without at the same time indicating the processes which they originate; nor, again, is it possible to describe the morbid processes without indicating to some extent the results of the same. Nevertheless, this is, I feel assured, the only satisfactory and logical method of covering the vast territory before us. It is the means whereby the surest grasp is obtained of the principles underlying and governing those disturbances of vital activity which we recognize as disease.

This, we acknowledge, is not the course usually pursued in works upon general pathology, and to this extent is disadvantageous. By tradition starting with the morbid processes, inflammation and disturbances of the vascular system are first discussed. By our arrangement inflammation is first considered in our third section, vascular disturbances not until the fourth. That more usual arrangement, we take it, is one of convenience coupled with prescription. When pathology is taught *pari passu* with medicine and surgery it is undoubtedly convenient that the student obtain a knowledge of such predominant processes as inflammation and infection as early as possible in the course, and when inflammation was regarded as essentially a vascular disturbance, it was natural that other vascular disturbances should be taken in close association. The result has been that the ordinary student has obtained an exaggerated idea of the importance of vascular disturbances, whereas what is of equal value for a general understanding of disease—namely, the pathology of the nervous system—has been relegated to the very end of the course, if, indeed, it has come in for treatment at all. The system has been imperfect. As regards convenience, we would point out that, conformably with our firm belief that the student should have a sound basis of physiology before entering upon the study of pathology, it is well that the matter contained in our first section should form a course in the "second year"—whether given by pathologist or physiologist is a

matter of indifference—and at the end of the second year a course on causation or etiology may well be introduced also. By this means the teaching upon the morbid processes comes to be given at the right moment—namely, when the student possesses his knowledge of physiology and is obtaining the first introduction to actual cases of disease in the hospital, and his first lectures upon "Internal and External Pathology."

We recognize, however, that the teaching and the periods of teaching of our subject vary greatly, and do not believe that the student should be a man of one book, mastering that book from alpha to omega. Hence we have arranged our material, so far as possible, in such a way that, while it forms a more or less progressive system, any one section or important subject becomes, by cross-references, etc., complete in itself.

We should add that, in order to afford illustrations of the different processes and their results, there are given, in the second volume of this work, that upon what may be termed *systemic* pathology, chapters dealing with the main outlines of special pathological histology. For these chapters, upon anatomy and the special pathology of the different organs, the reader is indebted to our colleague, Professor A. G. Nicholls.

The Principles of Pathology.—One more word before embarking upon our course. What we have already said will have indicated that we have no narrow conception of the scope of our subject. The time has passed when morbid anatomy and morbid histology could be regarded as the sum and substance of pathological teaching, and when "to name his tools" was what was, in the main, demanded of the student. In the evolution of every science there are three stages to be recognized: The first, that of its dawn, when, from the observations of a few facts, the wide possibilities of the science impress themselves upon the worker and stimulate the imagination, so that forthwith he proceeds to indulge in wide hypotheses. These, in their turn, form the basis of further observations in order that they be tested, with the result that time and again they are found either erroneous or inadequate. With this, a second (reactive) stage becomes manifest, in which it is appreciated that before any sound generalizations or laws can be established the facts and data of the science must be carefully accumulated and marshalled. It is when this has been accomplished that the science can enter upon its third (complete) stage, in which an adequate knowledge of the factors involved permits the establishment of general laws. Needless to say these three stages are apt to overlap. At an early period sufficient facts may be at hand, or some clear-sighted observer may arise, to lay down with precision one or more secure generalizations, and so certain broad principles may be developed perfect at the very beginning, born complete, like Venus out of the sea foam. And, on the other hand, when, after much study and accumulation of facts, some other principle or law becomes established, its very establishment leads us to further possibilities, to the study and recording of yet other phenomena. For knowledge is progressive, and, while one department of science may have reached its third stage, other departments may scarcely have entered upon the first.

A study of the history of medical science—of pathology—amply bears out this statement. Galen, indeed, may be taken as the archetype of those who, conscientiously systematizing the known facts of a subject, proceed to develop a system which is unavoidably false, because the facts on which it is based are too few. He is at the same time a striking illustration of the value of even such necessarily imperfect work as he accomplished—for it cannot be denied that his efforts created a medical science, and that for a period of more than a thousand years he and his system dominated the medical world. With the medical renaissance in the sixteenth century the gaining of new facts from experimental observation led to the downfall of the Galenistic philosophy—it was tested and found wanting—and led forthwith to a succession of hypotheses, as one series of observations followed another. The new development of mechanics and physics led to Borelli's investigations upon animal movements and the appearance of the *iatromechanical* school, which explained animal activities on a purely mechanical or physical basis. The remarkable experimental ability and genius of van Helmont led to the recognition of ferments; his no less remarkable imagination led to extraordinary speculations, some wholly wild, others so prescient as only nowadays to be found to approximate to the truth. The more immediate outcome was the development of the *iatrochemical* school under Sylvius, in which, more particularly in connection with digestion and respiration, chemical processes were seen to be at the basis of animal activities. And so, to the middle of the nineteenth century, school succeeded school—mechanicodynamical, Brunonian, vitalistic, Cullen's system, and so on; the last of influence, more particularly in Germany, being that of Oken. System after system was overthrown as successive observations demonstrated their inadequacy. Virchow represented the revolt against all such. His teaching was that hitherto theories had been founded on insufficient data; the time had come to gather facts and cease theorizing; and so potent was his influence that we have had the remarkable spectacle of the workers in pathology among that most philosophical of peoples, the Germans, restraining themselves for fifty years from philosophizing, and sedulously bending themselves to accumulate facts and record details. And the same strong influence has told upon the pathologists of all countries.

During these fifty years the amount of material collected has been extraordinarily great—in fact, overwhelming—so much that no one individual can pretend to master it. Never has there been such a period; much more has been garnered than in all the preceding ages together. If in 1855 the data were inadequate, today we experience the contrary danger of being overcome and blinded by excess of detail. The time has surely arrived to attempt to systematize our knowledge and so to order it that each new fact acquired is seen to have its place and to exemplify some general principle. Pathology, we hold, is now ripe to enter, and has entered upon its third stage of development. It is with this opinion in mind that we have written the pages that follow.

CHAPTER II.

THE HISTOLOGY OF THE CELL.

As already stated in our introductory chapter, we owe it to Virchow that, for more than half a century, pathology has held steadily before it the view that eventually the cell and the modifications undergone by it must be studied if we are to understand aright the disturbances affecting the tissues and the organism as a whole. The cell, and not the tissue, is our unit. Modern pathology, however, demands a much fuller study of the cell and its activities than is usually afforded in the physiological course. From this it follows that if we are to grasp the more recent advances in the study of disease and of the reactions to the same, some little space and time must be afforded to a consideration of the cell and its properties. Such facts as are matters of common knowledge may be passed over rapidly; others must be dwelt upon.

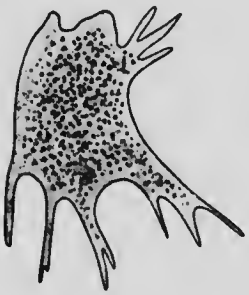
THE CONSTITUENTS OF THE CELL.

The animal cell, we recognize, consists of two main parts, the cell body and the nucleus; and this differentiation is clearly of great antiquity, for only the very simplest forms of life, whether animal or vegetable, do not show it. Even in these very simplest forms, if a sharply defined nucleus be not present we have evidence that nuclear material exists. It used to be taught that the lowest "animal" form—Haeckel's order of *Monera*—and the lowest plant forms—the *Schizomycetes*, or bacteria—are non-nucleated; but with the elaboration of more perfect staining methods, either a definite nucleus has been determined in those of the monera so far examined for this purpose, or again, in some, as shown by Gruber, granules of nuclear material are to be seen scattered through the cell body (Fig. 3). As regards the bacteria, there are parallel observations, observations which at first sight appear contradictory. Thus Bütschli, from his observations, regards all the stainable substance of the bacterial body as equivalent to the nucleus, and studying some of the larger forms demonstrated the existence of a fine surrounding substance, apt to be gathered at the poles, which he holds to represent the cell body or cytoplasm. This view is confirmed by other workers. Several more recent observers, dealing with the smaller forms, figure minute granules of stainable material diffused through the bacterial body. These they regard as nuclear material, and call attention to a characteristic rearrangement of these granules prior to fusion, which suggests strongly the "quadrille" of the nuclear chromatin preceding cell division in the cells of higher forms of life.

A full study of the divergent observations upon this subject up to the year 1900 is given by Professor A. B. Macallum.[1] Macallum denies that these lowest forms have a nucleus—that is, a sharply defined and well-differentiated organ presenting characteristic changes in cell division. Herein we cannot but agree with him. He admits, however, the existence of substances allied to the nucleus and to chromatin, substances containing phosphorus and "masked" iron, whether present in a "central body," as in the *Cyanophyceæ*, or as scattered granules. There is nuclear material, but no proper nucleus. Other more recent studies favor this view.

It may well be that both series of observations are correct; that, as in monera, there is in the lowliest forms no complete differentiation of the nucleus; but this differentiation has become developed in the higher forms. We may thus lay down that in all cells, animal and vegetable, there is present both nuclear and cytoplasmic matter. To the significance of their co-existence we shall revert later.

FIG. 3



Absence of nucleus proper with diffusion of scattered granules of nuclear material through body of a *monera*. (After Gruber.)

In the cells of man and of all save the lowest forms of life it can be seen that neither the nucleus nor the cell body is homogeneous. We are still very far from having resolved the minute anatomy of either. That anatomy, indeed, is beyond the power of the microscope to determine.

This much may here be laid down, that the nucleus is a well-defined body, most often approximating in shape to the spherical or oval; at times greatly elongated (as in plain, non-striated muscle tissue); at times irregular and lobate (as in the polymorphonuclear leukocyte); at times moniliform or beaded, as in *Stentor;* or, rarely, extensively branched, as in certain gland cells of insects, or possessing pseudopodia-like processes, as in the egg rays of the water scorpion.[2] In the higher animals a more or less distinct nuclear membrane is to be made out, within which the substance exhibits an alveolar or netted arrangement. Of this nuclear matter, at least three constant constituents are to be distinguished: (1) The *linin* or achromatic (non-staining) network in which is deposited (2) the *chromatin*, or material which is rendered noticeable by nuclear dyes. In the spaces of the network is (3) the *nuclear fluid* or sap. Inconstant features are (*a*) the *nucleolus*, a minute accumulation of chromatin-like substance, varying in amount, which nevertheless takes on certain differential stains, and hence would seem to have a somewhat different composition; (*b*) *vacuoles*—these are very rare;

[1] On the Cytology of Non-nucleated Organisms, University of Toronto Studies: Physiological Series, No. 2, 1900.

[2] Vide Korschelt, Naturwissensch. Rundschau, 18:1887:409.

they are to be seen in the nuclei of fat cells; (*c*) definite crystals; these have been recognized by Marchand. Podwyssozki, and others. These last two constituents afford indications that active metabolic processes occur within the nucleus.

The type cell has but a single nucleus; this is the general rule, but it is not uncommon in active glandular tissues to find cells with two, and other instances occur in which cells are multinucleate. Two processes are possible: either with growth the nucleus may divide without subsequent division of the cell substance, or what had been separate uninucleate cells may fuse, forming a *plasmodium*.[1] We have evidence that both processes take place, and shall have to refer to these matters more fully in discussing *giant cells*.

As already indicated, in some of the simpler forms of life nuclear material is scattered through the cell substance. In higher forms, this nuclear material, as a rule, is strictly confined within the nucleus. But it has to be laid down that this is far from being absolutely constant. In certain cells and under certain conditions minute masses of chromatin are to be detected lying in the cell body away from the nucleus. These and other not so definitely chromidial substances have been shown by numerous observers to be derived and discharged from the nucleus. Thus Maximow[2] describes and figures the secretory granules in serous cells of the salivary glands as originating on the inner surface of the nuclear membrane as adherent "nucleolar" matter, then projecting outward as buds, later becoming free in the cell body. These discharged masses of nuclear material are of very considerable pathological interest. Some of them are identical in appearance and reaction with certain so-called "cancer parasites," which thus must be regarded as nuclear products. Some, though not all, of the intracellular bodies seen in the vaccine lesions have similarly been shown by Ewing[3] to be explicable as diffusions of nuclear proteins into the cell body. To this discharge of the nuclear material into the cell substance we shall refer in fuller detail later.

The cell substance also exhibits indications of structure. Without there being in the animal cell the distinct membrane or wall so conspicuous in many vegetable cells, there is, nevertheless, often to be recognized a condensation of the cytoplasm or cell substance at the periphery, homogeneous, and constituting the *ectoplasm*, which passes almost imperceptibly into the main mass of cell substance, or *endoplasm*. This endoplasm is seen by careful study to possess, like the nucleus, an alveolated arrangement, regarding the exact nature of which cytologists are still at variance, it being most difficult, in the first place, to translate optical appearances under high magnification; in the second place, to assure ourselves that what is seen represents the natural conditions of the living

[1] Some writers draw a distinction between the *syncytium* caused by the fusion of cells, and the *plasmodium*, caused by nuclear multiplication without cell division; others include both forms as plasmodia.

[2] Arch. f. mikr. Anat., 58:1901:1.

[3] Journal of Medical Research, 13:1905:244.

substance, and is not a secondary effect brought about either by the death of the cell or by the action of reagents (Fig. 4); thirdly, save for deposits within it, the cell substance is obviously fluid; we have to differentiate between portions that are freely fluid and those which, if of greater density and more viscid, are still of fluid nature. We shall not here enter into the controversy which has raged, and continues to rage, regarding this matter, but would lay down the general conclusions reached, which are that the cell substance consists of (1) a coarse or finer reticulum, which may be termed the *cytoplasm* proper; (2) the cell sap, or fluid lying within the meshes of the reticulum; and (3) *paraplasmic* substances.

FIG. 4

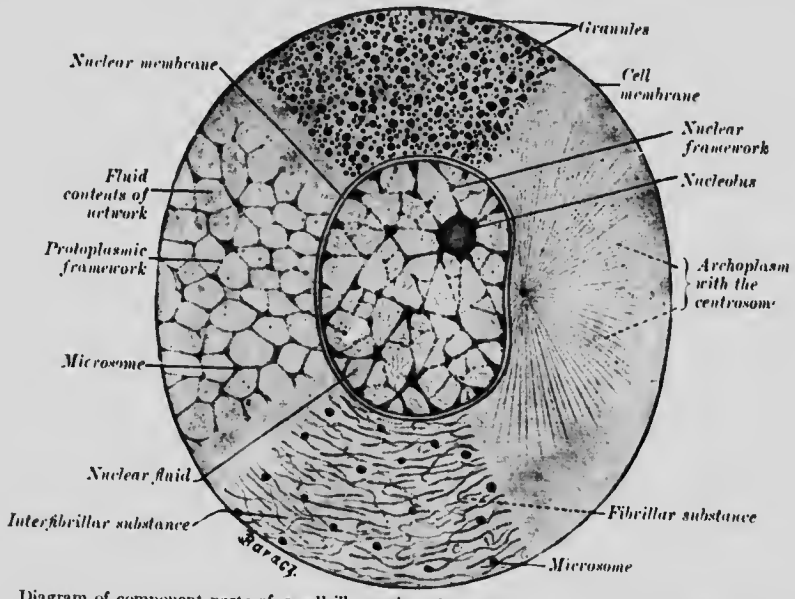


Diagram of component parts of a cell illustrating the various theories of the structure of the cytoplasm. The lower segment represents the *fibrillar* or *sponge* theory; the upper, the *granular* theory; the left, the *foam* theory. At the right the protoplasmic threads (archoplasm) radiate from the centrosome. (Szymonowicz.)

Under the term *paraplasm* we include (*a*) granules of solid matter taken up by the cell by phagocytic action and not yet dissolved or discharged; (*b*) granules of solid or semisolid matter, crystalline or amorphous, which are the products of cell metabolism; (*c*) the fluid contents of secretory vacuoles; and (*d*) inactive substances laid down as a framework within the cell. Passing beyond purely histological appearances, we may say that the cytoplasm is the active cell substance (termed by some the *bioplasm*), though it must be kept in mind that this term also includes, if, indeed, it should not be confined to, the active substance of the nucleus; the paraplasm, all material, whether in a dissolved or precipitated form, which is within the cell, and represents matter resulting from

the cell activity, whether products of disintegration of the cell substance or the unassimilated portions of absorbed material.

Regarding the granules constantly present within the cell substance, it deserves mention that some have given them a much more prominent position than is here ascribed to them. By special methods of staining, a fine granulation of the cell substance can be clearly demonstrated, and Altmann[1] has regarded these as the "elementary organisms, or bioblasts," as the units or fundamental elements in cell activities. Apart from the indications being, as we shall endeavor to show, that the primary cell activities are inherent in the nucleus, further study shows that Altmann's methods bring out granules of more than one order, and that there is no apparent relationship between the number of these granules

Fig. 5

Fig. 6

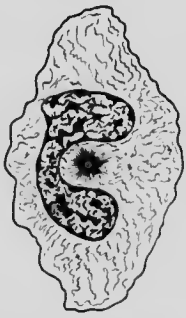


Fig. 5.—Section of normal tubule of kidney, stained to show the regular arrangement of Altmann's granules in the cells. (After Altmann.)

Fig. 6.—Leukocyte from larva of salamander, showing centrosome with surrounding cytoplasmic radiation. (Flemming.)

(which varies greatly) and the active nature of the cell. All that Altmann has accomplished has been to call attention to the existence of these granules; he has not brought forward a single valid argument in favor of their possessing the attributes with which he endows them. While his facts are accepted, his interpretation of the same is now generally discredited.

There is another important structure in the cell substance, important in that it is seen to be actively engaged in the process of cell multiplication. This is the *centrosome*, a minute dot or area of condensation surrounded by a fine areola, generally situated toward the centre of the cell in the neighborhood of the nucleus; in some rare cases it has been described as actually within the nucleus. It forms a centre from which, prior to cell division, the cytoplasmic substance becomes arranged in fine rays, and, even before the nucleus, it undergoes division. In the resting stage of the cell it is not constantly recognizable, and in some it has not yet been made out. Regarding its nature and relationship there

[1] Die Elementärorganismen und ihre Beziehungen zu den Zellen, Leipzig, 1890.

has been keen debate—whether it be an independent constituent, carried over by division from cell to cell, just as are the nucleus and the cytoplasm, or derived from the nucleus or from the cytoplasm. Martin Heidenhain,[1] for example, in a singularly full study, has suggested that it is the homologue of the *micronucleus* of the infusorian cell. (The infusoria have two nuclei, of which the larger, the *macronucleus*, is most in evidence in the functioning organism, but disintegrates and disappears during the process of conjugation and fertilization, the micronucleus then becoming active.) More recently Yatsu,[2] confirming E. B. Wilson, has shown that if the eggs of *Cerebratulus* be cut up, and fragments, devoid of nuclei and centrosomes, be placed in sterilized calcium chloride solution and then in sea water, a centrosome with surrounding aster develops in them identical with those of whole eggs subjected to the same treatment. From which it is evident that the centriole or centrosome can be formed *de novo* from the cytoplasm, that it is of cytoplasmic origin.

CELL CONNECTIONS.

These are the main histological details regarding the constitution of the animal cell. But if our pathology is to be cellular, more is needed. The organism, being multicellular, but derived from a single cell, it is necessary to have a definite conception regarding the histological relationship between the individual component cell units, and this because of the light this must throw upon the dependence of the cells one upon the other in disease as well as in health.

The usual conception of the organism, we take it, is that it is an accumulation of cells which are distinct separate entities, acting the one on the other, either by their products or by physical influences, through conduction. The general idea is that the multicellular organism has developed primarily from the unicellular as an aggregation of separate unicellular units which have remained associated for mutual protection and benefit, the separate units undergoing differentiation as a result of relative position, and so of environment. Such a conception has induced a false view as regards what constitutes the individual, and to some extent as regards the relationship of the tissues one to the other.

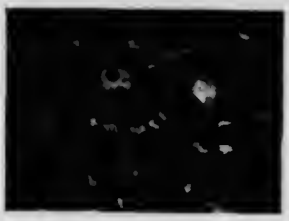
We owe to the botanists, first among whom must be mentioned Walter Gardiner, the demonstration that in the multicellular plant the individual cells are not isolated and wholly detached, but are united to each other by fine bridges. It has been proved by them that by the intermediation of these bridges stimuli are directly conveyed from cell to cell. Now, in the animal body, it is becoming proved for most tissues that the cells are similarly connected. The cogwheel-like appearance of the cells of the epidermis was for long suspected, and has now been proved, to

[1] Arch. f. mikr. Anat., 43: 1894: 423, see also Arch. f. Entwickelungsmechanik, 1: 1895: 473.

[2] Proc. Soc. Exptl. Biol., 1905, and Amer. Med., 1905: 493.

be the indication of a system of filaments passing from one cell to its neighbors, and Kolossow[1] has shown, and MacCallum, of Baltimore, has confirmed, that similar bridges pass between opposed cells of the endothelia. Ciliated and columnar epithelial cells are likewise joined together (Barfurth[2]) and similar direct connection has been described

FIG. 7



Cell bridges of "prickle cells" of epidermis. (From a photograph by Schridde.)

between the cells of both plain and striated muscle (Kultschitzki[3]). Even the neurons, which have been regarded so generally as independent cells, have now, by Apathy and others, been shown to communicate by extremely fine filaments. The difficulty in accepting Apathy's results has been due as much to want of recognition of this general principle of cell connection as to the prevalent theories of nervous action.

FIG. 8

Cell bridges of vascular endothelium. (Kolossow.)

These filamentous cell connections are evidently present from the very earliest period of individual existence. Mrs. Andrews,[4] studying the recently laid eggs of echinus and the starfish, and employing very high powers, noted that in the process of cleavage, while momentarily

[1] Arch. f. mikr. Anat., 42:1893, and Ztschr. f. wiss. Mikr., 9, Heft 1 und 3; see also W. B. MacCallum, Johns Hopkins Bull., 14:1903:105, and Musceatello, Virch. Arch., 142:1895:327.

[2] Anat., 1897: 79.

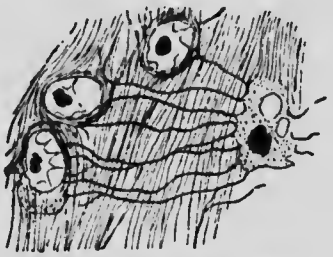
[3] Quoted by Waldeyer, Arch. f. mikr. Anat., 57:1901:2.

[4] Mrs. G. F. Andrews, Jour. of Morphol., 12:1897, and E. A. Andrews, Zoöl. Bull., 2:1898:1; confirmed by C. Shearer, Proc. Roy. Soc., 77:1906:498, who gives recent literature. The fullest study of this subject is by Schüberg, Zeitschr. f. wiss. Zoöl., 74:1903:155.

the blastomeres become separate, there follows an active discharge of fine threads across the intervening space, resulting in the union of the cells by protoplasmic processes. These could well be seen in the 8- and 16-cell stages, and, with their formation granules could be seen streaming from the one cell to the other.

In short, it may be laid down that the absolutely detached cell is the exception and not the rule. The lenkocytes—the wandering cells of the organism—are wholly independent; but this, judging from MacBride's[1] observations, is an acquired and not a primary characteristic. In the larval coelenterate, whose wandering mesodermal cells are the earliest homologues of the lenkocyte, these cells floating in the body cavity are found be connected by a network of singularly fine processes.

FIG. 9



Cell bridges between cartilage cells.

The organism or individual, therefore, is not to be regarded as essentially a conjugation or colony of detached units, but rather as a connected whole, in which, for reasons to be immediately discussed, there has been partial and incomplete division of the living matter; the cells in general are not detached, only semidetached.

The Significance of the Cell.—This conception leads up to a comprehension of the nature and significance of the cell. Studying this, whether among the unicellular individuals or in its many modifications among the multicellular organisms, one is struck by the fact that this in general is of minute size. The exceptions—the cases in which single cells are large enough to be visible to the naked eye—are of three orders:

1. Where the cells contain a large amount of stored-up food material. This is notably the case with the ova of very many species. Here, on fuller study, it is found that the cytoplasm forms a delicate membrane, spreading over and limiting the yolk. In this superficial layer lies the nucleus which thus, with the cytoplasm, is close to the exterior.

2. In certain of the infusoria the increase in size of the cell, until it becomes visible to the naked eye, is brought about by the development of the cell substance into a series of delicate radiating processes. By this means neither the nucleus nor any part of the cell is at a distance from the surrounding medium.

[1] Proc. Camb. Phil. Soc., 9:1896;153

3. As in *Gromia* and sundry other protozoa, the enlargement of the cell may be associated with the presence of multiple nuclei.[1]

In all these cases we appear to have a mechanism whereby no portion of the cytoplasm is remote either from the external medium on the one hand or the nucleus on the other. There is clearly a relationship as regards size between the nucleus, the cytoplasm, and the surrounding medium, and this is determined primarily by the size of the nucleus. As we shall point out, the evidence is conclusive that the nucleus is the dominant controlling element in the cell; it governs the cell body and cytoplasm; the larger it becomes the greater the disproportion between its surface area and its mass, and, as interaction between it and the cytoplasm must in the main take place at the surface, the greater its size the less its relative efficiency. If the nucleus exceed a certain size, the more centrally situated nuclear material must be largely inactive, and so useless. Thus it has come to pass that that living nuclear material has been most favorably circumstanced, or, in other words, best fitted to survive, *which has undergone division* and so increased its surface area at the same time as it has augmented its substance and mass. Thereby the maximum activity of the nuclear material has been insured. Hence the development in the first place of the multinucleated cell.

But if this be true of the interaction between nucleus and cytoplasm, it obtains also between the cytoplasm and the external medium. Here, again, we have to deal with surface action. It is obvious that, as in the radiolaria, the cell surface can be enormously increased by production into a large number of fine processes, but if, as already indicated, the cell activities are determined by the nucleus, by the reaction between nucleus and cytoplasm, such extension of the cytoplasm to a distance from the nucleus has its disadvantages. The most economical system is the spherical; of all simple forms, the sphere gives the largest surface relative to mass, and it is to be noted that free cells in general approximate in shape to the sphere. But here, again, we have the same considerations of economy of action. Materials are absorbed and built into the cell substance from the external medium, and as the process of absorption and formation of new cytoplasm proceeds, the mass of the cell increases in a greater ratio than does the surface, until the point is reached at which the accumulation of inactive cytoplasm is subversive to proper action. The same processes that induced nuclear division have brought about cell division.

We thus recognize the following successive stages:

1. The cell or mass of living matter in which the nuclear matter is scattered through the cytoplasm.
2. The unicellular organism having the nuclear matter aggregated into a central mass, the nucleus.
3. The multinucleate unicellular organism.
4. The multicellular organism.

[1] A stage leading up to this is seen in Stentor and other ciliated protozoa, in which the relatively large nucleus is moniliform, beaded, and elongate.

It follows, thus, that the multicellular organism is not to be regarded as the outcome of the fusion of a number of separate individuals for mutual advantage. Such fusion, it is true, does occur in nature; witness the myxomycetes. It is, however, the exception, and is not found along what we regard as the direct line of vertebrate ancestry. This communal idea must be replaced by one more directly in harmony with the facts of individual development and our knowledge of evolution—by what we may term the theory of decentralization, *which regards the individual as the sum total of protoplasmic matter capable of existing as an entity under particular conditions of environment, the multicellular individual acquiring its greater size and more complete activities by means of nuclear division, followed by cell division.*

As regards the nuclei, this division is complete, and as the nucleus is, we hold, the primary and controlling structure in the cell, to this extent each cell is an independent entity; as regards the cytoplasm, as stated (p. 33), the separation is incomplete, and to this extent the individual is a single connected whole. But, while making this statement, it must be borne in mind that the nucleus cannot persist without the cytoplasm; that there evidently is an intimate relationship between the two such that the nucleus is acted upon not directly by the external medium, but through the intermediation of the cytoplasm. From this it follows that cytoplasmic alterations, if conveyed from cell to cell, are capable of influencing the nuclei; these latter may control the individual cells, but are at the same time capable of being influenced by the cytoplasm. This conception of the relationship of the cells and tissues in the multicellular organism is fitted, we think, to throw light upon the otherwise somewhat paradoxical coincident independence and interdependence of the cells, to which we have already referred in discussing what is disease (p. 20), which must thus be regarded as primal.

CHAPTER III.

THE PHYSIOLOGY OF THE CELL.

We have stated that we regard the nucleus as the controlling constituent of the cell. Here it will be well to indicate the grounds upon which this view is based, more particularly because this view is not universally accepted, but is apt to be propounded with some hesitation in works upon physiology, and because a correct appreciation of the influence of the nucleus is, as we shall repeatedly have to indicate, of primary importance in the study of morbid processes. It is only of late years that the attention of pathologists has been attracted to nuclear changes; only, in fact, after the cytologists had established a basis of knowledge regarding the normal nucleus did it become possible to study departures from the normal.[1]

It has, in the first place, been fully established that without a nucleus, growth and reproduction of the cell cannot occur. The cell, deprived of its nucleus, can exist for a time, can be the seat of certain metabolic activities, but its substance is progressively used up, and, judging from its complete incapacity to reproduce itself, it cannot form new living material, either cytoplasmic or nuclear. The red corpuscle, for example, the type of non-nucleated cell in the normal vertebrate organism, can act as a carrier of oxygen, but cannot perpetuate itself. The individual erythrocyte, once it is liberated into the blood stream, has but a limited period of life. Hunter[2] estimates that the red corpuscles of the rabbit live, at most, three or four weeks. Quincke[3] and Worm Müller[4] give a life of about fourteen days to the red corpuscles of the dog. Throughout life there is a constant development of new erythrocytes to take the place of those undergoing disorganization.

What is true with regard to the red corpuscles has been experimentally proved with regard to unicellular organisms. Brandt,[5] in 1877, showed that pieces of *Actinosphæria Eichhornii* containing a nucleus assume a characteristic form typical of the whole organism; those without a nucleus fail to do so. With *Siphonocladus* (another simple multicellular form), Schmidt,[6] ten years ago, showed that when broken up the proto-

[1] For a fuller statement of these views regarding the dominance of the nucleus I would refer to my address at the meeting of the British Medical Association at Toronto, in 1906. Brit. Med. Jour., 2:1906.

[2] Brit. Med. Jour., 1887:i:January 29.

[3] D. Arch. f. klin. Med., 25:567 and 27:193.

[4] Transfusion und Plethora, Christiania, 1875; see also von Ott, Virch. Arch., 93:1883:125.

[5] Ueber Actinosphaeria Eichhornii, Dissert., Halle, 1877.

[6] Festschr. d. naturforsch. Gesellsch., Halle:1879:3.

plasm formed into spherical masses; those not having a nucleus failed to produce a surrounding membrane, and soon disintegrated, while those containing one or more nuclei developed into the typical organisms. Fuller confirmatory results were gained by Nussbaum[1] with *Oxytricha*, and by Gruber[2] with *Stentor*. Klebs[3] noted that enucleated cells of algæ, like spirogyra, might live six weeks, and during that time might produce new starch granules—might, that is, synthesize starch from the carbon, oxygen, and water absorbed. This starch was formed in the sunlight and used up in the dark. Notwithstanding, unlike nucleated portions of such cells, these enucleated portions produced no cellulose wall, and disorganization and death were inevitable.

Enough has been said to indicate that the nucleus is essential for the continued growth of the cell. There is not, to our knowledge, a single observation to the contrary. It is, however, worthy of note that, as Boveri[4] and Lillie[5] have pointed out, there is a minimal limit to the size of the separate (nucleated) cell portions capable of undergoing further development.[6] The nucleus, with the surrounding cytoplasm, is capable of regeneration and growth, provided that the amount of cytoplasm exceeds a certain minimal volume relative to the normal cell. For, as Verworn was the first to emphasize, the nucleus without the surrounding cytoplasm is as incapable of regenerating the cell as is the cytoplasm without nucleus. Nevertheless, Verworn[7] takes a position which is untenable. He admits freely that cell growth and reproduction are not possible in the absence of the nucleus, and that the nucleus plays an essential part in such conditions as the formation of cellulose by the plant cell, the formation of chitin in the insect cell, sundry secreting processes in gland cells of higher animals, and that the remarkable change in the size of the nucleus during cell life can be brought about only by the nucleus receiving substances from the protoplasm and giving off others to it. He, however, denies wholly that the nucleus is the dominating portion of the cell, pointing out that, although the spermatozoön, in fertilization, introduces a minimal amount of cell substance into the ovum, and is composed, as regards its functional head, almost wholly of nuclear matter, nevertheless that minimal amount is introduced and cannot be neglected; that if the cell without nucleus cannot exist, neither can the nucleus without cell substance, and demonstrates absolutely from his studies upon the ciliated infusorian *Lacrymaria olor* that the nucleus does not control the motor apparatus of the cell—that non-nucleated sections of the organism move as actively as do nucleated sections, and this for a day, sometimes for several days. *What he proves is not that the nucleus is not the dominating portion of the cell complex, only that the association of nucleus and cytoplasm is essential*

[1] Arch. f. mikr. Anat., 26:1886:485.
[2] Biol. Centralbl., 4:1885:717; 5:1885:253, and 6:1886:1.
[3] Ibid., 7:1887: No. 6, und Unters. a. d. botanisch. Inst., Tübingen, 1887.
[4] Arch. f. Entwicklmech., 2:1895. [5] Jour. of Morphol., 12:1896:241.
[6] In the cases studied, about one-twenty-seventh of the whole mass.
[7] General Physiology, translated by F. J. Lee, Macmillan, 1899, 504 et seq.

for full cell activity. He thus fails to grasp the significance of the nucleus, and his whole treatment of cell processes, if not vitiated, is, at least, greatly weakened.

All that Verworn's facts prove is that nucleus and cytoplasm are equally essential for the full function of the cell, not that they are of equal value. We might as well argue that in the community of bees the individual drone or worker is of importance equal to the queen bee, on the ground that, separate the queen bee from the rest of the community, and, being incapable of obtaining food for herself, she starves to death. Under no condition, that is, can the developed worker continue the race; this all-important function belongs to the queen bee, and to her alone. This simile, it is true, must not be pushed too far; advanced thus far, it will, however, illustrate our contention. The necessary association between nucleoplasm and cytoplasm does not contradict the evidence we possess that in the nucleus reside the controlling activities of the cell. Taking that evidence into account, it proves that *the nucleus cannot directly act upon the surrounding medium*, and that so *the function of the cytoplasm is to act as an intermediary between the nucleus and the environing substances.*

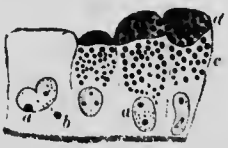
The prominent part played by the nucleus in simple cell division; the series of processes ensuring that each daughter cell obtains an equivalent amount of nuclear material; the remarkable part it plays in fertilization and the reproduction of the new individual—these matters need here but be referred to. They indicate, with a force that cannot be gainsaid, the controlling part played by the nucleus in the processes of cell and individual reproduction. The evidence that the nucleus is active in matters of cell metabolism is not so familiarly known, and deserves mention in a little more detail.

THE NUCLEUS AND METABOLISM.

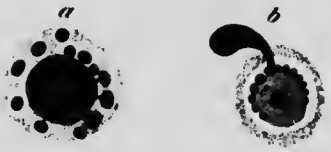
It is almost needless to repeat that not all the functional activities of the cell are initiated by the nucleus. Respiration, motility, the formation of contractile vacuoles, the seizing and destruction of minute living organisms, have all been seen to take place in cells deprived of their nuclei; even so elaborate a process as the formation of starch in the vegetable cell can occur under the same conditions. But what appear to be the specific activities of particular forms of cells and particular species would seem very largely to occur only through the intervention of the nucleus, through substances elaborated by and discharged from the nucleus, and this is especially true in connection with the specific secretory activities and, as we shall point out later (p. 53), the oxidative processes. Verworn noted that the non-nucleated pieces of foraminifera did not show the slightest capacity to secrete the calcareous salts which form so characteristic a framework in these unicellular organisms. In another lowly form, *Thalassicola pelagica* (and the same is true in the amœba), while non-nucleated

fragments can seize and kill living organisms, they cannot completely digest them, from which it would appear that the elaboration of digestive fluids, which Miss Greenwood,[1] Le Dantec,[2] and others have demonstrated in unicellular forms, is determined by the nucleus. The formation of the chitin in insects has similarly been shown by Korschelt[3] to be associated with active nuclear change; the secretion of slime by the amœba, Hofer[4] shows, does not occur when the nucleus is absent. In mucous goblet cells, F. Hermann[5] has shown that during secretion there appear in the immediate neighborhood of the nucleus, and apparently discharged from the same, minute globules, which in their staining powers resemble the nucleolus, and these are absent in cells which contain no secretion. Maximow[6] gives a still fuller account of very similar appearances in the serous salivary gland cells of the dog. The youngest, smallest, most deeply staining granules are situated in the

FIG. 10



Relationship of nuclear plasmosomes to zymogen granules and secretory substances of secreting cell: *a*, intranuclear plasmosome; *b*, granule (extranuclear plasmosome) in cytoplasm, near nucleus having same staining reaction, and evidently discharged from the nucleus; *c*, conversion of same into more feebly staining secretory (prezymogen) granules; *d*, further stage, zymogen granules about to be discharged. (After Maximow.)



Discharge of chromatin granules (plasmosomes) from the nuclear wall into the cytoplasm. (Schmaus and Albrecht.)

immediate neighborhood of the nucleus (Fig. 10). As these granules pass to a further distance from it their staining power diminishes, and they appear to give place to definite secretory granules. The exact stages of this conversion or development of the nuclear discharge into the cellular secretion is still under debate. Some authors, like Nicholas, Solger, and E. Müller, declare that when these granules have reached a certain ripeness they dissolve and are converted into secretion vacuoles, and empty themselves into the secretory capillaries of the cell which open upon the exterior. Maximow, while confirming the description given of the earlier stages, regards the granules as becoming directly

[1] Jour. of Physiol., 7:1886:251; 8:1887:263; 11:1890:576.
[2] Ann. de l'Inst. Pasteur, 4:1890:273, and 5:1891:163.
[3] Zoöl. Jahrb., Abth. f. Anat., 4:1899:1; also Naturwiss. Rundschau, 1887, 409.
[4] Jenaisch. Ztschr. f. Naturwiss., N. F., 17:1890:105.
[5] Anat. Anzeiger, 3:1888:58.
[6] Arch. f. mikr. Anat., 58:1901:52.

excreted. Outside the cell they are not to be recognized, for in the process of excretion they become converted into a homogeneous mass. Even within the cell these globules vary, it would seem, according to the amount of water imbibed by them.

Yet further observations might be quoted by Bensley,[1] Carlier,[2] Matthews,[3] etc., all harmonizing with these observations that the "prezymogens" of the cell are of nuclear origin, or, at least, are very directly controlled in their origin by the nucleus; that these in the cytoplasm become converted into the zymogens and become modified upon discharge into what we recognize as the specific secretions of one or other form of gland cell.

Macallum,[4] in 1890, had pointed out that similar processes occur in the formation of yolk and in the production of pancreatic zymogen. In the nuclei of developing ova in the ovaries of *Necturus* (the lake lizard) and of the frog at a certain stage the chromatin is principally collected in the form of "nucleoli" at the periphery, immediately beneath the nuclear membrane. These nucleoli are usually spherical and vary somewhat in size. At this stage yolk granules are absent from the cell. Employing the indigo-carmine stain of Shakespeare and Norris, he found at this stage that the peripheral nucleoli were apt to take on a deep blue stain, while the remainder of the nucleus and the cell were stained red. At what appeared to be a later stage, the peripheral nucleoli were smaller, and the yolk spherules which now were beginning to be formed were stained blue. Occasionally it was possible to encounter an ovum in which the nuclear substance around each nucleolus was, like it, stained blue, while the remainder of the nucleus and of the cell body was red. The nucleoli, therefore, generate a substance which diffuses gradually through the nucleus and then into the cell protoplasm, the [illegible]n coinciding in point of time with the formation of the yolk g[illegible] which he thus regards as formed by the union of a derivative o[illegible]uclear chromatin with a constituent of the cell protoplasm. As regards the pancreatic cell, his observations coincide with those of Steinhaus.[5] He found the nuclei to possess safranophilous nucleoli (*i. e.*, colored by safranin), while the rest of the nucleus in double staining took on the redder color of hematoxylin. As the nucleus lost its saphranophilous substance the cell protoplasm acquired safranophilous granules. He assumed that the chromatin of the nucleus of the pancreatic cell gives rise to a substance, "prozymogen," sometimes dissolved in the nuclear substance, sometimes collected in masses (plasmosomes), and finally diffused into the cell protoplasm, there uniting with a constituent of the latter to form "zymogen." Macallum had previously demonstrated that the hemoglobin of the red corpuscles of amphibia is derived from the chromatin of the nucleus, the hemo-

[1] Proc. Can. Instit., Toronto, 1:1896-11, and Quart. Jour. Micr. Sci., N. S., 41: 1898:361.

[2] Brit. Med. Jour., 2:1900, September 15, and La Cellule, 16:405.

[3] Jour. of Morphol., 15:1899:Supplement.

[4] Trans. Can. Instit., Toronto, 1:1891:247.

[5] Ziegler's Beitr., 7:1890:367.

globin so found diffusing through the nuclear membrane and becoming fixed in the cytoplasm, and hemoglobin, we would point out, may be regarded as functioning as an oxydase. The recent observations of Wright, of Boston, on the genesis of the mammalian erythrocyte amply confirm this view of the part played by the nucleus.

In this connection may be described Torrey's[1] observations upon the secretion of diastase in maize seeds. At the beginning of germination of the seeds the nuclei of the cotyledonar diastase-producing cells contain dark-staining granules, with few or none in the cytoplasm. Small breaks are to be made out in the membrane of the heavily loaded nucleus, and through these the granules exude in small streams. At first these granules are spread through the cell, but later they become collected at the end next to the endosperm. Here they become ultimately dissolved. It is following upon their dissolution that the first action of a ferment upon the cell wall and matrix of the endosperm is observable.

Other allied observations on shrinkage and loss of staining power of the nucleus in the course of active secretion are those by Schniewind-Thies,[2] on nectar cells in flowers, and by Greenough,[3] on the cells of the submaxillary gland.

Even the formation of fat in fat cells is evidently a nuclear process. The vacuoles in the nuclei of these cells have recently been shown by Sharlock[4] to contain and give the reaction for fat, and at times they can be seen fixed in the process of extrusion into the central fatty globule of the cell.

In the formation of the cell membrane in plant cells where this is local, as demonstrated by Haberlandt,[5] the nucleus is found eccentric in the immediate neighborhood of the region where the deposit of cellulose is localized—a similar localization is seen in cells which are developing root hairs. Lily Hnie[6] has studied and described the marked changes which occur in the nuclei of the secretory cells of the leaves of the well-known insectivorous plant, the *Drosera*, when these are fed with egg albumin.

Here, also, may be noted Heidenhain's[7] observations, made years ago, upon the difference in the appearance of the nuclei of salivary glands when at rest and after stimulation, and the interesting observations of Hodge[8] (confirmed by Gustav Mann,[9] Lugaro,[10] and others) upon the nuclear alterations in the motor ganglion cells of bees, birds, cats, and other vertebrates, brought about by natural and experimentally produced fatigue (Fig. 11).

[1] Bulletin of the Torrey Botanical Club, New York, 29: 1902: 121.

[2] Beitr. z. Kenntniss der Septalnectarien, Jena, 1897.

[3] Jour. Med. Research, 7: 1902: 560. [4] Trans. Path. Soc., London, 54: 1903.

[5] Die Beziehunge zwischen Funktion u. Lage des Zellkernes bei den Pflanzen, Jena, 1887; also, Sitzungsber. d. Kaiser. akad. d. Wiss., Vienna, Math. Naturwiss. Kl., 18: 1889, Abth. 1, 190.

[6] Quart. Jour. Micr. Sci., N. S., 39: 1897: 387.

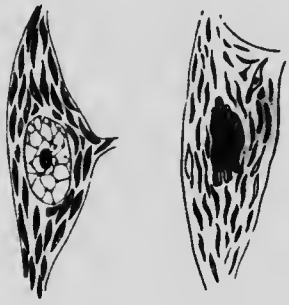
[7] Hermann's Hdb. d. Physiol., 5: 1883. [8] Jour. of Morphol., 7: 1892: 95.

[9] Jour. of Anat. and Physiol., 29: 1891: 100.

[10] Lo Sperimentale, 44: 1895, Sec. Biol., 2.

Similar changes in the nucleus have been made out under pathological conditions. In the liver cells in phosphorus poisoning, Stolnikow[1]

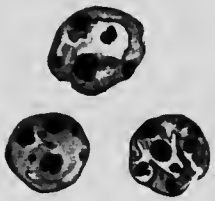
Fig. 11



A B

A, resting nerve cell with large rounded nucleus, showing chromatin network, the Nissl bodies in the cytoplasm (derived from the nuclear material) also large and prominent; *B*, exhausted nerve cell of same order, with shrunken irregular nucleus, chromatin network indistinct, Nissl bodies diminished in size and poorly staining. (After Gustav Mann.)

Fig. 12



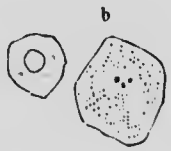
Leukocytes with disintegrating masses of nuclear material scattered through the cytoplasm (karyorrhexis).

has described this passage out of minute bodies from the nucleus into the cell body. These at first stain like nuclear substance; later they lose

Fig. 13

Hyperchromatosis of nuclear wall: nucleus vesicular, with disappearance of chromatin network and accumulation of chromatin masses upon the nuclear membrane. (Schmaus and Albrecht.)

Fig. 14



Karyolysis: extreme reduction or solution of nuclear chromatin, from a renal infarct. In *b* the nucleus is wholly disclosed save for some fine chromatin granules. (Lubarsch.)

the nuclear stain completely. Various transitional forms are to be recognized. Ultimately the nucleus becomes pale (karyolysis) and the

[1] Du Bois-Raymond's Arch. f. Physiol., Suppl. Band, 1:1887. Lukjanow, in the same year, described very similar appearances; as also Galeotti (Arch. f. mikr. Anat., 48:1897), in the secretory cells of lower animals; and Vigier (Compt. Rend. Soc. de Biol., 52:1900, No. 17), in the cells of the skin glands of the newt.

cell body filled with shell-like, scarce-staining globules, and yet smaller bodies, derived from the same.

Pathological workers, it is true, have been tardy in noting and describing these nuclear changes, but in the pages that follow we shall point out how frequently they are to be recognized. In general it may be stated that nuclear changes manifest themselves within physiological limits by (1) changes in size and (2) alteration in the amount and to some extent (3) of the disposition of the chromatin. In pathological conditions we observe still further alterations: extreme grades of reduction of the chromatin (karyolysis), abnormal arrangement of the same, œdema and swelling of the nucleus, with vacuolization, nuclear disintegration (karyorrhexis), abnormal discharge of nuclear material into the cell substance, etc.

Conclusions.—If, then, on the one hand, we regard the nucleus as the dominating portion of the cell, and, on the other, admit that this cannot act save in association with the cytoplasm, what must be our conception of the relationship of these two components of the cell and of the nature in general of cell activities? This question can, we think, best be answered after discussing the general principles of the chemistry of the cell. In the meantime the conclusion to be reached is that in the cell we have indications of the existence of living matter of two orders. There is in the nucleus matter which initiates growth, reproduction, and what we must regard as the very highest vital activities; matter which, moreover, can only react upon the cytoplasm, taking up substances from, and yielding other substances to this, and cannot react upon the external medium; in the cytoplasm, on the other hand, there is matter capable of taking up and acting upon other matter from without, from the external medium, but this is of a secondary order. It can manifest what may be termed the lower vital activities: absorption, respiration, mobility, and contractility, and these independently of nuclear control; it cannot initiate the higher activities of growth and reproduction.

Lastly, we may mention here, but will not discuss, a third order of matter that plays a most important part in cell activities; we refer to the organic ferments, substances produced by cell metabolism, capable of discharge from the cell and acting as a second group of intermediate bodies, this time between the external medium and the cytoplasm.

CHAPTER IV.

THE CHEMISTRY OF THE CELL.

THE PROTEINS.

If we make a broad survey of all forms of life, animal and vegetable, we find that there is one order of substances common to and to be extracted from all (dead) cells, however simple or however highly differentiated, namely, proteids, or, as it is becoming now the custom to designate the wider group of related substances, *proteins*. Apart from these, with the exception of water and the phosphorus and iron which appear to be intimately associated with the proteins, we can recall no other constituent common to all cells. A very great variety of other components can be isolated from cell substance—salts of one or other order, fats, alcohols (cholesterin[1]), and fatty bodies (lecithin, protagon, etc.), carbohydrates (starch, glycogen, etc.), chlorophyll, and other complex bodies which we regard either as the results of disintegration of proteid matter or as stages leading up to the formation of the same. And some of these in certain cells may be accumulated in such abundance as to be the main constituents. But each of them may be wanting in one or other form of cell. The proteins alone—and water—are common to all cells.

It is true that the very analysis of living matter, whereby we isolate these proteins, renders that matter dead; that when isolated these proteins are inert substances, manifesting few of the phenomena which we recognize as proper to living matter. We must, nevertheless, conclude that "life" is bound up with the presence of proteins, even if at the same time we are compelled to admit that the chemical or physical constitution of living matter is something different from that of the inert substances we gain in the laboratory. To be more exact, life is bound up with the presence of *proteidogenous* matter, and if later, in order to prevent any possible confusion between the living substance and the dead proteins, we speak of *biophoric* molecules,[2] it must constantly be kept in mind that we regard these as formed, in the main, if not essentially, of matter which, by rearrangement or by satisfaction of its affinities, becomes converted into proteins.

[1] And it may be added, ethyl alcohol, which has been distilled from normal brain and other tissues in recognizable amounts.

[2] Vide footnote, p. 68.

THE CONSTITUTION OF PROTEINS.

What, then, are these proteins?

They are singularly complex compounds of nitrogen, carbon, oxygen, hydrogen, and sulphur; the highest forms contain also iron and phosphorus.[1] Their molecules are of such size and complexity that in general they are incapable of undergoing crystallization, so that they remain in a colloid state. This colloidal character renders it impossible for us to be sure that we are dealing with pure substances, and so makes analysis in most cases at the best approximate. But some of the simpler proteids are crystallizable; these can be obtained pure, and can be analyzed. Of such, the most familiar is *hemoglobin*, or, more accurately, are the hemoglobins, for the analysis of hemoglobin from different species of animals demonstrates that the composition is not identical; indeed, the fact that the crystals of this substance from different animals have widely different shapes is sufficient to indicate the varieties in composition. The modern analyses vary between

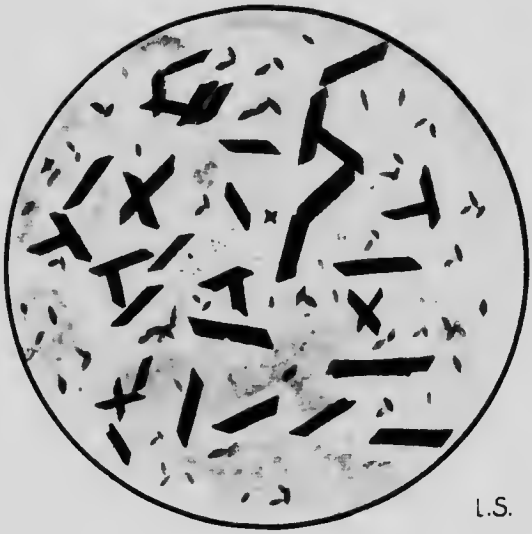
$$C_{680}H_{1098}N_{210}O_{240}FeS_2 \quad \text{and} \quad C_{712}H_{1140}N_{214}O_{245}FeS_2.$$

Whatever formula we take, we clearly have to deal with a molecule of enormous size, and this, to repeat, although we are dealing with one of the less complex proteins. It is, indeed, estimated that the average molecular weight of a proteid is in the neighborhood of 15,000; there can be little wonder that the large proteid molecules are unable to make their way through the fine pores of an animal or vegetable membrane—that they do not diffuse.

Classification.—These proteins are of various orders. Some, like the *albumins* (serum albumin of the blood, egg albumin, etc.) and *globulins* (serum globulin, myosin of muscle, fibrinogen, etc.), the *vitellins* (the "yolk plates" of egg yolk and aleurone grains of plant seeds, both of which are crystallizable), are free, *i. e.*, occur in a free state in the living body or cell substance. Others are combined—*combined proteins*—either with other proteins or with bodies of other nature. Thus hemoglobin can by simple means be split up into hematin, $C_{32}H_{32}N_4O_4Fe$, and a globulin, $C_{680}H_{1098}N_{210}O_{240}S_2$—and hematin is an iron-containing body, with proteid characters. The *nucleins* are compounds of a protein with *nucleic acid*, a compound of phosphoric acid with certain remarkable basic bodies intimately associated with the proteids, the so-called nuclein bases, regarding which we shall have to speak later, and these nucleins form a most important series of combinations with albumins and other free proteids—the *nucleoproteids*. Another group of combined proteids—the *glycoproteids*—show combination with carbohydrates. For us the most important among these are the *mucins*.

[1] For a full and clear presentation of the chemistry of the proteins, see Gustav Mann, Chemistry of the Proteids, London and New York, 1906.

PLATE I



L.S.

Hemin Crystals. (Simon.

To demonstrate crystalline form of a protein

PEPTONES, AMINO-ACIDS AND POLYPEPTIDS.

The leading chemists of Germany—preëminent among whom may be mentioned Emil Fischer, Hofmeister, Curtius, and Kossel—have in these recent years most materially advanced our knowledge of the composition of the protein molecu[le]. We cannot here pretend to give more than a very general indication of the direction in which their studies tend. It is to be noted, in the first place, that if individual proteins be analyzed, whether these be only obtainable in the colloid state or be, like hemoglobin, crystallizable, successive analyses, while approximating, do not give identical proportions of C.H.N. and O. In other words, while these clearly represent distinct compounds having well-defined properties, the constitution of each of them is not absolutely fixed. An interesting and profoundly suggestive feature in all of these forms is that they may be broken down with relative ease into simpler bodies which still possess proteid characteristics. This we have already indicated in our description of the combined proteins. It is equally true in regard to the so-called free proteins. We need but recall the fact that proteolytic enzymes break down albumin, globulin, myosin, etc., into peptones and albumoses. In other words, hydrolysis, whether produced by the action of these enzymes or by boiling with dilute acids, or by the action of alkalies, splits up more elaborate proteins in the first place into bodies which are still proteins and give the characteristic reactions of the same—*e. g.*, the biuret reaction—but which are evidently in the form of smaller molecules. That this is so is indicated by the fact that they diffuse through membranes. In this process of hydrolysis the proteins take up into their molecule one or more molecules of water, and the resulting *peptones* may be spoken of as degradation products. Thus the ordinary protein molecule is evidently a compound of like molecules, and is an example of polymerization, or the formation of a molecule of large size by the junction of a series of smaller similar molecules.

But now, by a continuation of this process, the peptones and albumoses afford still simpler degradation products, foremost among which are to be found numbers of the large group of *amino-acids*. About three-quarters of the albumin molecule is composed of such amino-acids. Thus, to give an example, the simplest bodies of proteid character thus far discovered in nature are the protamines (sturin, clupein, salmin, scombrin, etc.) obtained from the sperm of the sturgeon, herring, salmon, and mackerel. Compared with hemoglobin, the formulas of this class are relatively very simple, that of sturin, according to Kossel, being $C_{30}H_{69}N_{19}O_7$. They all give the biuret test, and by hydrolysis give first bodies of the nature of peptones (protones), and by further action break up into still simpler nitrogenous bodies. Thus, by hydrolysis, sturin, $C_{30}H_{69}N_{19}O_7 + 5H_2O$, affords:

$$\underset{\text{Histidin}}{C_6H_9N_3O_2} + 3\underset{\text{Arginin}}{C_6H_{14}N_4O_2} + 2\underset{\text{Lysin}}{C_6H_{14}N_2O_2}.$$

Kossel, indeed, has determined that all proteids yield these nitrogen-containing amino-bodies: histidin, arginin, and lysin, called by him the hexone bases.[1]

The Amino-acids.—These amino-acids are intimately related to the fatty acid series; they are, indeed, fatty acids—aminated fatty acids, *i. e.*, fatty acids given partial basic properties by the addition of NH_2 molecules; by processes of hydration they are converted into the hydroxyl acids of that series. It is these amino-acids to which the chemists have especially directed their attention—Curtius, in the first place, and of late, more particularly, Emil Fischer and his pupils. Their constant presence as degradation products of proteins and their relative great abundance indicated not only that they are to be regarded as primary nuclei of the protein molecule, and that the proteid molecule is essentially built up by a linking together of amino-acid molecules, but also that, experimentally, by bringing about such a linkage, it might be possible to build up—synthesize—more complex molecules of the proteid type; or, in other words, to accomplish that most ambitious and hitherto unattained object of the chemist, the experimental production of bodies of the proteid type.

The Polypeptids.—As a matter of fact, the first steps have been achieved toward this end, and that by Emil Fischer.[2]

Briefly, Fischer and his pupils have devoted five years to an active study of the amino-acids. Some eight of these had already been produced synthetically (glycocoll, alanin, amidovalerianic acid, leucin, aspartic acid, phenylalanin, tyrosin). Others of the long series they themselves synthesized, so that now some thirty members of the group are known. Fischer devised a method of gaining the mono-amino acids in a pure state by converting them into their esters, in which form they are volatile and can be distilled fractionally *in vacuo*. From these pure esters he gained the pure amino-acids and studied their compounds. The di-amino acids (ornithin, lysin, etc.) he similarly purified (by the phosphomolybdic acid method). From Biot (1815) and Pasteur (1860) onward the optical activity of compounds which are products of vital activity had been taken as one of the particular manifestations of vital activity, as an evidence that what Moore would now term "biotic energy," or vitalism, is distinct from ordinary chemical processes, the corresponding products when gained by the chemist being optically

[1] From a comparison between these bodies, which he would term *hexone bases*, all containing six carbon atoms, and the *hexoses*, the commoner sugars of the organism, Kossel was led to suggest that they give rise to the latter by the ordinary processes of oxidation and hydration. This view is not now generally accepted, because, save in the case of lysin, their carbon atoms are not arranged in the order of "normal" carbon chains as happens in the sugars. The sugars may at most be secondary cleavage products; thus Lusk has shown that in glycosuria the sugar does not appear alone in the urine, but in fixed proportion to the nitrogen excreted. Some proteins (*e. g.*, casein and vitellin) have not hitherto been made to yield any carbohydrate.

[2] Berichte d. Deutsch. Chem. Gesellsch., 39:1906:530.

inactive. Now, Fischer shows that he can gain both optically inactive and optically active forms of these amino-acids—that chemical methods outside the body can reproduce the products formed within, and that one of the last physical distinctions, if not the last, between "vital" and "laboratory" products has been swept away.

A characteristic feature of these amino-acids is that they are amphoteric; *they possess both acid and basic properties*, being slightly acid through the contained COOH group or groups, slightly basic through the NH_2 group or groups. It is this property that permits linkage. Thus to take one of the simplest of the mono-amino acids—glycocoll ($NH_2.CH_2.COOH$), or as, for convenience, we may write it, reversing the order of the NH_2 component, $HNH.CH_2.COOH$—by dehydration two molecules may become linked as follows:

$$\begin{matrix} & & & & OH & | & H & & \\ HNH.CH_2.CO & - & NH.CH_2.COOH; & & & & & & \\ \text{Glycyl} & & \text{Glycin} & & & & & & \end{matrix}$$

and in this way glycylglycin can be produced. If this be acted upon again by a halogen-containing acid chloride, and the halogen-salt be treated with ammonia, a di-glycyl-glycin can be obtained:

$$\begin{matrix} & & & & & & OH & | & H & & \\ H_2N.CH_2.CO & - & HN.CH_2.CO & - & HN.CH_2.COOH; & & & & & & \\ \text{Glycyl} & & \text{Glycyl} & & \text{Glycin} & & & & & & \end{matrix}$$

and this synthesis and process of polymerization can be continued until first the *pentapeptid* was obtained, with five nuclei linked in series; more recently the linkage of eighteen nuclei in series has been announced.

This linkage, it may be added, has been obtained not merely between identical nuclei, but between nuclei of different amino-acids. Thus, for example, Fischer has combined leucin and glycocoll into leucyl-tetraglycyl-glycin and leucyl-pentaglycyl-glycin. Leuchs and Suzuki have formed glycyl-phenylalanin and leucyl-phenylalanin; Fischer and Konigs, glycyl-asparagin, and, among the di-amino acids, Fischer and Suzuki have formed lysyl-lysin and histidyl-histidin (dipeptids), etc.

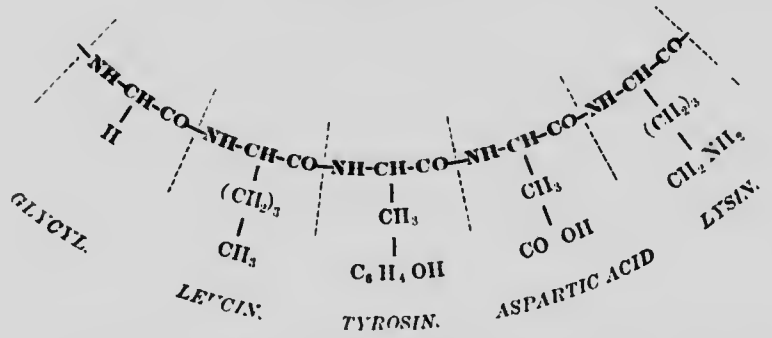
These polymeric amino-acid compounds thus gained have been termed by Fischer *polypeptids*. They are bodies which, in appearance, certain color reactions (such as the biuret test), behavior toward alkalies and acids, and toward enzymes, *so closely resemble the true peptones that*, to quote Fischer, *they must be regarded as their nearest relatives*. What is more, bodies of this order have been recovered from organic substances. P. A. Levene has discovered glycylproline anhydride among the products of the digestion of gelatin. Fischer and Abderhalden have isolated a tetrapeptid from silk fibroin, etc.: and, lastly, Fischer[1] notes that *l*-leucyl-triglycyl-*l* tyrosin, prepared artificially, has all the properties of the albumoses.

[1] Faraday Lecture, 1907, Jour. Chem. Soc., 91: 1907: 1749.

Conclusion.—Let it be clearly understood that these polypeptids are not as yet demonstrated to be identical with any known peptone, and that the peptones themselves are degradation products of the higher proteins. Nevertheless, these observations go very far toward confirming us in a conception of these peptones and the higher proteins as composed of polymerized molecules—as giant molecules, formed in the main of amino-acid molecules linked together by their otherwise unsatisfied NH and CO affinities. Thus, to modify Hofmeister's illustration,[1] we may represent a portion, at least, of the protein molecule, as follows (Fig. 15):

So as not to confuse the student, we have in our diagram indicated the nuclei as leucin, tyrosin, lysin, etc.; it will be seen on study that the leucin is minus an H on the one hand and an OH on the other; thus, to employ Fischer's terminology, it is a leucyl. The same is true of

FIG. 15



the other bodies. It will be seen that we represent the protein molecule as composed of a main chain in serial repetition with a number of side-chains of varying constitution. Further study will show that in the chain as here indicated each separate link in its simplest form may be regarded as:

$$(H)\text{-}\ \underset{\displaystyle (H)}{\overset{\displaystyle |}{NH.CH.CO}}\ (OH)$$

that is, as a glycocoll molecule, which the NH affinity on the one side and the CO affinity on the other have been satisfied by linkage with a like molecule, while one H of the CH_2 is substituted by butane, methyl-paraoxybenzene, acetic acid, and butylamin. In other words, we have a main glycocoll chain with a series of free swinging chains capable of being replaced.

This is, perhaps, the simplest case that we can conceive: the constant presence of lysin and histidin as degradation products in the analysis

[1] Vide B. H. Buxton, American Medicine, 6; 1903; 581. A clear and concise presentation of the data supporting this conception of the nature of the proteid molecule.

of proteins suggests that the links of the main chains may not be so simple as here indicated, and the preponderance of nucleoproteids in the cell nucleus points to the conditions there as being of a more complex nature. But the studies of many different schools converge toward this conception of the structure of the protein molecule as a linking in series or repeated series of amino-acid nuclei.

It may be added that I have represented these links as portions of a circle in order to indicate that the complete molecule is of the nature of a ring. This idea, I hold, best fits in with what we know regarding the proteins, namely, with their fixity to this extent; that we encounter in nature proteins of characteristic types and properties, bodies which cannot be conceived as capable of progressive linkage with an unending series of nuclei. The linkage in ring form best expresses the conception of completion and individualization of the compound molecules.

THE CHEMISTRY OF THE NUCLEUS.

The dominant position which we have already indicated as taken by the nucleus in the cell economy renders it important to determine whether there are differences in the chemical composition of the nucleus as compared with the cell substance in general. As a matter of fact, there are pronounced differences.

In the first place, we find certain substances stored up in the nuclei which are present to but a slight extent, if, indeed, at times they are at all recognizable, in the cell body. Of these, as shown by Lilienfeld and Monti[1] and by Macallum,[2] phosphorus is most noticeable; another constant in nuclei, not so constant in the cell body, is "masked iron," *i. e.*, iron so united that in ionization no free Fe ions are dissociated, the Fe being present as a constituent of what is probably a very complex ion[3] which has to undergo further dissociation before free Fe ions are liberated. On the other hand, certain substances commonly present in the cell body are absent from the nuclei. Among these may be noted potassium, carbohydrates, and—with the exception of the contents of the nuclear vacuoles already noted (p. 42)—fats.

When, now, we come to study more closely the proteid contents of the nuclei, these are found to exhibit certain pronounced features. Ordinary proteins, it is needless to say, are completely digested and dissolved by the gastric juice; but if a richly cellular tissue, or if free cells, such as are present in pus, be subjected to gastric digestion, as shown by Miescher,[4] the nuclei are found largely unaffected; they show little decrease in volume, and on farther study, as shown by Malfatti,[5] the portions which are thus unaffected are the chromatin of

[1] Zeitschr. f. Physiol. Chemie, 17:1893:410.

[2] Proc. Roy. Soc., 50:1891:277, Quart. Jour. Micr. Sci., N. S., 38:1895:175.

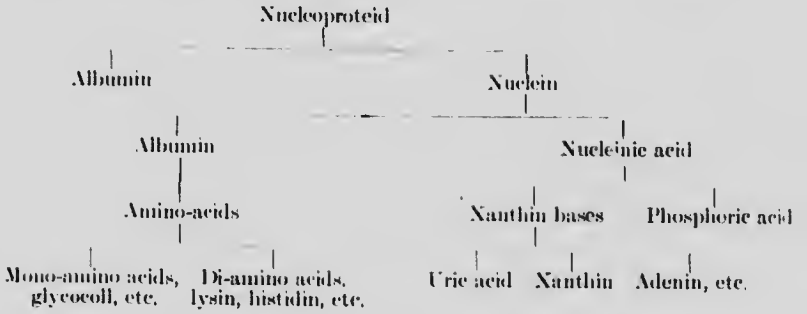
[3] A relatively simple example to the point is that $K_4Fe(CN)_6$ dissociates into potassium and ferrocyanic ($Fe(CN)_6$) ions.

[4] Verhandl. d. Naturforsch. Gesellsch., Basle, 1874.

[5] Ber. d. Naturmed. Verein z. Innsbruck, 20:1891-92.

the nuclear network, and, when present, the nucleoli. The *linin* or non-staining basis of the nuclear network is also undigested. We owe, especially to Kossel's[1] investigations, the explanation of these peculiar features of nuclear material. Briefly, the nuclei contain a special group of proteins, the *nucleoproteids*, which split up into albumin (histon) and *nuclein*, and it is the nucleins which are unacted upon by gastric juice, and, further, are characterized by a high phosphorus content, the amount of phosphorus varying in the different forms between 2 and 9 per cent. They are insoluble in water, dilute mineral acids, ether, and alcohol, but are soluble in alkalies. Like the nucleoproteids, they are of proteid nature, affording another example of this combination of protein with protein to form complex molecules. On further decomposition they yield an albumin and a *nucleinic* (or *nucleic*) *acid*. We say a nucleinic acid, for the different figures afforded by observers analyzing nuclear material from different sources would indicate that there are several of these acids. That obtained by Matthews from herring sperm gave the formula $C_{40}H_{54}N_{14}O_{27}P_4$. And nucleinic acid can be further disintegrated into the *xanthin*, and other *purin bases* and *bodies*, which have been so abundantly studied of late years: uric acid ($C_5H_4N_4O_3$), xanthin ($C_5H_4N_4O_2$), guanin ($C_5H_5N_5O$), adenin ($C_5H_5N_5$), and hypoxanthin ($C_5H_4N_4O$). These again, it will be observed, are all nitrogenous compounds. It will be noted that there is a parallelism between this breaking down of nucleinic acid into the xanthin bodies, and that of the protamins and free proteids into the nitrogenous hexone bases. Instead, however, of having 6-atom carbon bodies, we here deal with 5-atom carbon compounds. It is deserving of note that the nucleoproteids of the liver and pancreas yield not hexoses, but pentoses —sugars containing 5 carbon atoms.

To epitomize, the analysis of these nuclear proteids may be diagrammatically represented as follows:



Thus, so far as we can at present see, it is the existence of phosphorus and of these xanthin-base groups, or of compounds yielding these

[1] Zeitschr. f. Physiol. Chem., 22: 1896: 172, 188; 26: 1899: 588; also Deutsch. med. Woch., 1898, Nr. 37.

groups, that differentiate the nucleus from the cell body. How the iron is combined, which is also a feature of nuclear composition, is as yet undetermined.

In these xanthin bases which enter into the composition of nuclear material there is one structural peculiarity to which attention must be called—namely, the cyanogen-like (CN) linking of the carbon and nitrogen atoms not present in ordinary cell proteins. As Pflüger[1] pointed out many years ago in an article which, by its prevision, has become classical, cyanogen is a radical possessing great internal energy, and he calls attention to the striking similarity between its properties and those of living matter, or, more exactly, between the products of its oxidation, cyanic acid (H.C.N.O.) and living protein. "Both grow by polymerization, by similarly combining like chains into masses;" in this way the polycyanic acids ($H_nC_nN_nO_n$) are derived from H.C.N.O. Both are spontaneously decomposed in the presence of water into carbonic acid and ammonia; both afford urea by intramolecular arrangement; both are liquid at low temperature and coagulated at higher. Pflüger went so far as to suggest that it is from the "half-living molecule" cyanic acid, or from one of the cyanogen compounds, that living matter originated, although, considering that cyanogen and its compounds arise only at white heat, that origin must have been when the earth was still glowing.

Here, also, we may call attention to the coincident presence in the nucleus, as distinguished from the cell body, of iron and phosphorus. To quote Herter:[2] "This masked iron, as it is sometimes called, is doubtless of the utmost importance in bringing about the oxidative processes in the body, and any considerable diminution of the organic iron of the cell is probably attended by a diminution in the intensity of these processes. As regards the phosphorus, this also appears to be closely associated with oxidative changes."

It is, indeed, these oxidative powers of the nuclear matter that are, perhaps, its most striking features. Spitzer[3] has pointed out that those cells which are characterized by most active metabolism—the cells, for example, of the liver, kidney, and thymus, along with blood corpuscles—exhibit the greatest oxidative powers, and, what is more, that the nucleoproteids derived from these cells exhibit these properties to a marked degree, even when isolated. By appropriate staining methods Lillie has demonstrated that in the living cell oxidation proceeds in immediate association with the nucleus. It may thus well be that, as suggested by Loeb, the explanation of the difference between the nucleated and the non-nucleated cell is, that in the absence of the nucleus and its nucleoproteids, those oxidative changes that are at the basis of growth and regeneration cannot proceed.

Conclusions.—Let us now sum up the conclusions that may be reasonably deduced from the above data. They are:

[1] Arch. f. d. Gesammt. Physiol., 10:1875:251.
[2] Chemical Pathology. Lea Bros. & Co., p. 75.
[3] Arch. f. d. Gesammt. Physiol., 67:1897:615.

1. The one group of substances common to all dead cell material is the group of proteins, with which water holding certain simple salts in solution is constantly associated, apparently as a medium.

2. One particular group of proteins, the nucleoproteids, forms the main mass of the cell nuclei.

3. The presence of iron, phosphorus, and presumably of cyanogen-like radicals in these nucleoproteids differentiate them from the proteins of the cell body as a general group. While some of the cell body proteins contain iron (*e. g.*, hemoglobin) and other phosphorus (*e. g.*, casein and the nucleoalbumins), none contain both combined.

4. The oxidative properties of the cell are associated in a striking manner with the nucleoproteids. Their particular constituents suggest that the nuclear proteins are characterized by an "energy" superior to that of the cell body proteins.

These conclusion, it will be seen, support and strengthen the conclusions previously reached from histological and physiological considerations that the nucleus is the dominant portion of the cell economy.

METABOLISM IN RELATIONSHIP TO THE CHEMICAL COMPOSITION OF THE PROTEIN MOLECULE.

Thus far we have dealt with dead cell substance. We can by chemical and physical means break down these proteins; we cannot obtain substances which, when isolated, exhibit the properties of living matter. This, at least, is the usual statement. We shall point out that this statement does not express the whole truth; or, rather, that its truth depends upon what we regard as life. How are we to correlate our chemical with our physiological findings?

It is obvious, in the first place, that life and vital phenomena in general are directly connected with the presence of radicals peculiar to the proteins. We cannot escape this conclusion. The great variety of these substances, the enormous complexity of their molecules, the fact that scarce two analyses of any protein of what we may term moderate complexity afford identical results, all indicate that these contain very labile groups, that in the body they undergo constant change. We are forced to conclude, that is, that in the living organism they do not exhibit a fixed composition, but that there is a continual taking up and giving off of atoms and radicals; that in the living organism the bodies which we isolate as proteins exist in a condition of "moving equilibrium," what may be termed their average composition over a long period of time remaining constant, their composition at any two particular moments exhibiting variation. We can best picture such labile molecules as formed of a ring of nuclei after the type of the benzole ring, or, more accurately, of a ring of rings, each component primary ring being a primary protein of the first order (Fig. 16).

Each such ring, it will be seen, has some of its affinities satisfied by the adhesion of the components of the ring one to another, but others

are unsatisfied, and in such a compound ring as that here suggested, remembering that we are dealing with carbon containing nuclei, and that the carbon atom is tetravalent, the number of satisfiable affinities will be very great.[1] Accepting also what we know is the condition under which the proteid molecule exists in the living state, these rings must be conceived as present in a fluid medium containing free atoms, molecules and ions of electrolytes; and we must regard the difference between living protein matter and "dead" protein as this, that the "living" active protein molecule is so placed that, owing to the attraction and chemical activities of the surrounding atoms and molecules, the side-chains of the protein rings are in a state of continual change, an unsatisfied affinity now becoming satisfied by the adhesion of certain of these surrounding atoms or radicals; and, again, other side-chains of the protein ring becoming detached owing to the more powerful action

FIG. 16

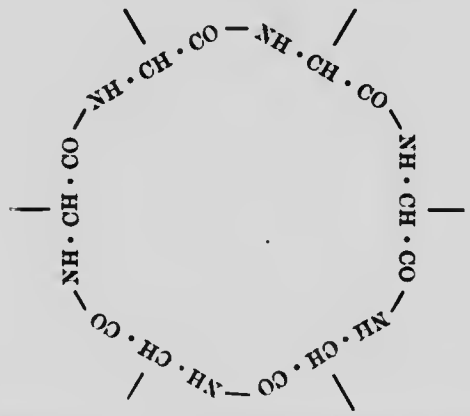


Diagram of suggested main ring of a protein molecule, without attached side-chains.

exerted upon them by the surrounding molecules; so that once again certain affinities of the protein molecule are unsatisfied; whereas in the "dead" protein molecule in the very process of preparation the side-chains have all become satisfied, and, being satisfied, the molecule is inert—that is unable to form other combinations.

Following this conception, *life* is to be regarded *as a state of persistent and incomplete recurrent satisfaction and dissatisfaction of certain protein, or, as we have expressed it earlier, proteidogenous molecules;* and *metabolism*—the constant reaction and interaction

[1] Here, in relationship to the prominent part played by carbon atoms in proteid and proteidogenous material, and to the constitution of the same, it is deserving of note that the carbon atom is not merely tetravalent, but, as shown by the organic chemists, these carbon atoms have a pronounced tendency to become linked to one another to form chains, and, thirdly, these chains tend to group themselves into ring formations.

between these molecules and the medium in which they exist—must be regarded as the primary and basal characteristic of living matter, whereby, on the one hand, certain of the constituents of the surrounding medium are acted upon by the proteidogenous molecule, are either attracted *in toto*, or some of their dissociated component ions become attracted, with the result that the molecule becomes enlarged; and, on the other hand, owing to the attraction of the surrounding molecules, certain of the side-chains of the molecule thus elaborated become split off and form new combinations with those other molecules.

The above definition demands that life be regarded as a kinetic state of matter of a certain order. Certain recent observations by A. Macfadyen[1] and Dewar open up serious doubts as to whether this is necessarily the case—as to whether we are not forced to recognize what we may term potential life. Macfadyen found that many pathogenic bacteria can be immersed in liquid air for as long as six months with no impairment of vitality. The temperature to which these organisms have thus been exposed is one equal to about —190° C. On removal, the organisms were found still to retain unimpaired their pathogenic and agglutinative properties; the pyococcus aureus still gave rise to active hemolysis. Dewar has obtained like results employing boiling liquid hydrogen, thereby subjecting the bacteria to a temperature which was surely within 20° C. of absolute zero (—273° C.). At these profound temperatures not merely is there a very great absence of heat, but also of what we have shown to be of the prime importance to living matter, namely, moisture; and we would imagine that intracellular metabolism must practically cease. A consideration further of the condition of living matter in the spores of many bacteria seem to point in the same direction, *i. e.*, that for life to continue it is not necessary that there be constant interaction with the surrounding medium. Such spores have been kept dry for twenty years and more, and when brought into favorable conditions have actively proliferated. Nevertheless, Macfadyen's remarkable observations suggest that (at —190° C.) there may still be some molecular change in his frozen organisms. He found, for example, that photogenic bacteria still gave luminosity at these low temperatures, whereas if, while freezing, he triturated the bacteria the luminosity was abolished; he thus determined that the luminosity was a function of the living cells. The matter must thus be regarded as still *sub judice*, though the presumption is in favor of the existence of such potential life.

[1] Proc. Roy. Soc., October 31, 1902. Some eighteen years earlier Pictet and Young had published similar observations, though the temperature they gained was not so low (—70° to —130° C.). Compt. rend. Acad. d. Sciences, 98: 1884: 747.

PROTEIN REACTIONS IN RELATIONSHIP TO METABOLISM.

It is of interest to call attention to the different effects of certain main orders of chemical action upon the (dead) compound protein molecule and the bearing of these data upon metabolic processes.

As we have pointed out hydrolysis effects characteristically a separation of the constituent nuclei. Inasmuch as enzyme action is hydrolytic in nature, we must imagine that this has eventually the same results, although, as will be pointed out in the next chapter, it has to be recognized that enzyme action is reversible; in other words, according to circumstances the same enzyme may be concerned both in the disintegration and in the building up of the cytoplasmic and nuclear protein molecules. If, further, as we would show, enzyme action is a property of the protein molecules themselves, it will be seen that in the living cell we must assume a most complicated series of dissociations of the contained protein and other molecules with liberation of simpler nuclei, and a like series of reconstructions.

In oxidative processes, on the other hand, what is characteristic is that not the main chain but the component nuclei are attacked. Just as the oxidation of toluol ($C_6H_5CH_3$) give rise to benzoic acid—the side-chain and not the main ring being attacked—so here the side-chains are acted upon until they are used up, with ultimate oxidation to urea and CO_2. But here, as in the preceding case, we have to keep in mind that there can be both extrinsic and intrinsic oxidative processes. Certain of the higher proteins—*e. g.*, the nucleoproteids—themselves possess oxidative powers.

Lastly, we must note a characteristic of bacterial activity, presumably a special instance of enzyme action associated with the presence of the living bacteria. This particular action is of the nature of a disruption of the individual nuclei accompanied by the splitting off of a CO_2 moiety whereby those nuclei are converted into amines and diamines. Thus from ornithin is produced tetramethylenediamin (putrescin).

$$NH_2CH_2CH_2CH_2\underset{\displaystyle NH_2}{\underset{|}{C}}HCOOH = NH_2CH_2CH_2CH_2CH_2NH_2 + CO_2$$

Ornithin. Tetramethylenediamin + CO_2

In this way are produced the ptomaines (and leukomaines). This reaction can be produced in the putrefactive disintegration of various proteins outside the organism; that it occurs to any extent in the living cell (in cases of bacterial infection) is still a matter of very considerable doubt.

CHAPTER V.

THE CHEMISTRY OF THE CELL—(CONTINUED).

ENZYME ACTION.

IT will be noted that in the above suggested definition of life we state "certain protein or proteidogenous molecules." Why, it may be asked, distinguish thus between proteid bodies? All are built up along the same lines, and all, we presume, in the living organism have affinities to be satisfied and side-chains which may be broken off. We introduce this word "certain" because it is still undetermined what is and what is not to be included in our conception of life. Let us for the moment leave it out and attempt to classify the proteins and potential proteins in the living organism according to the extent of their activities.

The Organic Ferments.—Attempting this, we discover that in the class of free organic ferments we encounter our simplest cases. We use the term "simple" relatively, for it may well be that the constitution of bodies exhibiting ferment, or enzyme action is very far from simple; we employ it because by it we would indicate that typical examples of this class exhibit *a single metabolic activity*, acting specifically upon one single order of bodies in the medium that surrounds them. Of these free organic ferments here referred to, numerous examples immediately present themselves: the ptyalin of the saliva, pepsin, rennin, trypsin, and the extensive series of other ferments of the pancreatic juice and of other digestive secretions. It is also important to obtain a proper grasp of the nature of these bodies, or, as will be made evident, of ferment action rather than of ferments—for the more we investigate, the more it is brought home to us that metabolic activities are of the nature of ferment actions, or otherwise, that, if not all, at least the majority of the manifestations of change in the proteidogenous molecule are to be included under this term. Constantly in studying cell functions, whether normal or perverted, we find ourselves brought to recognize that at base we are dealing with ferment action. It is, therefore, all important to gain, if possible, a right conception of what we mean when we employ the term. The above-mentioned group of free organic ferments present certain features in common:

1. Elaborated in certain cells they are discharged and act outside these cells.

2. Each acts upon a particular substance or series of substances in the external medium—ptyalin upon the starches, converting them into soluble sugar, but not upon proteins; pepsin upon proteins in an acid medium, converting them to peptones, but not acting upon starches; rennin upon casein and upon casein only; trypsin upon proteins in an alkaline medium; steapsin upon fats, and so on.

3. It has, so far, been found impossible to obtain the ferments in what can be regarded as a pure state; they are constantly found "associated with" bodies giving proteid reactions. More particularly are they brought down along with bodies of the nature of globulins.

4. Even though these apparent combinations of ferment and protein are present in extraordinarily minute quantities, given sufficient time they are capable of converting a maximum amount of the fermentescible substance, provided their action be not arrested by the accumulation of the products of fermentation. And in the action they are not themselves destroyed.

5. The attempts to obtain the ferment pure and isolated from the accompanying protein resemble those of the old woman who attempted to reduce daily the fodder of her horse. Just as the horse died when she succeeded in reducing that fodder to a wisp or two of hay daily, so with the reduction of material giving proteid reaction in the ferment solution to a minimum; and by repeated separations, it is found that the ferment is destroyed, or, more accurately, that the ferment action disappears.

What does this indicate? It may be asked, in the first place, do ferments as such really exist; is there a particular class of chemical compounds having this particular property of acting upon other matter and breaking it up, without themselves being altered; or, on the other hand, are ferments as a class non-existent; is ferment action simply the expression or outcome of the molecular arrangement of the compounds exhibiting this property; may there be several different classes of substances possessing ferment action? When we find that pure metals, like platinum, gold, iridium, and silver—or, again, metallic oxides—can exhibit properties identical in their nature with those possessed by the highly elaborate cell substance, and that the more we study chemical activity the greater the number of reactions we find which appear identical with this organic ferment action, the first of these alternatives cannot be wholly correct; at most we can lay down that there exist various inorganic bodies capable of manifesting ferment action, and with these a group of organic compounds manifesting like properties.

The Enzymes.—We may, that is, proceed to deal with the latter as a single class and give them a common name, that of *enzymes*. Even when we do this we recognize that under this term we include two orders, the *extracellular* and the *intracellular* enzymes, of which the former act when completely freed from the cell body, the latter only when in connection with the cell substance, and then in such intimate connection that we can only conclude that the enzyme action is part and parcel of the manifestation of the living (protein) molecules. To quote a familiar example, the yeast cell, growing actively, secretes and discharges something—*invertin*—which, when the yeast cells are wholly removed by filtration, is still capable of acting upon the malt sugar present in the solution, inverting it, that is to say, changing it into glucose, but this cannot proceed farther and break up the sugar into alcohol and carbonic acid. That process necessitates the presence of the living yeast cell, or, as Buchner demonstrated, the expressed living substance. Buchner found that if a mass of yeast cells be subjected to hydraulic pressure so great

that the cell membranes were ruptured, the thick, glairy fluid so obtained was capable of effecting the conversion of the sugar into alcohol, but this only when the experiment was conducted with great care, the results obtained being far from constant. When, by any means, the yeast cells have been previously killed, the reaction does not occur. The only conclusion to be reached is that here the enzyme, or ferment action is a function of the living and active cell substance; that in the experiment, while the yeast cells are ruptured, the cell substance is not actually destroyed, but still is able to manifest certain properties. The further conclusion is that some so-called intracellular enzymes do not exist as free bodies; were this so, we could extract from the yeast cell or from this emulsion the specific alcohol-producing ferment, and that we cannot do. We are forced, then, to the conclusion that in this case enzyme action is a function of the unaltered cell substance.

Having determined that this is the only adequate explanation in the one case, it may well be asked whether this is not the explanation of the activity of the other enzymes (*i. e.*, free organic ferments). These, as we have pointed out, are found constantly associated with, or affording, the reaction of proteins.[1] May not enzyme action be a function of active protein molecules, each particular enzyme action being due to the specific structure of a particular variety of these molecules? In other words, if we admit, as we have to admit, that metabolism throughout is determined primarily by enzyme action, and that metabolism is the property of living as distinguished from dead nitrogenous matter, may we not regard the free enzymes—ptyalin, pepsin, and so on—as free living protein molecules, divorced from cellular relationship, but continuing to manifest the one important function characteristic of living, as distinct from dead, protein, that, namely, of acting upon other molecules in their neighborhood, and bringing about a rearrangement of the atoms without at the same time being disintegrated? May we not, that is, regard the free enzymes as the simplest manifestation of life?

THE MODE OF ACTION OF ENZYMES.

This may, to most of our readers, be a novel and, indeed, a revolutionary conception. Before attempting to answer it, we must endeavor to gain a more intimate knowledge of the nature of enzyme action and what this demands.

There are two possible modes by which ferment action in general and enzyme action in particular may be brought about. We can, on the one hand, imagine that the ferment has no chemical action, *i. e.*, that it does not even temporarily enter into combination with the fermentescible substance; that its influence is purely physical. This view necessitates that we regard the ferment as a body possessing very

[1] There are a few apparent exceptions on record, but they are doubtful and possibly are explained by the extraordinary dilution in which these bodies may manifest their activity.

active molecular vibration, such that, in apposition to molecules of the fermentescible substance, it communicates its vibrations to these, so bringing about a rearrangement of the constituent atoms whereby the fermentescible is converted into the fermented substance. This "contact action" is held to be a not infrequent reaction in "inorganic" chemistry; it is by this means that the action of finely divided platinum, gold, or iridium, in converting hydrogen peroxide into water and oxygen, is held to be best explained. This we may speak of as *catalysis* proper.

The second mode may also be exemplified from inorganic chemistry by the manufacture of concentrated sulphuric acid from sulphurous anhydride by the agency of nitric acid. In this process the nitric acid is held to act as intermediary; a reaction occurs between it and the sulphurous anhydride, with the result that it gives up an atom of oxygen to the latter—sulphuric acid being formed and the nitric being converted into nitrous acid. This first stage affords the formula:

$$H_2SO_3 + HNO_3 = H_2SO_4 + HNO_2.$$

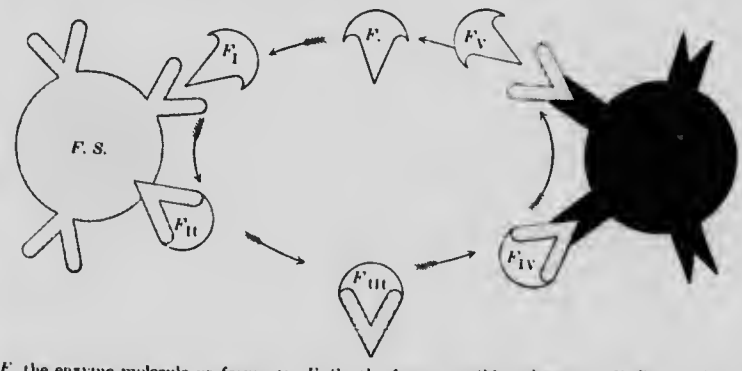
In the second stage the nitrous acid so formed, exposed to the air, combines with oxygen and so is reconverted into nitric acid, which now can act upon another portion of the sulphurous anhydride:

$$HNO_2 + O = HNO_3.$$

Theoretically, therefore, a single molecule of nitric acid can in infinite time convert an infinite number of molecules of sulphurous anhydride into sulphuric acid, and at the completion of the reaction will still exist as a molecule of nitric acid.

In such a process, it will be seen, three members or factors enter: the sulphurous anhydride may be termed the fermentescible substance, the oxygen the fermentator or complement, and nitrous (not nitric) acid the intermediary or the ferment. It is the nitrous and not the nitric acid that is present throughout the series of alternate reactions. We can visualize the process as follows:

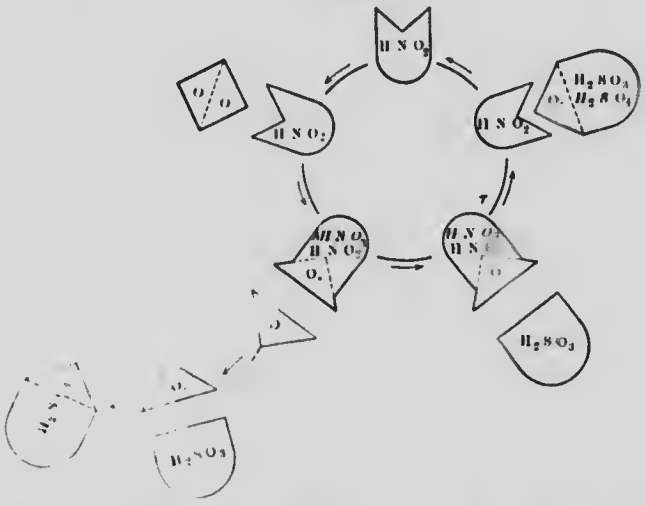
FIG. 17



F. the enzyme molecule or ferment; *F. S.*, the fermentescible substance; *F. R.*, the fermentator, or body with the moiety detached from the fermentescible substance forms the resultant compound.

And we can along these lines represent the particular reaction here described as:

Fig. 18



Many considerations lead to the conclusion that it is reactions of this order, and not simple catalysis, that take place in the living organism and in connection with the free enzymes, but preëminently the constitution of the protein molecule. This, we have pointed out, must be regarded as possessing unsatisfied affinities, satisfied by the junction of side-chains. Our conception of the whole process of metabolism, as already noted (p. 55), is along the lines here indicated. The whole proteid molecule may broadly be conceived as acting after the manner of the molecule of nitrous acid in the above reaction; constantly, that is, it attaches to itself atoms and radicals from the surrounding medium, either free in that medium or by its greater energy broken off from other molecules, and constantly it liberates these that they may enter into other combinations. So that, as already stated, the average composition of the molecule remains the same over long periods. Broadly stated, the condition of "moving equilibrium" is precisely that of the molecule of nitrous acid in the foregoing reaction.

It may be serviceable to express this diagrammatically (Fig. 19). Let the system *A B* to *F* represent the polymeric ring of proteidogenous molecules forming the centre of our ultimate compound biophoric molecule, no one of these *A*, *B*, etc., possessing all the properties of the whole system, but each having particular affinities whereby it becomes capable of attaching to itself and even of building up associated side-chains, the proteidogenous molecules thus built up being detachable from the central ring. The extracellular enzyme may be regarded as one of these side-chain molecules (*H*), or even as only one of the components of the same (*M*), still retaining on its part certain particular

affinities only, to which it can attach itself to and combine with specific substances, the act of combination causing a dissociation of those substances. The exact nature of such dissociations will be discussed later. In other words, we regard these free molecules as the ferments of common parlance. More accurately, such free primary proteidogenous molecules are possessed each of specific enzyme action.

FIG. 19

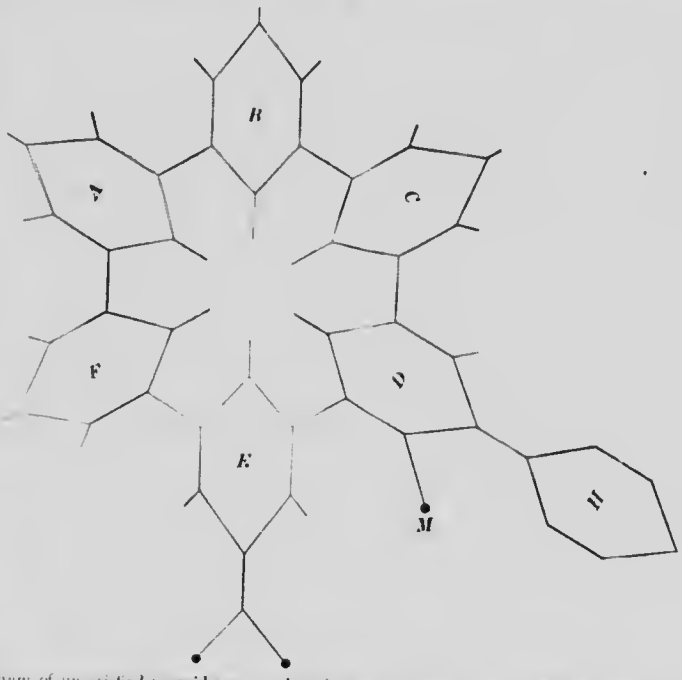


Diagram of unsatisfied proteidogenous ring formed of nuclei *A* to *F*, with side-chain (*H*) and unsatisfied affinities (*M*).

Enzyme Action and Metabolism in Relationship to Growth. This generalization, broad as it is, does not include every property of the active protein molecule, or, as we may term it for convenience in subsequent description, the *biophore*, using that term to indicate the ultimate molecule possessed of what we regard as the properties essential to life.[1] In its fully developed form that molecule, as stated (p. 54), is obviously polymeric, composed of a chain or ring of primary mole-

[1] This term was originally introduced by Weismann to indicate the ultimate collection of molecules of living matter endowed with specific properties. He had not apparently regarded the molecule as polymeric, and so demanded an accumulation of several molecules to carry out the requirements of his theory. The term is, however, so adapted to convey our present meaning that we employ it, believing that essential we indicate the same conception as did he, and that the word has priority over Verworn's *biogen*, which has the same significa

cules, each of which has proteid properties. That very constitution renders it at the same time intermediary body and fermenteseible substance. For another basal property of living matter, the result of metabolism has to be taken into acconnt. While its average composition in the state of moving equilibrium remains the same, *the number of molecules increases*. In other words, there is *growth*, and growth demands that not all the atoms taken up in the form of side-chains become released to form metabolites; some at least must undergo rearrangement and become built up into new biophoric molecules (Fig. 20).

We shall have more to say regarding the intimate nature of growth. What we would here emphasize is that all matter endowed with properties which we term vital does not coincidently possess this property of growth.

Fig. 20

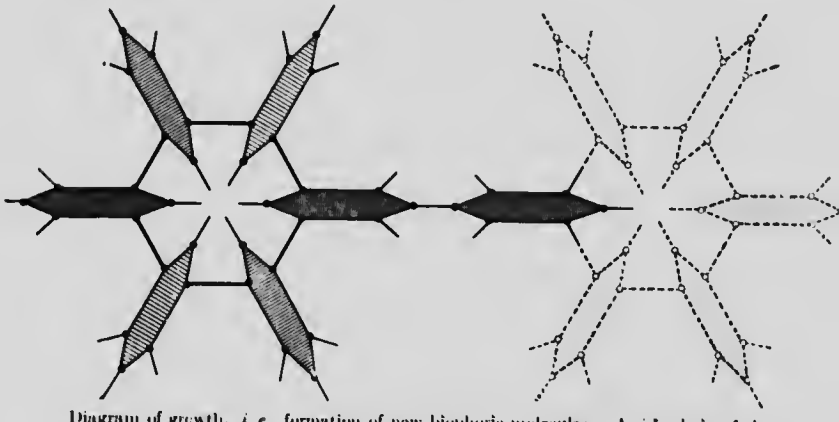


Diagram of growth, i. e., formation of new biophoric molecules. A side-chain of the main (dark shaded) ring has built upon it a like series of (light shaded) nuclei.

We have already brought forward the most pronounced confirmation of this statement, although its bearing may not have been immediately realized; we have shown that the non-nucleated cell may continue "alive" for days and, it may be, weeks—can perform several activities which we regard as characteristically manifestations of vitality—and yet it cannot grow; it becomes more or less rapidly used up in the performance of function. Translating this into the terms of proteid activities, it is obvious that the ordinary proteins of the cytoplasm, while capable of sundry enzyme actions—of respiration, for instance (which now we recognize more and more clearly is associated with the presence of oxydases), of converting starch into sugar, and so on—cannot grow, cannot build up new molecules of matter like unto themselves.

The nucleoproteids alone (in forms, at least, possessing nucleated cells) are associated with this capacity for growth, and, when present,

they are associated not merely with multiplication of the number of molecules of nucleoproteid, but also with the increase in the amount and number of molecules of the cytoplasm, and, lastly, judging from the observations of the histologists, they are directly concerned in the growth, if we may venture so to term it, of the enzymes, or otherwise discharge of nuclear matter precedes the evidence of active enzyme action in the cell.

THE ORDERS OF LIVING MATTER.

What, then, to come at last to our point, are we to regard as life? If we say that our conception must include the capacity for independent growth, it follows that we must regard the cytoplasm as not living—as dead. If, on the contrary, we deny that growth is an essential part of our concept, then, comparing the free enzymes and their properties with the cytoplasm and its properties, we must recognize three orders or grades of living matter:

1. The nuclear matter, capable of both metabolism and growth in a medium of cell proteins.

2. The cytoplasmic matter, capable of independent metabolism of several orders, but incapable of growth, save in relationship with the nuclear matter.

3. The free organic enzymes capable of causing "metabolism" of one or other order, but incapable of growth.

We confess that it is difficult to lay down positively which of these two views should be accepted as correct. Upon first consideration, we should be inclined to lay down that the property of growth is inherent in our conception of life, and therefore of living matter; but, on the other hand, it is scarcely possible to regard the non-nucleated cell—the red corpuscle, for example—with its active powers of metabolism, as non-living. For our purposes it is perhaps fortunate that we are not compelled to arrive at a positive conclusion. We have in general to deal with the cell, which, as a whole, manifests growth. We do not, however, think that the matter brought forward in the preceding paragraphs has merely an academic value; we shall, that is, have so frequently to deal with enzymes and ferment actions that at the outset it is important to possess an appreciation of the same and their relationship to the proteins and cell activities.

These considerations, it will be seen, taken alone, would lead us to regard these free molecules possessing enzyme action as the most elementary forms of life. Some would urge that, since this mode of action is common to these organic molecules and to other substances, therefore inorganic matter undergoing chemical change is also endowed with vitality; that logically, therefore, all matter, as urged by Haeckel, and yet earlier by the elder Lankester, is endowed with life. A little thought will show that we do not advance thus far. We do but lay down that enzyme action is a property of unsatisfied proteid—or

proteidogenous—matter and doing this *we limit our conception of life to proteidogenous matter, exhibiting a particular order of changes.*

Objections to the Above Hypothesis.—We have here, perhaps, overboldly laid down one view regarding enzyme action. We have done this after not a little consideration, believing that for didactic purposes this is the better course. The matter, however, is very far from being settled, and it is but due to our readers to point out that at the present time many leading physicists and physical chemists incline to the catalytic view of enzyme action, the view, namely, that enzymes act not by making temporary chemical combinations, but physically, and by propinquity, without combination. It has, indeed, been doubted whether the type example here afforded of what may be termed inorganic ferment action—the action, namely, of nitrous acid upon sulphurous anhydride (p. 61)—truly represents what happens, the suggestion being that here again what really occurs is a true catalysis.[1] Yet it has to be admitted that the objections brought forward are of a comparative nature and theoretical; no positive proof is adduced that the reactions indicated do not occur, and the actual detection of the intermediate bodies, even if only in relatively small amounts, definitely favors the occurrence of the stages we have indicated. The main objection to the chemical nature of enzyme action is, as Ostwald has pointed out, that such theory of intermediate action fails entirely to account for the action of *negative catalysts*, in which, if there be a direct chemical action, it must proceed more slowly than the direct action which takes place in the absence of the (negative) catalyst. These negative catalysts are bodies which, instead of accelerating, delay reactions; 0.0000014 gram per c.cm. of mannite, for example, reduces by one-half the velocity of oxidation of 800 times its amount of sodium sulphite in solution. Here, however, we are once more confusing catalysts and enzymes. We are prepared to admit that catalysis does occur among inorganic substances; the enzymes we place in a different category. Now, as a matter of fact, no negative enzymes are known, no proteid or "proteidogenous" bodies having such properties. The objection, therefore, does not hold. So far as we can see, the intermediation theory is adequate for all enzymes proper.

There is yet a third theory, that of *surface action*, first propounded by Faraday to explain the catalytic action of spongy platinum, powdered charcoal, etc. In the union of hydrogen and oxygen on the surface of spongy platinum, Faraday supposed a condensation of the gases on the surface of the metal, through which condensation there proceeds a more rapid action between the two gases. Applied to enzymes, this supposes an attraction of the fermentescible substances and what we may term the fermentator, and condensation of the same on the surface of the enzyme, so that under the altered conditions the two can act directly and more actively the one on the other. This conception of surface

[1] Vide Moore, loc. cit., p. 126

action would seem to promise most valuable results in explaining many vital phenomena. The conception, it will be seen, is for practical purposes not very far remote from that of the loose chemical union on the one side and on the other demanded by the intermediation theory. It does, not, however, fit in so well with the facts of growth and increase in substance brought about by the intracellular enzymes, for growth demands actual chemical union. Further, if, as we shall point out later, the amboceptors (in hemolysis, etc.) are best regarded as enzymes, then with them we obtain evidence of chemical union with the fermentescible substances (or, as German writers term it, the substrate), and that in the absence of the fermentator (complement). While, again, the fact that enzymes when in the presence of proteins or other body upon which they exert specific action are able to withstand a higher temperature without loss of properties than they can in the absence of these bodies, is also in favor of the view that they enter into combination with the same.

We speak here, however, with some diffidence. The increased study of the phenomena of surface action and of the allied *adsorption* during the last few years, of phenomena, that is, which are intermediate between chemical and physical activities, makes it possible that such adsorption is at the basis of enzyme action. Thus, Bayliss[1] points out that were this purely chemical in nature then concentration of an enzyme to twice its value should double the reaction velocity; but this is not the case, the increase, as in adsorption phenomena, is something less than this. The fact also that they are of colloidal nature, and as such are heterogeneous systems (Bredig) favors the view that they form adsorption compounds.[2]

The Reversibility of Enzyme Action.—In this connection, as throwing a peculiarly strong light upon the nature of metabolism, attention

[1] Science Progress, 1906; see also his article upon "Adsorption Phenomena," Biochemical Journ., 1:1906:175.

[2] While this chapter has been passing through the press we have received from Dr. Brailsford Robertson his study upon the behavior of casein in acid solutions (Jour. of Biol. Chem., 4: 1908: 35), with its carefully reasoned protest that "it certainly appears premature at the threshold of our physicochemical knowledge of proteins to declare a group of their compounds or reactions to be 'adsorption compounds' or 'adsorption reactions,' and to thereby . . . group them with phenomena which are not improbably essentially different in character and in mechanism, and to import into a field already sufficiently obscure a conception so misty as that of 'mechanical affinity.'" That adsorption very probably occurs in the cell in connection with its lipoid constituents we are very ready to accept, but are far from assured that enzyme action comes into the same category. For fuller studies upon ferments and enzyme action, consult Reynolds Green, The Soluble Ferments: Fermentation, Cambridge, 1899, and Duclaux, Traité de Microbiologie, 1:1899, 1. Other important studies are O'Sullivan and Tompson, Jour. of the Chemical Soc., 57:1890:834; Croft Hill, ibid., 73:1898:634; and Jacobson, Ztschr. f. Physiol. Chem., 16:1899:340. As also the very full article by B. Moore already cited.

must be called to a remarkable property of the enzymes first demonstrated within the last few years by Croft Hill,[1] of Cambridge. The sugar, maltose ($C_{12}H_{22}O_{11}$), is split up by the enzyme *maltase* into two molecules of glucose ($C_6H_{12}O_6$), but in the flask or test-tube the reaction is never complete; there remain a mixture of maltose and glucose. Hill found that if the enzyme maltase be added to a solution of glucose, he obtained a similar reaction—some molecules of glucose became dehydrated and combined to form maltose, and the solutions came to contain a mixture of two sugars. Maltase, therefore, can, according to circumstances, either disintegrate maltose into glucose or accomplish the reverse process of synthesizing glucose into maltose, and having these properties, it is inevitable that, so long as the products of either the disintegration or the synthesis are not removed from solution, neither the glucose nor the maltose can be entirely used up in the reaction; there must result a stage of equilibrium at which the enzyme becomes inactive, the tendency to disintegrate the one substance balancing the tendency to synthesize the other.

This reversible reaction we may express as follows:

$$\underset{\text{Malto-e}}{C_{12}H_{22}O_{11}} + H_2O + \text{maltase} \rightleftarrows \underset{\text{Glucose + Glucose}}{C_6H_{12}O_6 + C_6H_{12}O_6} + \text{maltase.}$$

Here the resultant molecules, being of the same structure, it might seem at first sight that the enzyme splits the maltose into equal halves. A little consideration shows that this cannot be. From its constitution the simplest dissociation of maltose is into one molecule ($C_6H_{11}O_5$), requiring for its completion an hydroxyl ion, and into another ($C_6H_{11}O_6$), that is completed by a hydrogen ion. We might represent the action of the enzyme as being primarily upon the molecule of water, the resultant O and OH ions combining with the maltose and leading to reduplication; or, on the other hand, regard the primary action of the enzyme as being upon the maltose. The latter clearly is the reaction that occurs, and this because the enzymes as a body act by hydrolysis, and thus, were the splitting up a molecule of water into free ions of H and OH their primary action, then a multiplicity of specific enzymes such as we find in nature would be unnecessary. The maltase must act upon the maltose primarily. The steps in the process must, therefore be (1) attraction between enzyme molecule and either the $C_6H_{11}O_5$ moiety of the maltose, or the $C_6H_{11}O_6$; (2) this becomes detached from its fellow and joined to the enzyme; (3) a yet greater attraction between the moiety thus detached and joined on to the enzyme and an hydroxyl or hydrogen ion, respectively, free in the medium with (4) combination with the same and simultaneous detachment of the enzyme ion which now becomes free to repeat the process with another molecule of maltose. Where the reverse action occurs, there the surrounding conditions must be such that the enzyme ion is so placed as to exercise a greater attraction upon

[1] Trans. Chem. Soc., 73:1898:634; also Proc. Chem. Soc., 18:1901:184; and Trans. Chem. Soc., 83:1903:578

the glucose molecule, combining with it and leading to the simultaneous liberation of either an hydroxyl or a hydrogen ion.

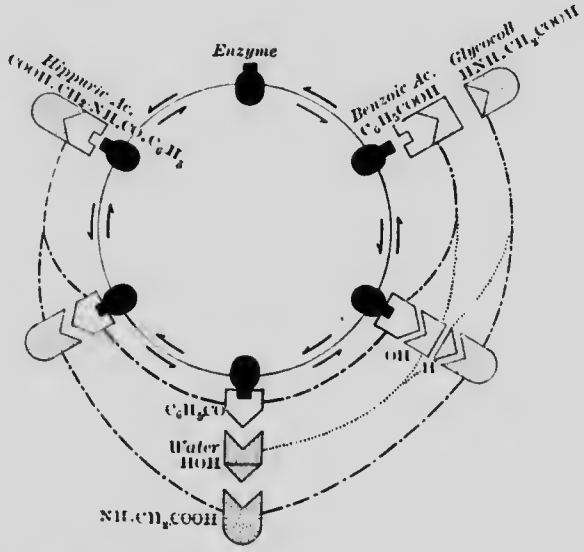
Even in cases in which, through enzyme action, the fermentescible molecule is split up into still more dissimilar molecules, the same reversible action is found to occur. Wells[1] gives a good illustration of this in a reaction noted by Schmiedeberg in 1881, although its significance was not comprehended by him. It is a well-known fact that benzoic acid and glycocoll introduced into the circulation are synthesized in the kidney into hippuric acid, and Schmiede' rg found that, similarly, hippuric acid can in this organ be split up into benzoic acid and glycocoll. What is more, he succeeded in extracting from renal tissue an enzyme *histozyme*—which brought about the splitting-up process. He did not advance so far as to establish the fact that the histozyme accomplished the reverse reaction, though with our present knowledge this is seen to be evident; it may be expressed thus:

$$C_6H_5.CO.NH.CH_2COOH + H_2O + (E) \rightleftarrows C_6H_5.COOH + NH_2.CH_2.COOH + (E).$$

Hippuric acid + water + enzyme $\rightleftarrows$ Benzoic acid + glycocoll + enzyme

Here we deal with the same type of reaction as in the former case. An hydroxyl (OH) ion and a hydrogen ion, respectively, combine with separate moieties of the hippuric acid so as to form benzoic acid and glycocoll. We may express this graphically as follows (Fig. 21):

FIG. 21



[1] Jour. Amer. Med. Assoc., January 25, 1902, gives an excellent *resumé* of the work accomplished in this direction.

The evidence now accumulated indicates that all enzyme action is, at least potentially, reversible. Kastle and Loevenhart[1] have shown that this is the case with *lipase* or *steapsin*, the fat-splitting ferment of the pancreatic juice, and Hanriot[2] has confirmed. Wroblewski[3] has studied the reversible action of invertase. E. Fischer and E. F. Armstrong[4] have noted the like action of kephir lactase. Acree and Hinkins[5] have found that the hydrolysis of triacetyl glucose by pancreatin is reversible, while Emmerling[6] has shown that yeast extract will synthesize glucose and mandelonitrile glucoside into amygdalin. Quite recently and independently, A. E. Taylor[7] has described the synthesis of a protein (protamin) through the action of a trypsin obtained from the liver of the soft-shelled Californian clam, and Brailsford Robertson[8] has synthesized one of the first products of the peptic digestion of casein, gaining the substance or substances to which the name "paranuclein" has been applied. The latter subjected an alkaline suspension of casein to peptic digestion for several days, heated to 100° C., to destroy the ferment; filtered, gaining thus a solution free from either casein or paranuclein; treating this with a pepsin solution, he gained in two hours a thick white precipitate giving the reaction of paranuclein.

The observations of Kastle and Loevenhart are of peculiar interest for our present purpose. Lipase acts on all the fats proper, and the results obtained apply to all the fats of the food; they employed ethylbutyrate for greater ease in analysis, and found that the lipase not only split up this into alcohol and butyric acid, but could unite these two latter to form the fat; and they employed this second reaction to detect the existence of the enzyme in different tissues. By this means they discovered that the liver is peculiarly rich in lipase; that this exists also in fair amount in the mucosa of the small intestines and in the kidneys, and to some extent in nearly all tissues. We shall have occasion to revert to these matters when dealing with the cell fats.

Thanks to these studies, we have gained a much clearer conception of the course of enzyme action in the organism, and can understand why now it proceeds actively, now is arrested. Equilibrium and arrest of enzyme action, we see, occurs when the products of that action accumulate up to a certain point, while, on the other hand, if those products be removed as they are formed, the action may proceed until all the fermentescible substance is taken up. In the alimentary canal, for example, the products of the action of the various extracellular enzymes, being soluble, are absorbed, diffusing into the mucous membrane and thence passing into the blood and lymph; there is thus in

[1] Amer. Chem. Jour., 24:1900:491; and Chemical News, 83:1901.
[2] Compt. rend. de l'Acad. de Sci., 132:1901:212.
[3] Bull. Acad. Sci., Cracow, 1901:94.
[4] Ber. d. Chem. Gesell., 35:1902:3146.
[5] Ibid., 34:1901:3810.
[6] Amer. Chem. Jour., 28:1902:370.
[7] Jour. Biol. Chem., 3:1907:87.
[8] Ibid., 3:1907:95.

health complete disintegration of the proteid, starches, fats, and other foodstuffs. Within the organism in the cells, and in connection with the intracellular enzymes, it is again a matter of diffusion. Take, for example, the glycogenic activity of the liver cell. If the cell, in its metabolic activities, has used or burnt up the sugar, glucose, brought to it by the blood, and so becomes deficient in carbohydrates, more sugar will diffuse into it from the blood, and, acting on this sugar, the enzyme will synthesize it into glycogen, and will continue to do this until there is a local equilibrium between the sugar and the glycogen in the cell. Glycogen, being insoluble, remains within the cell—becomes stored up. And there it must remain until one of two things happens: until either owing to stimulation, the cell being called into activity dissociates the contained sugar—uses it up at a greater rate than other sugar can diffuse into the cell from the surrounding medium. So soon as this happens, the glycogen-sugar equilibrium is destroyed, and now the reverse enzyme action comes into effect and the glycogen is dissociated, until through this formation of sugar the equilibrium is restored, when the dissociation comes to a stop. Or again, the amount of sugar in the circulating blood and lymph becomes lowered in consequence of dissociation and consumption by the tissues occurring at a greater rate than the absorption from the digestive tract. When this happens, so soon as the percentage of sugar in the surrounding lymph becomes lower than that in the cell, the cell sugar, being soluble, will tend to diffuse out into the lymph. Here, also, the glycogen-sugar equilibrium within the cell will be destroyed, and the enzyme will become active until it may be, if the sugar contents of the blood remains lowered for any considerable period (as happens in prolonged starvation), with the steady passage out of the sugars as they are formed, all the glycogen of the cell is eventually used up.

These considerations open up a new vista regarding disturbances of metabolism. These are seen to be dependent primarily upon the enzyme activities of the cell; the cell equilibrium, in fact, depends upon the amount of enzymes of different orders present within and produced by it, and this to a greater extent than it does upon the material absorbed by the organism and acted upon by these enzymes. By which we mean that the cell and the organism by their constitution possess, within certain rather wide limits, a power of regulating the absorption of matter from without, but if enzyme production be interfered with, then the regulating power is largely destroyed. If our conception be correct, that the enzymes are proteins, or, more exactly, that enzyme action is a property of the constitution of the protein molecule, we find ourselves brought back to the fundamental conception that the due and orderly carrying out of the cell activities is a function of the composition of the proteid-ogenous constituents of the cells. When, further, we recognize that the development of the free enzymes in the cell is associated with active discharge from the nuclei, we gain additional support for our view that the nucleoproteids are, or are immediately connected with the biophores, the primary molecules of living matter.

CHAPTER VI.

THE CHEMISTRY OF THE CELL—(CONTINUED).

NON-PROTEID CONSTITUENTS OF THE CELL.

WE have discussed in some detail the proteid groundwork of the cell, and must refer to the non-proteid constituents, if only to afford a due appreciation of the cell complex. As in our treatment of the proteins, so here our object is not to afford an elementary treatise upon physiological chemistry, but to bring together those facts which have a direct bearing upon cell function, and more especially upon perverted function, or disease.

Water.—First and foremost, it is well to take into consideration the water contained in the cell. That water is an essential constituent. It may be reduced to a minimum, as in the seeds of many plants and the spores of bacteria, but when this is the case we find that the living substance passes into a state of *latency*, or inaction. *Cell activity is associated with the presence of water*, or otherwise water is the medium in which occur the chemical processes constituting metabolism. So important a constituent is it that close upon 60 per cent. of the human body, as a whole, consists of water, and of certain organs, like the kidney, water forms rather more than 80 per cent. Leaving out of account matricial, extracellular, matter, such as bone substance, it is safe to state that the ordinary active cell of the human tissues contains not less than about 70 per cent. H_2O; *i. e.*, seven-tenths are water, three-tenths proteins and other constituents; so large a proportion that it is still with some a matter of debate whether we should regard living matter as existing and acting in a state of solution or as solid undissolved molecules suspended in a fluid medium.

The discussion is of something more than academic importance, especially in the light of the more recent studies of the chemicophysicists upon the nature of solution and the molecular changes which take place in dissolved substances. These studies, in short, suggest that an intimate knowledge of the physics of solutions must be of the very highest importance for a correct understanding of metabolic processes. At the same time it must be admitted that we are only at the threshold. We know from these studies that when a simple salt like sodium chloride is suspended in water and sundry other media, a certain number of its molecules become dissociated into their constituents, and these free constituents (Na and Cl, for example), charged some with negative, others with positive electricity, we term *ions—cathions* and *anions*, respectively; that, if the dilution be sufficient, all the molecules undergo

this ionization; that these free ions thus charged conduct themselves like independent molecules and are in a state in which they may readily be attracted by other ions having an opposite charge, and thus simply, but indirectly, pronounced chemical reactions may be brought about. It is, indeed, these dissociated molecules that are active in chemical processes.

Stable chemical compounds, according to modern views, are formed by the coming together of ions—electrolytes—having contrasted electrical charges, and the very act of combination neutralizes or liberates the energy represented by these charges. These combinations in the case of solid substances may be broken apart in two ways, either by heat or electricity (by means, that is, of imparting, if we may so express it, such violent action to the molecules that the constituent ions are dissociated), or by solution. The act of solution, provided the amount of water be adequate, will similarly bring about the dissociation of all the molecules of a salt; or, more correctly, at a given temperature each molecule requires a certain fixed amount of water to effect its dissolution. We say "at a given temperature," for here, also, in solution heat favors dissociation. It is when molecules are thus dissociated that fresh chemical combinations can occur; it is the liberated ions and not the compounds as such that react one with the other; considerations which indicate the importance of water to the cell. In its absence, metabolic processes could only take place at high temperatures. The fact that matter is assimilated by the cell in a state of solution permits the extensive disintegration, rearrangement, and combination of ions which are essential to metabolism and growth, and this *without the cell or the economy being called upon to afford abundant energy in the form of heat, etc., to bring about the dissociation.*

The presence of so large a proportion of water in the cell cannot but indicate that metabolic processes are brought about essentially by ionization, resulting from solution and not primarily from the dissociative effects of heat, although the bodily warmth promotes the process. What is more, judging from what has been gleaned concerning hydrolytic action and saponification, it would seem that the dissociated hydrogen (acid) and hydroxyl ions (alkaline) play dominant parts in metabolic processes in general. Enzyme action would seem to resolve itself largely into processes of hydrolysis—and dehydrolysis—either the breaking down of a molecule into two through the combination with an hydroxyl or a hydrogen ion, or the reverse process of the withdrawal of hydroxyl ions. But so far anything like adequate studies upon ionization in connection with the protein molecule are very largely wanting, although a distinct advance has been made by Brailsford Robertson in his studies upon "ion-proteids."[1] We have to keep in mind the point upon which we have already laid stress, namely, that the chemical composition of the *dead* protein molecule is not identical with that of the living—a point demonstrated by the fact that, while living

[1] Jour. of Physical Chem., 10:1906:524, and 11:1907:437, etc.

cell substance is alkaline or neutral, with death it takes on an acid reaction; from which it follows that observations upon albumins, etc. outside the body do not by any means fully inform us as to the processes taking place within the cell.

Turning now to the question whether the cell is to be regarded as liquid or solid, it must, in the first place, be noted that a characteristic of liquids is that in them the constituent molecules can vary their position freely in relationship one to the other, whereas in solids the relationship of the molecules one to the other is fixed. The distinction it is true, is only relative, and in the cell we encounter conditions which are, to say the least, ambiguous; on the one hand, by careful study of certain cases—the white corpuscle, for instance—we can observe a streaming motion of the cell substance, *i. e.*, a free change in the relationship of the constituent molecules. On the other hand, the nuclear material is, to a large extent, fixed both in relationship to the cytoplasm and in the relationship of its individual parts one to the other. The idea of structure, it may be laid down, involves relative solidity. The explanation of our difficulty depends largely upon the colloid constitution of living matter. The cell in general and proteids in particular are colloidal, *i. e.*, are composed of molecules so large that they cannot enter into perfect solution. Our conception of a solution is that of a liquid in which the molecules of the dissolved substance lie between or in the interstices of the molecules of the solvent. The molecules of proteins are so large that the process must be reversed; we must imagine the molecules of water as lying between their interstices; nay, more, it may be from the very complexity of these large molecules and the associated looseness of texture that molecules of water actually infiltrate them, and this apart from the water of constitution. This very conception of the molecule of the colloid as being, from its size and structure, capable of imbibition, carries with it the idea that the constituent parts are held loosely together and capable of dissociation with relative ease.

Simple Salts.—Certain salts, without being built up into the protein molecules, are obviously essential to the cell; the protein molecules, that is, do not manifest their activity in a pure watery medium, but in a dilute saline solution. More particularly we encounter chlorine salts, alkaline carbonates, phosphates and sulphates, and salts of the alkaline earths, notably those of sodium, potassium, ammonium, calcium, and magnesium. From the more recent studies upon electrolytic dissociation we have learned to be cautious in laying down how these are combined; many, indeed, are under ordinary conditions present in such minute quantities that they must exist largely dissociated into their constituent ions, and so must actively promote metabolism. That their presence is essential for cell activity was shown many years ago by Ringer. More recently, Jacques Loeb and Moore have called attention to their importance and to the profound effects upon cell activity of comparatively slight variations in their relative amounts.

Certain salts, on the other hand, even when present in extraordinary small amounts, are most deleterious to different forms of life. Thus,

years ago, Raulin[1] showed that while a minimal trace of zinc (0.07 gram to 1500 c.cm. of the medium) favored markedly the growth of aspergillus niger, silver in amounts too small to be detected (the mere keeping the water to be used for growth in a silver jug for a short time) absolutely arrested the growth of the same. A similar deleterious effect has been noted in connection with forms much higher in the chain of living forms: a strip of copper placed in a vessel containing tadpoles leads to arrest of activities in two or three hours; while, again, it is a matter of familiar knowledge that hydrocyanic acid can arrest enzyme action, and arrest cell and individual life when present in quantities wholly disproportionate to its effects as a mere acid. These bodies possibly act as negative catalysts, arresting enzyme and cell action; but this is a mere statement, and does not explain how they produce such remarkable results. We do but mention these to indicate the subtlety of cell activities.

Turning to the more ordinary salts, their existence within the cell, or, perhaps more exactly, their dissociation and the building up of certain of their ions into the biophores, and the combinations undergone in the cell sap, are accompanied by important phenomena of endosmosis and exosmosis, *i. e.*, alterations in the amounts of fluid of the cell brought about by diffusion. Salts of higher concentration within the cell tend to pass into the medium of lower concentration without the cell, and *vice versa*, and this process is accompanied by a reverse passage of water into and out of the cell, the colloidal cell substance, and more particularly the more condensed ectosarc, acting as a semipermeable membrane, permitting this interchange of water and soluble salts, while at the same time preventing the escape of larger (colloidal) molecules.[2] Nay, more, it would seem probable that in regard to simple salts there is with different colloids a marked difference in the rate of escape.

This matter of osmotic change is one of no little significance; it helps us to understand why it is that the biophores and the most complex protein molecules remain in the cell, and why, on the other hand, smaller and partly dissociated proteid molecules—for such, as already indicated, we must consider them to be—namely, the peptones, pass out or again are absorbed with relative ease. The same considerations apply to the discharge of the free organic ferments, or enzymes, if our contention be correct that these, also, are simple non-polymerized protein molecules. There are yet other proteids which apparently are on the border line. Their retention within the cell body is largely dependent upon the state of the cell in relationship to the external medium. The red corpuscle

[1] Ann. des Sci. naturelles, Botanique, 1870.

[2] Ramsden has shown that solid or highly viscous films are rapidly formed at the surface of protein solutions, and probably, as Brailsford Robertson points out, it is such a concentration film, rather than the coarser ectosarc that is the agent mainly involved. Zeitschr. f. phys. Chem., 47: 1904: 336; B. Robertson, Jour. of Biol. Chem., 4: 1908: 1; Hardy, Jour. of Physiol., 24: 1899: 158.

retains its hemoglobin only in fluids having more than a certain osmotic pressure. From the red corpuscles of man the hemoglobin is extruded at a concentration of or corresponding to that of 0.47 per cent. NaCl; of the chicken, of 0.44 per cent.; of the frog, of [illegible]21 per cent. If the osmotic pressure of the medium be less than these amounts, the diffusion of salts out of the corpuscle is associated with so extensive a passage inward of water that the ectosarc is ruptured, and now the hemoglobin—which is one of the simple, crystallizable proteins—undergoes solution in the surrounding fluid, and colors it.

This limit of tonicity at which the corpuscles lose their hemoglobin is, we may point out, very different from the normal "tone" of the blood serum. According to Hamburger's observations, the serum of man and many animals is isotonic with a 0.9 per cent. sodium chloride solution. We employ the term *hyperisotonic* for solutions having an osmotic pressure higher than this; those the osmotic pressure of which is lower, as *hypisotonic*. The blood serum must, therefore, be markedly hypisotonic to bring about a condition of *hemoglobinæmia*, or passage of the hemoglobin out of the corpuscles, purely through reduction of the saline constituents of the serum.

We shall have to discuss later how far variations in the saline contents of the cell and difference between the percentage of these and the percentage of saline contents of the surrounding medium determine the watery contents of the cell, and are the basis of œdema of the cell, and how far, again, considerations of isotonicity help in explaining general œdema. As a general rule, it would seem evident, from what we have said, that the greater the passage out of water from the cell and the less the amount of contained water, the less must be the amount of ionization occurring within that cell, the less its metabolic activity, and this as a matter of experience we find to be the case; while, on the contrary, extreme absorption or osmosis of water must favor dissociation and disintegration.

Carbohydrates.—From the fact that carbohydrates are never found in association with the nucleus, we must conclude that as such they do not enter into the composition of the biophoric molecules, and that, when present in the cell body, they represent either material absorbed from the external medium (or lymph) and not yet dissociated, or material so absorbed and partly dissociated, or, lastly, material built up within the cell as the result of cytoplasmic activity; *i. e.*, through the cell energy other substances have been dissociated, certain of their ions have become seized by the cytoplasm, while those not so seized have interacted between themselves to form carbohydrate molecules. This last process occurs notably in the vegetable cell, in the building up of the starch granules in the chlorophyll grains. There the chlorophyll, under the influence of sunlight, breaks up carbonic acid, and the carbon so dissociated enters into combination with oxygen and hydrogen. The starch so formed undergoes ultimate cleavage—through enzyme action—and by hydration is converted into soluble sugars, which, in their turn, are dissociated, and the carbon containing molecules, in the nucleated cell,

are utilized for growth. The botanists have demonstrated clearly that these starches can give origin to fats.

In the animal cell the direct synthesis of carbohydrates from carbonic acid and water, if it occurs at all, must be an unusual event, but, *a priori*, there would seem to be nothing opposed to the view that in the dissociation of the protein molecule carbohydrates may be evolved, and, as a matter of fact, the continued excretion of sugar by the urine in advanced cases of diabetes in which carbohydrate food has been wholly cut off can have no other explanation than this, while Lusk's observations on phloridzin diabetes, in which he found a definite relationship between the amounts of nitrogen and sugar in the urine, indicate that certain protein molecules under certain conditions becomes split up into a nitrogenous and a carbohydrate moiety. It seems, however, equally clear that the carbohydrates found in the cell are, in the main, absorbed from the food—assimilated; and, further, that they are rapidly "burned" or dissociated to provide energy, unless they are by them converted into storage compounds within the cell, into the more insoluble *glycogen*, into a form, that is, allied to the starches. This storage occurs particularly in certain cells, notably in the liver and the muscle and (in pathological states) the lenkocytes. We see, in short, that the carbohydrates of the food undergo a remarkable series of alternate conversions into soluble and insoluble forms. In order to be absorbed they must be in a soluble state, and so we find that the starches are acted upon by extracellular enzymes—by the *ptyalin*, which converts them into the sugar, (maltose), and by the *amylopsin* of the pancreatic juice, which is even more active, although, as Herter points out, it is doubtful whether by either process there is complete conversion into dextrose or glucose, the form in which the sugar is eventually utilized within the organism. This conversion is held to take place in the cells of the intestine, and from these the glucose is passed into the portal blood. From this it is taken up particularly by the liver cells, in which, if not broken up and utilized in metabolism, with the coincident production of heat, it is stored up, becoming for this purpose acted upon by an intracellular ferment and converted into the more insoluble glycogen. Here, it would seem, it remains until the amount of glucose in the blood circulating through the liver falls below a certain percentage; when this happens the altered relationship between cell and surrounding medium favors a reversal of the enzyme action, and now the glycogen is reconverted into glucose and diffuses out. The loss of glucose from the systemic blood is evidently, in the main, due to absorption by the muscle cells. F. S. Lee[1] has proved clearly that these utilize carbohydrates in their activity, that deprived of carbohydrates by phloridzin poisoning they pass into a state of fatigue, from which they recover rapidly when carbohydrates are given in the food. In the resting muscle, as in the liver, the soluble carbohydrates are converted into and stored up as, glycogen. With activity, this glycogen is broken down and disappears, an important cleavage product being lactic acid.

It is clear from the above that in the animal cell the carbohydrates

[1] Amer. Jour. Physiol., 4: 1900: 9.

are characteristically metabolites in the broadest sense; they are taken up, dissociated into simple compounds, combined into more complicated bodies under the influence of the cell substance. Where energy is needed it is obtained from their dissociation; where there is excess energy it is stored up within the cell in the form of the built-up, more insoluble glycogen molecules.

Fats, Soaps, and Alcohols.—These form another important group of metabolites—of substance appearing in the cell and utilized by it. As with the carbohydrates, so with these, there is still considerable debate as to whether they may be directly split off from the cell protein, and, if so, to what extent. As with these also, they are not found in the nuclei (with the exception already noted of fatty contents of the nuclear vacuoles of fat cells); they must, therefore, be regarded as being acted upon, in the main, by the cytoplasm.

Just as the carbohydrates are stored in the cell as starch or glycogen, so we find certain cells containing stores of fatty substances in the form of insoluble neutral fats, and we recognize a curiously parallel series of processes in connection with the metamorphoses that these undergo. These neutral fats are triglycerides of the fatty acids, combinations of a triatomic alcohol (an alcohol containing three hydroxyl groups, $C_3H_5(OH)_3$ with one of the fatty acids, the fatty acids replacing the hydroxyl groups. The three most important of these are stearin (tristearin), $C_3H_5(C_{18}H_{35}O_2)_3$; palmitin, $C_3H_5(C_{16}H_{31}O_2)_3$; and olein, $C_3H_5(C_{18}H_{33}O_2)_3$. Other neutral fats and fatty acids occur, but are found only rarely, in the economy; thus, in milk, butyric and caproic acids and their glycerides are to be differentiated. It will be seen from the formula that these neutral fats contain a "ha'p'orth" of oxygen to an "intolerable quantity" of carbon; in other words, that their dissociation and combination with absorbed oxygen is capable of setting free a relatively enormous amount of energy; hence their value to the cell. How, it must be asked, are they acquired?

Briefly, they come in the food almost entirely as neutral fats. Vegetable oils, it is true, contain fair amounts of free fatty acids, but these are little employed for food purposes. We will, therefore, consider the neutral fats only. They are emulsified by the action of the bile, but even when emulsified they are incapable of being absorbed save by phagocytic action. Now, there is a certain amount of phagocytic action in the intestine—a constant passage out of leukocytes into the lumen, and, as Heidenhain demonstrated, a passage back of the same between the cells of the mucous membrane loaded with fatty particles. This fat, as such, is to be followed into the lacteals of the villi, and then is no more seen. With and without disintegration of the leukocytes it undergoes a process of solution, *i. e.*, is converted into a soluble form, presumably a soap. This, however, affects only a minor portion of the ingested fats; the major portion comes under the influence of the fat-splitting ferment, or *steapsin*, discharged by the cells of the pancreas into the pancreatic juice, and is split up into free fatty acid and glycerin. Regarding the fate of the glycerin nothing absolute is known, though everything indicates that it is taken up by the cells of the intestinal

epithelium. The fatty acids are in part dissolved by the bile salts and so rendered capable of absorption; the main reaction, however, is their conversion into *soaps* by the alkaline medium in which they find themselves in the small intestines—soaps of sodium, potassium, calcium, and magnesium. Of these, the sodium and potassium soaps are readily soluble, the calcium and magnesium soaps are rendered more soluble by the lecithin of the bile. It is, in the main, as soaps that the fatty acids pass into the intestinal cells. They are not stored in these cells, but pass through them, and are to be found in the chyle or lymph of the thoracic duct as neutral fats. Either in the cells themselves or in the lymph there occurs a breaking down of the soaps into a fatty acid combination of the latter, with glycerin (probably that absorbed from the intestines) and synthesis of the neutral fat. But save in rare conditions little neutral fat is to be found in the blood, while recent observations show that soaps are present in fair amounts. A second conversion must, therefore, take place. It is as soaps that the fats are ultimately taken up by the cells from the blood and tissue lymph. Save in the dead cell we do not encounter free fatty acids; the soaps so absorbed are either dissociated under the action of the cell substance and "burnt up" for the production of energy, or are stored as neutral fats. There is a third possibility, demonstrated recently in our laboratory by Dr. Klotz, namely, that the soaps form an immediate combination with the protein molecules. If a solution of sodium stearate, for example, be added to a solution of white of egg or blood serum, there develops slowly a precipitate, and when this is filtered off it is found that both the soap and the albumin are lessened in amount.

This combination, we would suggest, throws light upon a series of rather remarkable facts in connection with the fatty contents of the cells. In several tissues, the muscles and the kidney, for example, the ordinary methods for the microscopic detection of fats may reveal nothing. Osmic acid and sudan III show not a globule present within the cells, and yet, after desiccation of these tissues, ether extracts afford very definite amounts of fat. But this is not all. After simple extraction of this nature, if the tissue be pulverized and treated with acid, subsequent treatment with ether extracts a farther not inconsiderable amount of neutral fats—so much so that as much as 17.9 per cent. of the dry substance of the normal kidney is found to consist of fats,[1] and this although, as above stated, the organ microscopically appears to be wholly free from fat. The difficulty in extracting these fatty acids is evidence of their presence, not in a free but in a combined form.

We shall have much more to say upon these matters when discussing the subject of fatty degeneration. Here we would only say that the importance of soaps (using this term in the broadest sense) as intermediate stages in the utilization of absorbed and synthesized fats is becoming more and more realized. The lipolytic and fat-forming ferments have been practically isolated, and as a group are referred to

[1] Rosenfeld, Berl. klin. Woch., 1904, Nr. 22.

as *lipases*. We see that these may be extracellular, as in the case of steapsin, or intracellular, as has been shown more particularly in the case of the liver cell, the great storehouse of transit fat, as it is of transit carbohydrates. And here, again, as indicated by Klotz's observations, it would seem that the protein molecules of the cytoplasm can enter into direct relationship with the fatty molecules.

Whether under normal conditions fats or fatty acids are dissociated products of the protein molecule; whether in its disintegration protein gives rise to fats, is a subject of hot debate at the present time. We know that in the process of ripening of cheese the fats increase at the expense of the proteins; but here bacteria are concerned, and although in the cold process of ripening (at 40° F.) bacterial activity is greatly reduced, we cannot wholly eliminate this as a factor in the process. It may be that bacteria break down proteins into simpler constituents, from which the fats become synthesized. We know, also, that eggs of the blow-fly deposited upon moistened fibrin give rise to maggots, which, feeding in the fibrin, become abundantly fat. But here, also, the process may be indirect. Still there is no reason, *a priori*, why these same processes of dissociation of the protein followed by subsequent synthesis should not occur in the individual cell. Proof positive that they occur is, in the first place, still wanting. The observations of Hildesheim and Lœathes,[1] that in the *autolysis*, *i. e.*, the self-digestion of sterile portions of liver tissue removed from the body, there is a definite increase in the percentage of fatty acids, would seem to be vitiated by the fact that there was no thorough extraction of the neutral fats from the fresh tissue, after the method of Dormeyer, and by a failure to take into account the possibility that assimilated fats are capable of combining more or less firmly with the protein molecule. We once more find ourselves face to face with the question, What is the pure protein molecule? Until we solve this we cannot decide whether in its disintegration that molecule directly gives rise to fats or fatty acids. It is at least suggestive that the amino-acids, which, we have seen, form the main constituents of the protein molecule, are themselves members or substitution products of the fatty acid series. It may, however, be said, on the other hand, that the work so far accomplished by the physiological chemist assures us that the fats of the body, as a whole, represent the fats taken in from the food. If the protein affords fats, these must be but a small proportion of the total amount.

In this connection, and very possibly bearing upon the point at issue, must be mentioned the *lecithins*. These appear to be constant, or almost constant, constituents of the animal cell, and in some cells, notably those of the nervous system, and in egg yolk, they are relatively abundant. We still know little regarding them, save that they possess a fatty moiety, and so may be considered along with the fats; that they are nitrogenous, suggesting some affinity with the proteins; and, thirdly, that they are richly phosphorized. These last two facts suggest that they are cleavage products of the nucleins or compounds of such cleavage

[1] Jour. of Physiol., 31:1904:1.

products with fats. More precisely, they are compounds of fatty acids and glycerophosphoric acid with the nitrogenous base *cholin*, $(CH_3)_3N(CH_2)_2OH.OH$.

The conviction has been rapidly growing during the last few years that lecithin and the other lipoid bodies are essential constituents of the cell economy. Overton has determined that those substances which are able to penetrate into the living cell have in common the property of being fat-soluble, and of being soluble in lecithin, cholesterin, cerebrin, and protagon, and he and Albrecht have independently suggested that the lipoids by peripheral concentration constitute the semipermeable membrane investing the cell, although more recently Brailsford Robertson demands a membrane of concentrated protein with an underlying lipoid layer. These lipoids, in short, have an extraordinary power of taking up a large variety of other substances, apparently by adsorption rather than by chemical union, and this because they take them up in most varying proportions. Thus, as Craven Moore[1] points out, a mixture of cholesterin and lecithin forms a colloid mass which can take up extraordinary amounts of water, forming a permanent emulsion; in short, from the soaps upward to the more complicated forms, we observe the tendency of these bodies to assume a colloidal state. We would here only note Preston Kyes'[2] remarkable observation that lecithin plays the part of complement to the amboceptor of snake venom, and to the observations of Koeppe,[3] Peskind,[4] and others that the hemolytic activity of substances, such as chloroform, ether, bile salts, etc., probably depends upon their being solvents of lecithin, which is an important constituent of the red corpuscle. A great variety of other substances may be encountered in one or other form of animal cell.

Protein Compounds.—We have already referred to one group of these, namely, the lecithins and other protein-fat compounds. Another group is of some importance—the protein-carbohydrate compounds, or glycoproteids, chief of which are the mucins. These are to be seen within the cells as definite globular accumulations of so-called mucinogen, which, through imbibition of water, becomes converted into mucin proper. These may be regarded as modified proteins, so modified as to be largely inert. Among them may be mentioned gelatin, elastin, chondrogen, chondrin, collagen, amyloid matter, and mucin, all characterized by being relatively poor in carbon and rich in oxygen, yielding carbohydrates on dissociation. Yet other "albuminoids" may here be mentioned, occurring both within the cell and as extracellular deposits: the products of disintegration of hemoglobin, hematin, etc., melanin, the pigment of the skin, hair, and choroid coat of the eye. All of these may under certain little understood conditions be produced in excess, in association with one or other pathological state. These we shall have to discuss in connection with the infiltrations and degenerations.

[1] Manchester Med. Chronicle (Dreschfeld memorial number), 47: 1907: 204. A valuable article on cholesterin.

[2] Berl. klin. Wochenschr., 1903: Nos. 38 and 39.

[3] Pflüger's Arch., 99: 1903: 33. [4] Amer. Jour. of Physiol, 12: 1904: 184.

CHAPTER VII.

GROWTH—RESERVE FORCE—STATES OF CELL ACTIVITY.

GROWTH OF THE CELL.

If, as has been indicated, we leave it an open question whether growth is to be regarded as an essential attribute of living matter; whether, that is, we can still, or cannot, regard certain forms of matter as living which do not in themselves possess the power of growth, this, nevertheless, is evident, that the cell as a whole manifests the capacity to grow, and, studying the cell as a unit, growth must be regarded as an essential and primary attribute. And being so, it is necessary to inquire more closely into the nature of the process, and this more particularly because we shall find that a correct appreciation of what is included in growth is all-important for a fuller understanding of certain most important and widespread pathological processes, notably tumor formation or neoplasia—processes in which, before everything, we encounter disturbances of this fundamental property of growth. Only a little less important in this connection are the processes of repair and regeneration.

Whatever our conception of the exact nature of living matter, the idea—and the facts—of growth demand an increase in the amount of living matter; whatever our conception of the biophore, or ultimate molecule of living matter, in the process of growth of two biophores must develop where previously there was only one. How is this brought about? The general idea we have gained of the constitution of the protein molecule here comes to our aid; that molecule, we recognize, is polymeric—formed of a recurrence of simpler molecules, which become attached one to the other in series. In bodies, therefore, of a proteid nature growth must be dependent primarily upon conditions which favor the building up of the simpler molecules. Once these are formed, their inherent nature and constitution, and their surroundings, must be such as to lead them to combine in series. In this process there must (*a*) be eventually reached a point at which the series is complete, and the biophore, as such, becomes an integral whole; but (*b*) with the completion the biophore cannot be a satisfied compound molecule. All our data regarding metabolism show that this is far from being the case; the constituent primary molecules must possess affinities to be satisfied, and what happens in growth is that these are satisfied by the building up and attachment of other primary molecules which, in their turn, attract other molecules of like order; and so there is gradually built up a lateral compound molecule which, in its turn, becomes com-

plete, whereby now two biophores are present where previously there was only one.

We can best visualize this process by regarding the complete biophore as a ring, or, more exactly, a ring of rings, each constituent being constructed after the type of the benzole ring. It is not essential to conceive each primary ring (proteid molecule) as identical, although for diagrammatic purposes we so represent them. And that the biophore is actually built up in ring fashion we do not pretend to lay down categorically; but such ring formation best fulfils the requirements of the case, namely, that the polymerization of the primary molecules is determinate, leading to the formation of larger units.[1] To represent the primary molecules as arranged in linear series would fail to indicate rationally the need for the series to combine or break up into these larger units or the inevitability of this process (Fig. 22).

FIG. 22

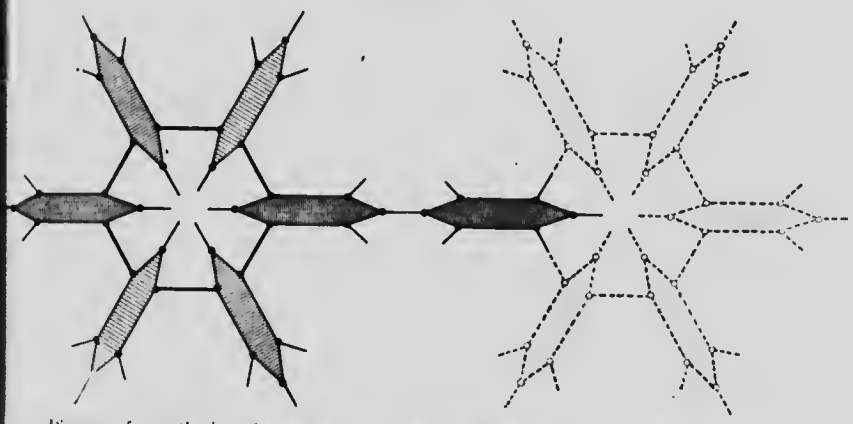


Diagram of growth, i. e., formation of new biophoric molecules. A side-chain of the main (dark shaded) ring has built upon it a like series of (light shaded) nuclei.

Such a conception of the building up of new biophores may seem at first sight to assume a selective capacity on the part of the preëxisting biophores and their affinities, which is unknown in inorganic nature. A little thought will show that this is not so. All that is demanded is the action of the same laws as govern crystallization. In a mixed solution of salts and colloids, for example, provided the concentration of the sodium and chlorine ions exceeds a certain degree, we know that these ions combine to form sodium chloride, and if, again, the concentration of the sodium chloride similarly exceeds a certain degree, its molecules combine to form solid crystals, independently (to a very large

[1] The use of the term polymerization is here convenient, but possibly, from a chemical standpoint, not accurate. Your true polymer is formed of a series of nuclei of like constitution; our conception is more that we have here to deal with repetitions of *series* of nuclei of unlike constitution.

extent) of the other salts and ions in solution; just these particular molecules of NaCl are attracted one to the other, and so in this mixed solution of various salts there are built up the specific crystals of sodium chloride. We might have chosen for an illustration some salt of more complicated constitution, but this simplest example is adequate for our purpose. What is demanded in growth and multiplication of the biophores is a like attraction of ions and molecules, a like assumption by those ions and molecules of precise relationship the one to the other that we see in the process of crystallization.

Accepting this as a working scheme of the constitution of the biophore, it would demand too elaborate a discussion, and one perhaps somewhat out of place, to lay down the apparent stages in the process whereby the complete cell with its nucleus, cytoplasm, and excreted enzymes has become evolved. All we would say here is that if we accept reversible enzyme action as a primordial function of living matter, we can then figure the various steps in the evolution of the cell from a mass of undifferentiated bioplasm. We reach, however, the following conclusions:

1. That the fundamental cell material is formed of complete biophores, and these alone have the capacity to reproduce themselves and so initiate growth.

2. These biophores, we must assume, at the beginning were able directly to assimilate and build up into primary protein molecules material presenting itself in the surrounding medium, and these again gave origin to new biophores; but with the evolution of the more complex biophoric molecule the stage was attained at which newly formed (compound) biophoric molecules could not act directly upon the surrounding medium, but required the intermediation of primary molecules of proteid type constituting a surrounding cytoplasm.

3. In the completely developed cell the first stages of assimilation are accomplished by these subsidiary cytoplasmic molecules; the material is taken up by them in the form of side-chains, and these act as carriers or "enzymes" for the biophores, which, in their turn, (*a*) still further dissociate the matter so presented to them, thereby liberating energy (p. 86); (*b*) build up that matter into primary protein molecules, which are returned to the cytoplasm, and so bring about cytoplasmic growth; (*c*) build it up into or govern the formation of the constituent molecules of new biophores. In other words, the nuclear material must be regarded as initiating and controlling the growth both of the nucleus and the cytoplasm. The above conception, it will be seen upon consideration, is the only one possible and consonant with the facts known to us, unless we accept a primary duality of living matter.

It may seem to the reader that in discussing these matters we pass into the region of transcendentalism. But if we recognize so fully as we do the constant differentiation of the cell into nucleus and cytoplasm, and if, further, we have before us a series of facts bearing upon the relative activities of those two constituents, we surely are bound to ask what is the intimate meaning of this differentiation, and how we can best harmonize these facts and bring them into line. While it is true that our pathology

is cellular, and that we take the cell as our unit, to understand the activities, and the disturbances in the activities of the cell, we must form for ourselves some working scheme which shall take into account the indications afforded by the cell structure. With the accumulation of new facts it is possible that the views here enunciated may have to be considerably modified. For that we are fully prepared. In the meantime the facts already possessed appear to us to give a satisfactory interpretation only along the lines here suggested. And this conception of the essential nature of the cell must be the basis of our subsequent treatment of our subject.

The Relationship between Growth and the Other Cell Activities.—Before proceeding farther it will be well to say a few words regarding cell dynamics, and this in order that we may realize the relationship between growth and the other activities of the cell.

It is clear, in the first place, that, speaking broadly, in the performance of function the cell is to be regarded as a machine for the evolution of energy. Motion, for example, demands the liberation of energy; secretion and the discharge of various formed substances from the cell indicate similarly a loss of material, or, in other words, a discharge of potential energy from the cell; in the so-called warm-blooded animals the increase in temperature of the organism as a whole above that of its surroundings necessitates that individual cells liberate energy in the form of heat; the nerve cell liberates energy akin to electricity. On the other hand, growth and the accumulation of new molecules of living matter demand not the evolution, but the storage, of energy. Each complicated molecule of proteid type represents a relatively great store of potential energy. Speaking broadly, therefore, growth and the performance of other functions by the cell are widely contrasted. Both demand that energy be previously acquired by the cell, but in the one case this is stored up, in the other it is dissipated.

Looking more closely into the matter, we recognize that in the cell, in general, the necessary energy is acquired through the assimilated foodstuffs. These main foodstuffs—the proteins, carbohydrates, and fats—even in the soluble, assimilable state, are complex carbon-containing bodies, which, when decomposed and burnt up outside the body, yield relatively abundant energy. The excreta of the organism *i. e.*, of its component cells—the carbonic acid, water, urea, etc., as a class, have exactly the opposite characteristics; they are relatively simple in constitution, are dissociated with difficulty, and yield little energy in the process. In the breaking down of the foodstuffs by the cell it follows that much energy is acquired by the cell, and this energy is utilized either in the performance of function or in growth.

These considerations are apt to lead the physiological student to conceive that energy is evolved in the dissociation of matter. Paradoxically, the reverse is the case. In the act of dissociation energy is used up and becomes potential; it is in the act of combination that energy is liberated. The explanation of the paradox is that the ultimate result has to be taken into account. In the dissociation of the

molecules of the foodstuffs there is a primary loss of energy. But these foodstuffs are unstable, their elements loosely combined, and when in dissociation their ions become freed they combine among themselves or with other free ions to form more stable compounds, and *in this combination of ions having greater affinities it is that an amount of energy is evolved, much greater than that set up in the primary act of dissociation.* When the candle burns it is not the dissociation of its wax that causes the light and the heat; it is the combination of the dissociated carbon with the free oxygen of the air that is the cause. Heat and energy, in fact, are used up in the dissociation of the wax, but its carbon being relatively lightly combined, the loss is small compared with the evolution that occurs in the combination of the carbon and oxygen to form CO_2. Similarly, energy is required to bring about the dissociation of the cell molecules, and similarly, also, it is the oxygen absorbed that is the great source of cell energy—combining with liberated carbon ions to form CO_2, with hydroxyl ions to form H_2O. It is these ultimate combinations that are the great source of energy.

In short, the biophores and protein molecules in general are not to be compared with simple salts, but with such highly unstable bodies as nitroglycerin. It is a matter of familiar knowledge that dissociation of the molecules of this compound may be brought about by very slight stimuli—as by sharp vibration—and that the dissociation is accompanied not by a loss of energy, but by a rapid and abundant evolution of the same—by an explosion—with the production of light and heat, this being brought about by a reconstruction of the ions of O, C, H, and N into simpler, more stable compounds.

It is thus that dissociation of the cell molecules leads to liberation of energy, and that growth and the building up of the complex biophores represents, on the whole, a using up of energy, *i. e.*, a conversion of kinetic into potential energy. Or, in other words, the energy provided by the assimilated food may be:

(*a*) *Katabiotic*, dissipated in the performance of function.

(*b*) *Bioplastic*, stored up in the formation of the complex molecules of the cell substance, *i. e.*, in growth.

Growth and the performance of function other than growth (which in succeeding paragraphs we shall refer to briefly as the "performance of function") are two contrasted states of cell activity.

It must next be asked, If contrasted, can they proceed simultaneously in the cell? Can the cell simultaneously perform function and grow? All, it will be seen, depends upon the rate of assimilation of food and energy compared with the grade of functional activity of the cell. And here we require another distinction between the two processes now under discussion. The conditions which, for general purposes, we group together as functional are all the responses, or the preparations for responses, to external stimuli; it is the external stimuli that call them into activity, whether directly or through the intermediation of the nervous system. Growth, on the other hand, is an inherent property of living matter, and depends primarily upon intracellular

conditions. If abundant food is presented to and assimilated by the cell, and if at the same time the cell is highly stimulated, all the energy so acquired may be utilized in the performance of function, and no growth may ensue. If the stimulation be still more intense, not only will all the foodstuffs be broken up to afford the requisite energy, but also the living cell substance will undergo dissociation in order to supply the energy needed. If, again, the external medium provides little food material, and the cell is called upon to perform work, then also, to afford the requisite energy, the molecules of cell substance proper must undergo disintegration. We have to recognize, however, that there is a certain stage or grade of adequate assimilation coupled with stimulation from without of medium intensity, in which the dissociation of the foodstuffs provides more energy than the cell is called upon to dissipate, and it is at this stage that the surplus energy may be rendered potential in the process of growth. *We can, that is, conceive growth and the performance of function as occurring pari passu*, and, what is more, this conception harmonizes with experience—that whereas excessive muscular activity results in exhaustion and shrinkage of a muscle, a moderate grade of muscular activity, if persevered in and if accompanied by adequate nutrition, leads to the growth and enlargement of the individual fibers.

Indeed, while we recognize that growth is inherent and the performance of function a response to external conditions, we have at the same time to admit a certain relationship and interdependence of the two processes. To take again the case of muscle, it is a familiar fact that abundant food, unaccompanied by exercise, does not lead to muscular overgrowth, but rather to the reverse. A certain grade of functional activity appears to be essential, not merely for the maintenance of the *status quo* of the cell, but for its growth. When, however, we look more closely into the matter, we encounter difficulties which prevent us from making any more precise statements, for there are certain apparent exceptions. In the embryo, for example, growth is at its maximum, function at a minimum; throughout adult life, after a certain stage has been reached, the reverse may be said to obtain; by steady exercise the muscles may be brought to a certain bulk, but further exercise leads to no further increase; there is a maximum size induced by the due performance of function, and this cannot be exceeded. And, thirdly, as we shall see in studying tumors, at all life periods there are cells in the body which may take on excessive growth, and this, so far as we can determine, irrespective of functional activity. Only within certain rather narrow limits does this relationship obtain. We may say that the normal cell of the adolescent and adult individual exhibits a relationship between growth and function, but that under certain conditions growth is largely irrespective of function. What these conditions are we must attempt to determine.

Active assimilation and active growth with little apparent functional activity characterize the embryonic and fœtal stages of existence. The more the cells become differentiated and recognizable as the specific

constituents of the different organs the less the capacity they exhibit for growth and the more their katabiotic activity.

Accumulation of energy, in short, characterizes the growing stage of the individual and of the growing cell, and we may regard this storage as continuing until the volume of the cell—and of the individual—reaches the point beyond which further increase in mass becomes not merely uneconomical, but actually harmful to the system. To repeat, we have to recognize that there is a definite relationship between surface area and mass, and that when the mass of a cell exceeds a certain point its surface area, proportionately to the unit of mass, decreases at a rapid rate, and both assimilation and discharge are hindered. When this point is reached there are the alternatives: either of cell division (by which there is a rapid increase in surface area relative to mass), or of diminution of the mass through the performance of function; or, in other words, through dissociation of some of the cell substance and liberation of energy. The first of these methods obtains more particularly so long as the system as a whole (the individual) is below what we may express as the economical ratio between its mass and surface area relatively to external medium and environment; the second becomes more and more marked as this ratio is approached.

Carrying this chain of reasoning to its logical conclusion, it will be seen that the size of the adult individual of any species is a function of the constitution of the biophores; is the expression of the optimum economy of interaction between those biophores and the external medium. Growth of cell and individual continues until this optimum is reached. Function—katabiosis—with the liberation of kinetic energy is the means whereby the optimum is maintained.

But what is more, in the developed cell there must be a constant alternation between these two. So soon as the cell performs function, be it glandular and excretory, or motor, or what not, it liberates energy, and this it can only do by a dissociative process; in other words, by the disintegration of the cell substance. Thereby the cell falls below the limit of optimum efficiency, and here, again, it is in the position to take to itself new matter and grow; or, as Weigert[1] expresses it, "the katabiotic use of material in function removes the obstruction to growth."

The most highly differentiated of all cells, namely, the neurons, once they have attained to full development and differentiation, almost cease growing, save for diurnal variations in size and the making up of loss brought about by the performance of function; neither do they multiply, remaining fully differentiated and active throughout the whole period of existence of the normal organism. Cell differentiation, in short, manifesting itself mainly as cytoplasmic change, necessitates a modified metabolism. It may well be that the formation of more complex cytoplasmic molecules in itself is a hindrance to the formation of new biophores; that these cytoplasmic molecules have to be dissociated

[1] Deut. med. Woch. 1896, 635.

into molecules of a simpler type before their material can be utilized in the formation of the biophores. We shall have to revert to these matters in discussing the subject of cell multiplication.

PHYSIOLOGICAL INERTIA AND HABIT.

A factor of considerable importance in determining whether a given cell employs its acquired energy for growth or for the performance of function is clearly what Fraser Harris[1] has termed the "physiological inertia" of living matter. When a resting muscle is stimulated it does not immediately pass from the inert to the actively contracting state. There is, as is well known, a definite *latent period* before it responds to the stimulus. Contrariwise, when a gland cell is stimulated, it continues to secrete after the stimulus has been withdrawn. The cell acquires momentum, resembling the wheel set spinning, which continues to rotate after the hand has been withdrawn. Many other examples might be adduced showing that the inertia of the cell leads it to continue in the same state, whether of rest or of activity, after the conditions have changed. Prior to Harris, Weigert[2] had called attention to the same property of living matter, although, perhaps, in not such clear terms. And Ehrlich, basing himself on Weigert, makes this the basis of his theory of immunity. In fact, as we shall have occasion to point out, it affords the basis of our comprehension of all cases of individual adaptation.

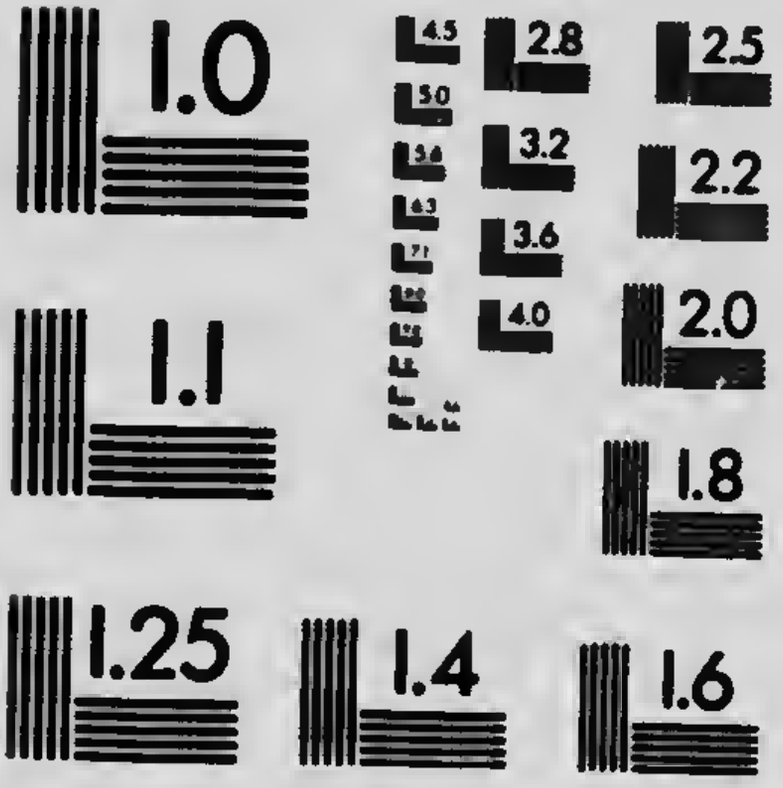
For this physiological inertia is the starting point of what may be termed "habit." A cell stimulated to perform a certain act does not merely continue to perform that act for some little period after the stimulus has ceased, but, what is more, on a second occasion a slighter stimulus will induce the like series of molecular rearrangements, until a period is reached when the minimal stimulus produces an optimum

[1] Brit. Med. Jour., 2: 1900: 741. See also the Functional Inertia of Living Matter, London, Churchill, 1908.

[2] This at the conclusion of a celebrated address (Deutsch. med. Woch., 1896: 635, and Gesamm. Abhandl., 1906: 1), already referred to, in which Weigert considered the relationships between the functional and vegetative activities in the cell, or as he terms them, and perhaps more clearly, the "katabiotic" and the "bioplastic" cell activities. In this address Weigert laid down most decidedly that the doctrine that growth may be introduced directly by stimuli from without is purely hypothetical, and, what is more, is an hypothesis that cannot be sustained. These views of Weigert have had great influence in pathology ever since their enunciation. But it will be seen from what has already been said that I do not agree with him. New growth, he holds, is due to removal of the resistance which keeps the potential energy in leash; consequently, with the removal more can pass over into the kinetic form. The weakness in Weigert's reasoning lies in the fact that he failed to appreciate the possibility that stimulation of a certain grade, by causing increased metabolic activity, coincidently favors increased associative changes in the cell, thereby setting up growth. We shall, however, in a later portion of this work have to again refer to Weigert's doctrine.

MICROCOPY RESOLUTION TEST CHART

(ANSI and ISO TEST CHART No. 2)



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reaction, and with this the cell energies become employed in one or more particular directions, and activities in other directions are distinctly lessened. Once a cell starts to grow, there is a tendency for it to continue to grow rather than to perform function, until the increasing size and increasing tension and other (external) stimuli attain such an extent that now functional activity is called into play. This, in turn, once started, is apt to continue.

It may be urged that here we assume for living matter properties not possessed by non-living matter and thus go counter to our main deduction or guiding principle that essentially vital properties are but particular instances of properties possessed by matter in general. Now it is interesting to observe that pure physicists like Lord Kelvin have independently called attention to phenomena exhibited by inorganic matter (*e. g.*, the "fatigue" exhibited by steel wire undergoing recurrent torsion), which curiously resemble phenomena seen in the tissues. Professor Bose has brought forward experiments of a very striking order to illustrate the parallelism.[1] From this it will be seen that in the nature of its responses to stimuli, living matter differs at most in degree, and not in kind for non-living.

RESERVE FORCE.

These considerations lead us to mention another prominent characteristic of living matter, namely, the possession of what is well termed "reserve force." It is a property which deserves the fullest recognition by the student of disease, for upon its existence depends the whole process of healing. Every living organism is so constituted that, under ordinary conditions, its cells and tissues do not work to their utmost limit. Just as, acting on sound mechanical principles, we construct, or ought to construct, a wall, a floor, or a bridge, so that it is capable of bearing a load several times greater than any to which in the ordinary course of events it is likely to be subjected, so are the cells of the organism constructed. There is a large reserve of force or energy within them over and above that which they exert under normal conditions.

[1] He used a "sensitive cell"—a photo-electric cell—composed of brominated silver plates connected with a galvanometer to record changes in the electric current through the system, and was able to show that every kind of response characteristic of a vital organ, such as the eye, could be obtained from the non-living mechanism. "In both we have under normal conditions 'a positive variation' (of the injury or resting current, or current of reference), in both the intensity of response, up to a certain limit, increases with the duration of the illumination, in both there is comparatively little fatigue, the increase of response with intensity of stimulus is similar in both, and, finally, even in abnormalities, such as reversal of response, preliminary negative twitch on cessation of illumination, and decline and reversal under continued action of light, parallel effects are noticed." He even obtained electric after-oscillations strictly comparable with the after-action (after-image) in the retina when light is shut off. Response in the Living and Non-living, Longmans, 1902. I am indebted to Dr. Fraser Harris' work upon the Functional Inertia of Living Matter, London, Churchill, 1908, for this reference.

Numerous illustrations of the fact immediately suggest themselves: The huge reserve of muscle power which there is in the ordinary individual, unsuspected by himself and by those around him until he is profoundly excited or the subject of delirium; when the patient, so weak a few hours previously as scarcely to be able to raise his arm from the bed, requires all the force of two or three strong men to hold him down. Similar to this is the sudden and great strain which the heart muscle can successfully withstand in violent exercise: it has been calculated that the heart can perform from three to four times as much work as it accomplishes under normal conditions, and this without producing the state of overstrain. Examples of another order are to be recognized in connection with the various glandular organs. Thus, three-quarters of the rabbit's liver may be removed and yet the animal continue to live in apparently sound health. In other words, one-quarter of that organ suffices to satisfy the needs of the organism, or, what comes to the same thing, under normal conditions the liver cells are working only at one-quarter of their capacity. Nine-tenths of the dog's pancreas may be removed without glycosuria supervening. Almost all the thyroid gland may be successfully removed without apparent harm (provided the removal be not permitted at a single operation); or again, the whole of the spleen of the dog may be excised and health be unaffected.

In the last case, presumably, other related tissues take on and perform the functions of the spleen, exercising thus a *vicarious activity*, just as, according to certain observers,[1] does the pituitary body (hypophysis cerebri), when the thyroid is atrophied or removed; or as, according to others, do the Brunner's glands of the duodenum when the pancreas undergoes loss of function. Taking the organism as a whole into consideration, it is clear that these examples of vicarious activity are at the same time examples of reserve force. Yet other examples indicating the existence of abundant reserve force are met with in connection with the various paired and multiple structures of the body: a single lung is capable of carrying on satisfactorily the all-important process of respiration; a single kidney, urinary secretion; numerous lymph glands, teeth, or fingers may be removed without evident harm to the organism. Even the most highly specialized organ of all, the brain, is largely composed of paired "centres," and when one of a pair is thrown out of action the other may often take up its functions.

It is thus very clear that *the organism is so constructed as to possess in most or all of its functions an abundant margin of reserve force.* This is capable of explaining how it is that the human body is at once so marvellously complex and delicate a mechanism—responding to a variety and extent of stimuli in a way that no machine constructed by man can nearly approach—and so able to withstand wide diversities of environment and extreme strains upon and injuries to individual organs without

[1] Rogowicz, Ziegler's Beiträge, 4: 1888: 453; Boyce and Beadles, Jour. of Path., 1: 1893: 223 and 359; see also Schönemann, Virch. Arch., 129: 1892: 310

being destroyed; as also the fact that there may be extreme local disease or destruction of parts without of necessity constitutional disturbance. Until injury or disease of a tissue has reached a certain point the cells of that tissue are able to fulfil the needs of the organism, and in many cases even after this point has been reached, other tissues may vicariously perform its functions.

In short, in the existence of this reserve force lies the secret of the continued existence of the individual, the explanation, as we shall point out, of immunity to disease, and of the healing of injuries of every order if, indeed, it be not the keystone of adaptation, and, in brief, of the evolution of the race. This, however, may rightly be said: that if the existence of this reserve force be kept steadfastly in mind, we are saved from continual misconception of the mechanism and meaning of many processes.

If, for example, we appreciate the existence of this reserve force, there is no longer an inclination to suggest that the action of the leukocytes in inflammation is purposive. If, then, they take up and digest living bacteria, this is not the assumption by them of a new function, or the exercise of a new force to meet the exigencies of the case. We now know that in conditions of health bacteria constantly, if only to a slight extent, gain entrance to the tissues and are destroyed by endothelial and other cells; that if a drop of the blood of any normal individual be taken, the contained leukocytes can be shown to have these *phagocytic* properties; in short, that it is a normal property of sundry leukocytes to ingest, and, when possible, digest, foreign substances. Or if, again, we find that in the majority of cases in which there is destruction of the pancreas, glycosuria shows itself, whereas in some rare cases an equal destruction of this organ is followed by no glycosuria, we must not forthwith conclude that severe injury to this organ can play no primary part in the production of diabetes mellitus. There is the possibility, that must not be ignored, that in the exceptional cases above cited so great a reserve force exists or is developed by the vicarious activity, it may be, of other organs that excessive exhibition and waste of sugar in the system is effectually prevented.

And underlying the development of this reserve force we must see the action of this same force of physiological inertia. Life is more than the continual precise adjustment of internal conditions to external changes of environment. Through inertia there is over-adjustment; through it, when the cell assimilates, it continues to assimilate more than is actually needed; when it is stimulated to metabolize, it continues to form more paraplasmic matter than is necessary for immediate excretion; when it starts to grow, the extent of growth is over and above the extent of the initial stimulus. And, although these are the exception and not the rule, we are not without instances of cases, such as the cells of the mammary and sebaceous glands, in which, when once dissociative changes are initiated, these continue until the cell is completely disintegrated.

THE STATES OF CELL ACTIVITY.

These considerations prepare us to recognize certain states of the cell depending upon the ratio between assimilation, growth, and stimulation from without; states which it is well that we should recognize, for in conditions of disease we constantly encounter transitions from one to the other of these.

1. **Subnormal Activity.**—Under wholly normal conditions the process underlying the accumulation of reserve force leads to the presence in many tissues of redundant cells, cells which, from the accident of position, receive minimal stimulation and so pass into a latent, relatively inert state. Under abnormal conditions many cells may pass into this state. With lack of stimulation these cells undergo a very distinct atrophy: the paraplasmic matters are used up, the cell body becomes shrunken and inconsiderable, the stainable substance of the nucleus diminishes in amount, the nucleus as a whole becomes inconspicuous. An excellent example of the passage into this state of subnormal activity and its results is to be seen in the muscles of a limb, whether of man or animal, kept forcibly at rest. If, for instance, through injury to the knee, or fracture, one lower limb of a muscular young adult be enclosed in plaster, it is a matter of familiar experience that within a week there is a marked diminution in the circumference around the middle of the thigh of the immobilized as compared with the free limb. A similar and more extreme atrophy is to be encountered in the muscles of cases of hysterical paralysis. We mention these more particularly because in organic paralysis, due to recognizable injury to the nervous system, it is still a matter of debate to what extent injury to the "trophic" nerves is responsible for the atrophy.

If this condition of subnormal activity and latency be continued too long, the cells, or some at least of them, die and wholly disappear. That this is the case is well exemplified in the brain. In that organ, we need but remind the reader, nervous impulses are in many instances conducted through relays of cells; there are definite tracts along which specific impulses, and those impulses only, are conducted. If the neurons of the upper portions of such a tract be destroyed by disease or by removal, the second series of neurons with which they communicate can receive no impulses, and, as a consequence, are rendered largely inactive. As a matter of fact, in such cases we find that these secondary centres show pronounced atrophy of their constituent cells; these cells become greatly shrunken, and in the course of a few weeks or months their number is markedly reduced. We can proceed so far as to lay down with confidence that where the cells of basal nuclei do not exhibit this atrophy and disappearance, there the centres have not been connected with the destroyed area, and that where the atrophy is only partial or transient, there the affected centres have been, and are, in connection with more than one peripheral centre, thus continuing to receive stimuli, although not to the normal extent.

While we cannot follow Grawitz to the whole extent of his theory or accept all the arguments upon which that theory is based, we have to admit the existence of certain orders of *Schlummerzellen* or "sleeping cells"—cells atrophied through inaction, but capable under stimulus of returning to full vigor and full development. That these undergo such a grade of atrophy that, as he insists, they become invisible, I cannot accept.

2. **Vegetative Activity.**—Cells in the process of active growth present certain well-marked characteristics. The nuclei are relatively large, rounded or oval, and deeply stained; paraplasmic granules and deposits absent, or, if present, in but slight amounts; the cell body unformed, tending to be rounded or oval, the cytoplasm exhibiting little differentiation. Such cells are apt to multiply, and we shall have more to say regarding them in our chapter upon Cell Multiplication. Here we would only give the warning that, from their general resemblance to the cells of the growing embryo, in which this type of cell predominates, it is customary to speak of these as *embryonic* cells. This is a misnomer, leading to false conceptions, for cells of this type are to be encountered in normal tissues at all life periods. It is better to speak of them as vegetative cells.

FIG. 23

To show the distinction between functional and vegetative cells. Two "clear cells" of regenerating liver, rounded, large and clear, owing to relative absence of paraplasmic granules seen in surrounding active cells. One of these exhibits mitosis. (Adler.)

3. **Functional Activity.**—Cells actively functioning as a general rule present signs of differentiation according to their specific function. Either, as in the case of muscle or nerve cells, the cytoplasm is highly elaborated, or, as in the case of gland cells (and the bodies of the neurons), there are paraplasmic deposits, granular or in the form of minute globules. The nuclei are relatively not so large; the staining of the same varies with the stage of the cell activity. Here, however, distinctions are to be made between the cell action under a mean or normal stimulus and one that is more highly stimulated. We can thus further distinguish the following states:

4. **Hyperactivity within the Limits of the Reserve Force of the Cell.**—When, as already indicated, increased stimulation is accompanied by adequate nutrition, the functional activity of the cell is, up to a certain extent, accompanied by growth. In this way and to this extent increased work of the cell leads to what is termed *hypertrophy*. The dimensions of the cell are increased, the nucleus is of good size, the cell body presenting well-marked differentiation.

5. **Excessive Functional Activity.**—When, on the other hand, the work that the cell is called upon to perform exceeds a certain point, the energy dissipated in the performance of function being greater than that acquired from the assimilated foodstuffs, provided that the stimulation be continued sufficiently long, then, first, the reserve force of the cell is used up, all the paraplasmic stores becoming exhausted, and next, the extra energy demanded has to be obtained from the disintegration of the active cell-substance—cytoplasm and nucleoplasm. The result is cell exhaustion. The nucleus becomes poorly staining; the cell body exhibits a variety of changes, according to the specific activity of the cell. In some cases, *i. e.*, cells of the convoluted tubules of the kidneys, there is actual breaking off and discharge of portions of the cytoplasm; in other cases, abnormal deposits occur within the meshes of the cytoplasm; in others again, owing to osmotic changes, the cytoplasm becomes vacuolated. These we shall have to describe more fully when dealing with the degenerations. If the stimulus be further continued, the result is cell death and complete disintegration.

CHAPTER VIII.

CELL MULTIPLICATION.

INCREASE in size of the tissue and of the multicellular organism as a whole is brought about by two processes: by enlargement of the individual units, the cells, and by the intercalation of new units derived from those already present. We speak commonly of increase in size of the individual as growth, by whichever of these two processes it be produced, and thus are apt to confuse the two, considering cell growth and cell multiplication as practically synonymous. While admitting that the second process is a sequence of the first, it is, nevertheless, well to keep the two perfectly distinct in our minds, and this we have endeavored to do thus far. In our treatment of the subject of growth we have taken into account purely the enlargement of the individual cell units by increase in the amount of living substance of the same. Following upon this, it is essential that we pass in review the subject of cell multiplication.

The *rationale*, if we may so express it, of cellular structure has already been touched upon (p. 84). It has been shown that the nucleus is to be regarded as the dynamic centre of the cell; that the nuclear biophores are to be regarded as requiring for their full activity a certain proportion of cytoplasmic matter, and that, in its turn, this cytoplasmic matter, for the due exercise of its functions, must be in intimate relationship with the external medium; that in a roughly spherical body, with increase in diameter, the surface increases at a far less rate than does the mass, so that growth of the individual cell beyond a certain limit is self-inhibitory, unless some means be employed to increase the surface in proportion to the mass of the cytoplasm. When this is accompanied by coincident growth of the nuclear mass, means have also to be employed to increase the nuclear surface in relationship to its mass; that cell and nuclear multiplication, respectively, are the simplest means of accomplishing these objects.

Now, it is in place to describe the mechanism whereby this multiplication is brought about. The finer details and the variations in the process belong to the domain of the histologist and cytologist. Fortunately, throughout the cells of the higher animals, which more especially interest us, the same broad plan is to be recognized—the variations are very slight. Hence it is possible to describe in general terms the processes of cell division, knowing that what is said applies to individual cells, to the cells of the different tissues of the human body. We recognize two main types—direct, or *amitotic* division, and indirect, *mitotic* or *karyokinetic*.

DIRECT DIVISION: AMITOSIS.

This is the rarer form, although not so rare as it has been the custom to describe it. In text-books published within the last five years the statement will be found that among higher animals it is confined to the leukocytes. This is incorrect. There is an increasing number of observations indicating that it obtains also under certain conditions in cells that we regard as much higher in the scale. This, however, may be laid down, that it is wholly absent in the process of development; the cells of the metazoan (multicellular) embryo never exhibit it. On the other hand, in the fully developed organism, in tissues formed of aggregations of similar cells, in the liver, for example, we may encounter it, and it would appear to be particularly liable to occur in cells having the tendency to be multinucleate, cells exhibiting two or more nuclei without immediate separation of the cytoplasm into distinct cell bodies around each of the nuclei. It is in leukocytes and in cells of endothelial type that we encounter it most frequently, and in yet another group of cells, namely, those of pathological new growths.

It is frequent also in the cells of the embryonic envelopes of insects, of the periblast of yolk nuclei, and in the syncytial (epiblastic) cells of the mammalian embryo. All the cells of this order are destined to but a temporary existence. As Wilson[1] points out, *these cells are on the way toward degeneration.*

It is possible that further study will show that the cells in glandular and other organs already referred to which exhibit this direct division of the nuclei are also not wholly normal, or otherwise that amitosis is a sign of regressive change. As regards the leukocytes, it is worthy of note that in normal lymph glands, where the lymphocytes are continually being produced, we encounter frequent cases of mitosis or indirect division, while it is in the blood and in the tissues in conditions of inflammation that we meet with the amitotic division. Vom Rath,[2] indeed, lays down that "when once a cell has undergone amitotic division it has received its death-warrant; it may, indeed, continue for a time to divide by amitosis, but inevitably perishes in the end." This may be too extreme a conclusion,[3] nevertheless, the facts at our disposal do appear to point in this direction and to indicate that direct division in the higher animals is a secondary or reversionary process.

What happens in *amitosis* is that the nucleus divides without any

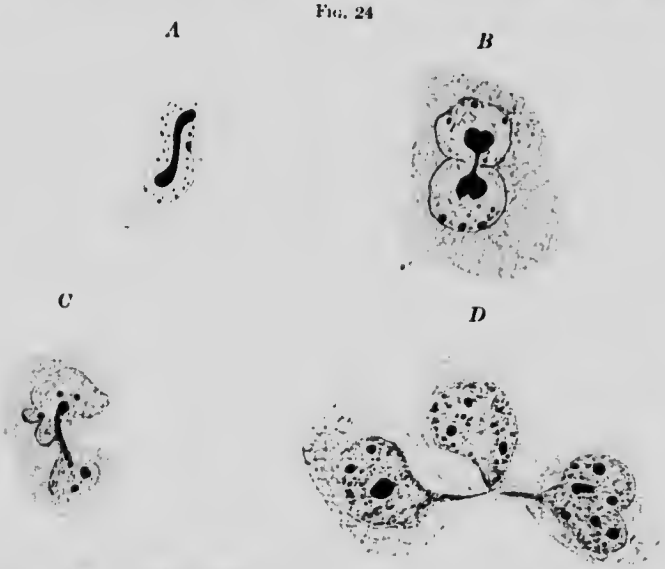
[1] The Cell in Development and Inheritance, 1897: 82.

[2] Zoöl. Anzeiger, 14: 1891: 331.

[3] Thus Bashford (Second Report of the Imperial Cancer Commission, London, Part 2, 1905) notes in connection with the connective-tissue cells of the host in the neighborhood of transplanted portions of mouse cancer, that these cells at first divide by amitosis, and that eventually the products of amitotic division undergo active mitosis, eventually giving rise to the stroma of the growing tumor. A somewhat similar case is the early amitotic proliferation of the cells in an inflamed area followed by later mitosis

apparent preliminary re-arrangement of its structure. It becomes elongated, then dumb-bell shaped, and after a period in which (as can better be followed in the amœba) there is a certain amount of streaming of the nuclear material between the poles, the connecting neck becomes broken across and the two daughter nuclei pass apart, their separation being in some cases followed by division of the cell body, so that thus two complete daughter cells are developed; in other cases this further division is wanting, and the binucleate or multinucleate cell is produced (Fig. 24).

Fig. 24



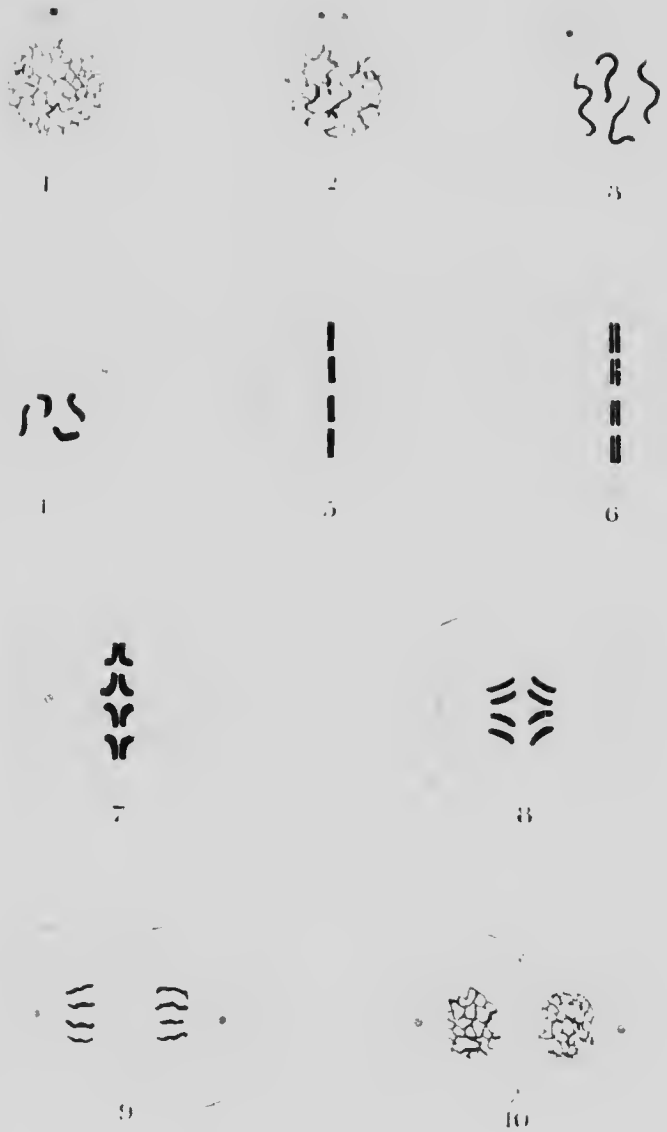
Amitosis. Stages of direct division in tumor cells: *A*, from an ovarian cancer; *B*, from an epithelioma of the lip; *C*, from a uterine sarcoma; *D* from a metastatic cancer of t' ver, showing the last stage of division of a cell in' hree equal parts. (Nedjelski.)

It deserves note that in this process, according to the majority of observers, the centrosome either plays no part or at most the attraction sphere forms a ring around the equator of the dividing nucleus, *i. e.*, the part played is distinctly abnormal and unlike what is seen in mitotic division.

INDIRECT DIVISION: MITOSIS.

This is, *par excellence*, the natural mode of cell division, and that in animals and plants alike. That it should be so widely distributed indicates that the remarkable succession of changes seen in both nucleus and cytoplasm is not a matter of chance. The full significance of these changes we are still far from comprehending. One thing is obvious, namely, that they indicate a mechanism whereby the nuclear material is distributed with remarkable exactitude between the two daughter

PLATE II



The Phases of Mitosis.

cells. And they indicate clearly something more. Were the biophores or essential constituents of the nuclear material all of the same nature and composition, the law of economy suggests that no such elaborate "quadrille" of the nuclear material would be indulged in; simple direct division into two equal halves would suffice, each daughter cell receiving approximately equal amounts of the nuclear material. That the nuclear material arranges itself in this remarkable manner prior to division may, in itself, be taken as proof positive that there is a differentiation of the biophores, and that mitosis is a mechanism whereby identical groups of biophores are conveyed into the daughter cells. Light will, we think, be shed upon the significance of the process when we come to consider the subject of heredity. For the present we shall merely detail the usual stages in the process of mitotic cell division. (See Plate II.)

The Stages of Mitosis.—For a full discussion of the phenomena of mitosis, as again of the part played by the cell in inheritance, the reader is referred to works upon histology, and more especially to Professor Wilson's valuable monograph.[1] Here I can but in the briefest possible way recall the main features of the process:

1. **Prophase or Preparatory Stage.**—The nuclear chromatin which is the resting state of a cell is seen as an irregular and nodulated network, becomes modified into a continuous single (or, very rarely, a segmented) thread, having the appearance of a *skein* or *tangle*, and then proceeds to divide into a definite number of short lengths, the *chromosomes*. While these changes are proceeding the nuclear membrane disappears, so that the chromosomes come to lie naked in the cell. Every species of animal and plant has a fixed number of chromosomes, and in the mitosis of the cells this number regularly recurs. In man, certain observations by Bardeleben would indicate that the number is sixteen. Side by side with these changes other changes take place outside the nucleus, in the cytoplasm or cell substance, leading to the development of the *amphiaster* or *spindle*. This arises under the influence of the *centrosome;* very frequently, while the nucleus is still at rest, this divides into two similar halves, around each minute dot the protoplasmic network of the cytoplasm becomes concentrated, the fibrils radiating in all directions so as to form star or *aster*, and, as the two separate, journeying toward opposite ends of the cell, a *spindle* of fine fibrils is seen to stretch between them.

2. **Metaphase.**—Each chromosome splits lengthwise into two exactly similar halves, the daughter chromosome becoming apparently attached to certain *mantle fibers* of the spindle. This *splitting of the chromosomes*, discovered by Flemming in 1860, *is the fundamental process of cell division.*

3. **Anaphase.**—The daughter chromosomes diverge, the two members of each pair passing to opposite poles of the spindle. Here the chromosomes become closely crowded near the centre of the aster.

[1] The Cell in Development and Inheritance, New York, 1897.

4. **Telophase.**—The cell body now divides into two in a plane passi through the equator of the spindle. Thus, each daughter cell contai half the daughter chromosomes, half the spindle, and one centroso and aster. The two latter may persist or disappear; if they persist th form the *attraction sphere*. Before, during, or after the process of c division there occurs the construction of the daughter nucleus. T commoner process is for the daughter chromosomes to fuse into a ske or tangle, which in its turn becomes irregularly swollen and dissociat into the chromatin network of the "resting" nucleus. Several rece observers claim that in the resting nucleus of certain species it is possib to distinguish the course of the original chromatin thread, and even the different chromosomes that go to compose that thread.

CHAPTER IX.

ADAPTATION.

We have suggested (p. 98) that the procession of changes seen in mitosis indicates that the biophores or specific ultimate molecules of living matter are not all identical, and in this and the succeeding chapters it will be seen that what we have to say practically centres around biophoric modification; around the extent to which the biophores, and through them the cells in general, become modified in their properties and—as the properties of any substance depend upon the constitution of the same—in constitution. Here, again, it may at first seem a far cry from matters such as this to the needs of everyday pathology, but in reality, as we hope to demonstrate forthwith, a comprehension of these matters is essential for a proper grasp of the remarkable and superabundant facts elicited during the last few years in the study of immunity—a branch of pathology which has received of late more attention than has any other. And, although it is far from being generally recognized, it is through these studies that the pathologist and the bacteriologist are laying the foundation of an adequate theory of variation and inheritance.

Descent and variation are subjects which we have to dwell upon in future chapters as a foundation for our treatment of the inheritance of diathesis and disease and of the remarkable group of abnormal growths which we include under the heading of monstrosities and abnormalities. As a basis for our study of all these subjects, it is fitting that we first take up the subject of adaptation.

That living matter has adapted itself to its environment is a commonplace. Man and all other animals and plants exhibit countless evidence of the fact that each form of life is adapted to the particular environment in which it flourishes. But, admitting this, we are apt to ascribe the process of adaptation to chance. The zoologist and the botanist, recognizing that all living beings vary one from the other, that no two individuals are exactly alike, are apt to ascribe adaptation to the retention and descent of favorable variations; the individual, varying from "type" in a direction which gives it the advantage over other members of the species or tribe, is more liable to survive; if the variation be unfavorable, life is rendered more difficult and the individual and the stock descended from that individual tend to die out, they being at a disadvantage. There is seen to be a survival of the fittest, and it is by the summation and descent of favorable variations that the different species are adapted to their particular surround-

ings. This is the prevailing doctrine. Studying it, we see that adaptation is regarded as based on chance; chance variations are at the bottom of the whole process.

If our studies in infection and immunity have any meaning, they teach us that this is not the truth—or at least not the whole truth. *Adaptation is primarily an active process, or at least inevitable, and in no sense subject to chance.* It is not the mere fortuitous passive modification of living matter in a favorable direction, but a process whereby that living matter is able to a greater or less extent to change and suit itself to its surroundings, a given change in those surroundings leading to definite and corresponding alteration in that living matter. This we would emphasize.

For a comprehension of racial and species adaptation we have to begin with a study of individual adaptation. In connection with conjugation and amphimixis chance undoubtedly enters, but only secondarily. We would, in the first place, afford the proof that adaptation is a regulated process affecting the individual, and, in the second, would seek to determine how a property apparently so wholly unlike those possessed by matter of all other orders has come to be developed.

It is a well-known fact that bacteria, like other living organisms, assimilate food through the action of enzymes, and these both extracellular and intracellular. Some bacteria, for example, living in media containing proteins and albuminoids possess active proteolytic ferments, whereby these bodies are reduced to soluble peptones, and may be still further dissociated, with indol as one of the ultimate products. Others more particularly act on sugars, splitting up these with the production of organic acids and gas (H and CO_2). On removal from their natural habitat and growth upon the artificial media of the laboratory, the different bacteria exhibit these proteolytic and glycolytic properties in varying degrees: some have little or no proteolytic activity, others little or no glycolytic power; some ferment one particular sugar only, others a variety. We have, indeed, established our classification of the B. coli and allied forms largely upon these fermentative properties.[1] But now, as we believe was first pointed out by Peckham,[2] if the typhoid bacillus, which normally does not produce indol, be grown in a relatively strong proteid medium free from sugar, and be passed, over a considerable period, from tube to tube of this medium, there is eventual

[1] See Ford, The Flora of the Human Intestine, Studies from the Royal Victoria Hospital, 1: 1903: No. 5. In this most painstaking and elaborate study of the bacterial contents of the intestines of 50 cases Ford isolated as many as 50 different "species" of bacteria. Of these, 36 were non-spore bearing and non-pigment producing, and of these it will be seen that there are several groups containing three to seven members, each of which differs from its fellows only according to the fermentation or non-fermentation of one or other sugar. The recent studies upon the bacillus of epidemic dysentery recognize at least four "species" undistinguishable morphologically, but each having a different action upon a series of sugars added to the medium of culture.

[2] Jour. of Exp. Med., 2: 1897: 549.

indol production. This cannot be said to be the result of chance—it is inevitable. Take any apparently normal culture of the B. typhosus and place it under one particular set of conditions, and the proteolytic indol producing function will manifest itself. Similarly, as pointed out some years ago by Sir Lauder Brunton and Macfadyen,[1] growth of certain bacteria in media containing particular sugars eventually results in those bacteria gaining the power to ferment the particular sugars. The property is not acquired immediately, but, with a given species, we can foretell absolutely that it will be acquired within the course of a few days, or at most weeks. Thus, in a recent paper, Klotz[2] has pointed out that the B. perturbans—a form intermediate between the B. coli and the B. typhosus—was able to ferment glucose when first isolated from water, but only gained the power of fermenting lactose and saccharose after growing in lactose and saccharose broths for some days.

The organism was then placed in a celloidin capsule and inserted into the peritoneal cavity of a rabbit. Left here for three days, it was found to have lost its power of fermenting the two latter sugars, regaining it, as regards saccharose, after forty-eight hours' sojourn (two passages) in saccharose broth; as regards lactose, after four days' incubation. The experiment was repeated by placing some of the stock culture in a celloidin capsule in the peritoneal cavity of a rabbit and leaving it there for one hundred and forty-four days. On removal, there was a slight fermentation of the glucose broth at the end of the first day; saccharose fermentation appeared on the fourth day; lactose fermentation on the sixth transfer, and then only at the end of seventy-two hours' growth; by the eighth transfer gas appeared in fair quantity. Work along these lines has recently been carried still farther by Twort,[3] who, taking a series of members of the B. coli group which had been grown for a long period upon ordinary laboratory media, retaining fixed type characters, was able, by growing them now for long periods upon media containing unaccustomed sugars to cause a certain number to eventually dissociate sugars which at first they did not ferment. He thus found that all members of the paratyphoid subgroup would ultimately ferment saccharose; the typhoid bacillus acquired the property of fermenting lactose and dulcite, and the dysentery bacilli of Shiga and Flexner ultimately fermented saccharose within twenty-four hours.

The same is true also as regards pathogenic properties. As Vincent[4] has shown, it is possible to take absolutely non-pathogenic forms, like the B. megatherium and B. mesentericus vulgatus—forms which may be inoculated by the million into warm-blooded animals without the slightest disturbance being set up—and accustom or adapt them to growth within the warm-blooded animal by inserting celloidin capsules

[1] Proc. Roy. Soc., 46: 1889: 542.
[2] Jour. of Inf. Disease, Supplement, 2: 1906: 35.
[3] Proc. Roy. Soc., B., 79: 1907: 329.
[4] Ann. de l'Inst. Pasteur, 12: 1898: 785.

containing pure cultures of the same in the peritoneal cavities of these animals. These capsules, it may be explained, permit the diffusion of the body fluids, and so of nutritive material, and at the same time prevent the direct action of the body cells on the bacteria and the escape of the contained bacteria. After being grown thus for some months, upon removal of the capsules and making growths in culture media outside the body, it is found that the bacteria have become pathogenic, are capable of growing within the tissues when injected direct, and of causing the death of the inoculated animals. In other words, the bacteria now produce enzymes and other products capable of acting deleteriously upon or poisoning the animal tissues.

Similar observations have been made with forms somewhat higher in the scale; thus one of the molds, *Aspergillus*, cultivated on a nutrient medium containing lactose, or β-methyl galactoside, has been found to acquire the property of hydrolyzing these uncommon saccharides. Transferred to a medium containing methyl galactoside, it acquires the property of attacking this substance.[1]

All these, it will be seen, are examples of the acquirement of new properties on the part of the lower organisms by adaptation. Within certain limits—at present by no means clearly defined—the simple forms of life are able to adapt themselves to their surroundings, and the adaptation cannot be ascribed to chance, for, *with a given environment, the one particular alteration in properties surely results.*

Let it be clearly understood that we do not pretend to lay down that these lower organisms can eventually enter into combination with and adapt themselves to every possible substance dissolved in the medium of growth or that every attempt to modify the properties of bacterial species is fraught with success. This is far from being the case. All we state is that the observations made so far indicate that there are certain substances with which living matter, or its metabolites, can enter into a more or less close combination, and toward which, therefore, it can adapt itself.

To these conclusions it has been objected that what, after all, we are dealing with is the survival of the fittest; that it is still a matter of chance; that among the thousands, not to say millions, of bacteria in a culture—owing to the *inherent tendency of living matter to vary*—it happens that some exhibit variation such that now these particular bacteria are able to ferment the unaccustomed sugars, etc.; that these having gained the new power, by chance, are at an advantage as compared with the others which have not varied in this direction, and multiply at the greater rate, and their descendants, starting from this vantage ground, are even more likely to vary farther in the same direction, so that the particular property becomes exalted; so that, in short, in the process of time the descendants of the form exhibiting the favorable variation alone are represented. It is admitted that the new property

[1] Quoted by Moore in Recent Advances in Physiology, etc., 1906, p. 116.

is not gained at a bound; that a considerable number of "generations" of bacteria must pass before the acquired property is pronounced.[1]

So far as it carries, *i. e.*, as affording an alternative explanation of the phenomena, but not, it must be noted, as proof positive that adaptation is not active, this argument is quite valid. It is, however, demolished if we can show that adaptation can take place under conditions in which there can be no question of the survival of the fittest in individual cells, and that with such certainty and in so short a period relatively to the life period of those cells that the process can only be of an active nature. And this we can do—at the very other end of the scale of living beings.

Acquired immunity in man, as in all animals, is adaptation, and this, again, is not a chance process; we can take germs—the cholera spirillum, for example—which, from their habit of life, must have at all times had a purely local existence until man came on the scene and aided in their distribution, germs which, therefore, cannot at any time have affected certain of the lower animals in other regions, so that there can be no valid suspicion that at some remote period the ancestors of those animals had been subject to infection by, or had responded to, those particular species of microbes. Injecting these microbes into such lower animals, guinea-pigs, rabbits, and so on, we determine that they and their toxins are poisonous; so that with very considerable accuracy we can measure what fraction of a centigram of the toxin will cause the death of 100 grams of guinea-pig, rabbit, or other animal, within forty-eight hours. And, having determined this, we can by repeated injections of fractional portions of the lethal dose of the toxin so alter the constitution of the warm-blooded animal that now it can withstand ten or one hundred times the lethal dose without ill effect. Granted that we deal with healthy animals, animals having the normal powers of reaction, we can bring about this immunization with what, under the circumstances, is a marvellous precision. It is along these lines that Pasteur initiated the process of immunization against anthrax and other diseases, and upon these is based the now very considerable industry of antitoxin preparation. Here, again, is no matter of chance acquirement. Animals adapt themselves to, and combat, the toxins of disease according to very definite laws, the process varying somewhat, it is true, in connection with the different pathogenic microbes, nor is the animal body able with equal ease to gain immunity against each particular germ and its toxins. Against some, indeed, the immunity gained is either very feeble or is short-lived; but in any particular instance we realize that given amounts of toxin administered in a given way will in given time result in the production of approximately the same grade of immunity in members of any one species of higher animal. And what is more, the adaptation is not merely temporary, existing only while the toxins

[1] It has been calculated that bacteria growing actively and under favorable conditions can divide, and so give rise to a new "generation" every fifteen minutes, and so afford close upon one hundred generations in the course of a single day.

are present and exerting their effects in the system. It is, in many cases, more or less permanent, so that in certain cases we see that it is in action for months, if not years. There must, that is, be impressed upon the cell substance an alteration in constitution which (remembering that the cells, as such, have most of them but a limited life period, becoming replaced by others of like nature) is conveyed from one cell generation to the other.

We shall, in our discussion upon immunity, adduce abundant instances affording proof of the statements here made and of the fact that the cell substance within certain limits can adapt itself adequately to alteration in the cell environment. And what is true of bacterial toxins is true also of not a few animal and vegetable poisons. For these, also, the system acquires a tolerance; or, expressed otherwise, while at first a certain quantity of each of these, absorbed and circulating in the blood and lymph, arrests cell activity either by breaking down the active cell substance, or by forming with it combinations which satisfy the biophoric molecules and so arrest metabolism, thus bringing about cell and systemic death; quantities less than the lethal act, and are reacted upon, in such a way by the cell substance, that this gains the property of dealing with quantities far in excess of what previously had been lethal.

Some of the most remarkable studies in this direction are those by Ehrlich and his pupils upon *abrin*, the active principle of the plant *Abrus precatorius*, and *ricin*, that of *Ricinus communis*, the castor oil plant. Both of these are intensely poisonous, are substances which, in the ordinary course of nature, are eminently unlikely to gain entrance into the systems of animals of the laboratory, and yet, with remarkable precision, those animals can, by repeated sublethal doses, be immunized so that they can stand doses several hundred times the ordinary lethal amount.

THE PHYSICAL BASIS OF ADAPTATION.

Along what lines can we explain this adaptation, so different from, or at least so far in advance of, anything we encounter in substances not endowed with life?

This we may safely say: that the capacity to adapt must be inherent in and depend upon the constitution of the molecules of living matter and upon the conditions under which those molecules carry out their ordinary activities. It is not so much that *the tendency to vary is inherent*, as that the labile nature of the biophores leads to their variation when subjected to modifications of environment; they vary according to circumstance, *i. e.*, according to law.

Let us try to reason out the simplest case first: that of the assumption by bacteria of new, or at least greatly exalted, powers of dissociating and fermenting unaccustomed foodstuffs—proteins or sugars.

We have already shown that substances in aqueous solution (and all the foodstuffs of the bacteria are assimilated in a state of aqueous

solution) are liable to undergo ionization to a greater or less extent. We may, therefore, more than suspect that, either by direct ionization or by the secondary effect of free ions from other sources present in the cell sap, potential foodstuffs undergo dissociation—that the more complex bodies are broken down into others of a simpler type. This may well be a most important factor in the process we are discussing; the cytoplasmic molecules combining not with the molecules of the unaccustomed foodstuff as such, but with bodies of a simpler type, yielded by it, with bodies which are either ordinary constituents of the cytoplasmic and biophoric molecules, or which are so relatively simple that direct combination is possible between them and the molecules of living substance. An unaccustomed sugar, lactose, for example, may in this way be broken down and afford assimilable material to the bacterial cell.

This is, however, only one stage, the stage favored by the conditions under which the cell substance exists. It explains at most the assimilation of unusual foodstuffs, not the active adaptation to the same. For this latter we have to fall back upon the considerations already brought forward regarding the structure of the cytoplasmic and biophoric molecules—upon what, in brief, we may term the "side-chain theory" (p. 50). We are led, that is, to regard the molecules of living matter as a ring of subordinate radicals, each having numerous satisfiable affinities. If the environment remain unaltered, one constant series of "foodstuffs" diffuses or is absorbed into the cell; one regular order of dissociation products of the same is in solution in the cell sap, and the various affinities of the cytoplasmic and biophoric molecules are satisfied in one particular manner, associated with which growth proceeds. With a given environment, that is, these molecules build up side-chains which, having a particular composition, manifest particular properties.

But let the environment be altered; let a new potential foodstuff be introduced; through it and its dissociation products a new series of free ions is brought into the immediate sphere of action of the molecules of living matter. According to the strength of these ions, according also, it may be, to their number, these are attracted to the molecules of living matter and combined as side-chains, it may be replacing others in the process, others that on their part do not possess such strong affinities. If ions of a new type be thus taken up, new orders of side-chains will be developed and the molecular complex as a whole will acquire an altered composition—and altered properties.

At this stage we can figure to ourselves the central constituent rings as unaltered—merely the side-chains different. So long as the new foodstuff is presented, for so long will the cell molecules continue to form the new order of side-chains. And here let it be clearly understood we do not regard these side-chains as composed of the molecules of the foodstuffs combined in their entirety with the central cytoplasmic or biophoric molecules. The side-chains must, from every consideration, be regarded as tending toward the type of primary

protein molecules. The new ions are built into them. If we regard the biophore as a polymeric molecule, and the simpler protein molecule as of the same order, we cannot, as we have pointed out, regard growth as other than a process of development of new molecules by a process of accretion or building up of side-chains until these become united into new rings identical with the primary. And carrying out this idea, it is difficult to conceive side-chains in general as other than complete or partial polymerizations of the constituent nuclei of the biophoric molecule. Once a side-chain of a particular order is developed, it must, on its part, tend to polymerize, and if the radicals and ions identical with those that went to form it are present in the surrounding medium, a series or chain of like side-chain molecules will be developed within the cell.

Two, or it may be three, possibilities now present themselves:

1. The side-chain molecules may become detached in the cell sap or actually discharged into the surrounding medium, and being, as suggested, of the nature of primary protein molecules, may there present enzyme action. They may, in short, continue to dissociate the specific foodstuffs from which certain of their constituents were derived. As the whole molecule of cell substance was able to attract to itself certain of the constituents of that foodstuff, so, it may be, through side-chains formed, in the first place, from the products of disintegration of the foodstuffs, the cell now gains the power of acting directly on those foodstuffs. We shall encounter some very remarkable facts in our study of antitoxins, which can only be satisfactorily explained along the lines here laid down, namely, we have to assume that, in the first place, the cell gains its power to form antitoxins by combining with certain constituents of the toxins.

2. The second possibility is that these new side-chain molecules become utilized to form constituents of new cytoplasmic or biophoric rings—that they become utilized, in short, in growth. We conceive the biophore (p. 83) as being formed of a ring of primary (protein, or, more exactly, amino-acid) molecules, the constituent molecules not being necessarily identical in constitution. We can conceive the new side-chain molecules as replacing other molecules of simpler nature in the new biophoric rings that are in the process of being built up. If this should happen, then it is that we can regard the adaptation as not merely transient, but impressed upon the actual central living matter of the cell.

3. We mentioned above three possibilities; the third is the possibility that this combination takes place in three stages; that first, the constituents of the new foodstuff are incorporated in the side-chains; next, that they become constituents of the cytoplasmic molecules, and only in the third place become integral portions of the biophoric rings. This is likely to be the case if, as has been suggested, the biophores do not take up their specific constituents directly from the external medium, but only from the cytoplasm, and through its intermediation. It is, indeed, possible to regard the cytoplasmic substance as of the nature of biophoric side-chain molecules.

The very fact that adaptation is in no case immediate, but requires some little period for its development, and this even in the simplest forms of life, favors this view of the existence of a succession of stages in its development.

But this is not all. Once the living matter of the cell becomes modified the modification is apt to persist, and apt, as we have said, to be carried on to later cell generations. A microbe that from the first moment of study has exhibited the power to ferment a given sugar, or that has acquired this power, is apt to retain that power if grown for a considerable period on a sugar-free medium. Under these conditions, no sugar being present, it cannot manifest this particular property, but, grown once more in the sugar-containing medium, it may immediately cause the fermentation. This must be said, that the power is apt to be weakened and not to show itself for a little time, and that the more recent the acquirement, the more rapidly is the power lost. Whether this last is a constant law we cannot say with absolute certainty. It is, however, a law of singularly wide application, this law that characters of more recent acquirement are those which are most easily lost, and its corollary that the older the character or property the more tenaciously is it retained. Specific properties are more firmly fixed than racial, racial than familial, and to this law we shall have frequently to refer. But, while admitting this, we are compelled to recognize that properties impressed upon the cell are retained for a longer or shorter period after the conditions which led to their acquirement have ceased to act. There is, as it were, a constitutional inertia, and this is at the base of heredity.

We can only explain it by assuming that, whereas at first the modified constitution of the side-chains and primary molecules was due to the actual incorporation of dissociation products of the novel foodstuff, once these molecules become part and parcel of the biophores, these have the power to attract and combine not merely the already partly elaborated dissociation products of the foodstuff, but also simpler combinations of other origin, and to combine these in due proportions. We must admit that the biophores are capable of synthesizing (if the expression be permitted) the simplest hydroxyl ions, carbon compounds, etc., present in the cell sap, so that from them rings or primary molecules identical with the original continue to be produced.

In favor of this hypothesis, certain calculations of McFarland may here be quoted:[1]

A horse may easily be so immunized against diphtheria that each cubic centimeter of its blood serum comes to contain 500 immunizing units of diphtheria antitoxin. Such a horse, it is calculated, has circulating sufficient blood to furnish 30 pounds—or 15,000 c.cm.—of antitoxic serum, of which 1 c.cm. will protect against, or neutralize, 225 c.cm. of the toxin. The amount of toxin injected to furnish such an immunity is 4200 c.cm. As against this amount injected, the productive energy

[1] Text-book upon Pathogenic Bacteria, fourth edition, Philadelphia, 1903 : 125

of the immunized horse is adequate to neutralize 3,375,000 c.cm. of toxin; or, in other words, the blood drawn from his body is sufficient to protect 806 horses from doses of toxin as large as the total amount administered during the entire course of treatment, or against a very much greater amount than what, injected into an *untreated* horse, would lead to its death (1 c.cm. of strong diphtheria toxin administered to an untreated horse has, on more than one occasion, been followed by the death of the animal). It is obvious from these figures that the injection of a given amount of toxin leads to the development within the organism of not simply a corresponding, but a vastly increased, amount of antitoxin. What is more is that if a treated animal be bled repeatedly, and the floating antitoxins be largely removed, the newly formed blood comes in a few days to contain amounts approaching those present previous to the bleeding.

Resumé.—Before proceeding farther it will be well to sum up the successive stages in our argument:

1. All living matter exhibits obvious adaptation to the conditions under which it manifests its activity.

2. Specific and racial adaptation is best understood from a study of individual and cellular adaptation.

3. Study of individual and cellular adaptation demonstrates clearly that adaptation is a regulated process, and not the result of chance. Modify the conditions of life of one of the bacteria in certain particular directions, and, provided the modifications be not so severe as to arrest vital activities, the bacteria inevitably exhibit modifications in their properties, and these modifications are in direct relationship, or adaptation, to the particular alteration in environment.

4. The study of immunity shows that what is true of the simplest unicellular organisms obtains also with individual cells in the highest animal forms.

5. Modifications in properties demand modification in the constitution of the cell substance; at base, therefore, adaptation indicates molecular alteration and rearrangement in the living matter of the cell. At base, therefore, we have to seek a chemical or physicochemical explanation for adaptation.

6. We find this according to the biophore theory, which regards the molecules of living matter as arranged as rings, and rings of rings, each ring being capable of attracting and affixing ions from the surrounding medium and building these up into side-chains.

7. The rings of which the biophores are composed are, we hold, of proteid nature, and the tendency of protein molecules to undergo polymerization indicates that the side-chains are built up as polymers, *i. e.*, are also of proteid type.

8. What happens in adaptation, therefore, would seem to be this, that with modifications of environment new compounds are introduced into the cell sap; these undergo or have undergone dissociation into their constituent ions, and these new ions, either replacing other groups of ions in the cell sap, or having greater affinities to the mole-

cules of living matter, become fixed by those molecules and built up into side-chains. In this way we have the first alteration in the constitution of that living matter; they come to possess altered side-chains.

9. Such side-chains may (*a*) when complete become detached and free in the cell sap or be discharged into the surrounding medium, or (*b*) may become units in the building up of new cytoplasmic and biophoric (nuclear) molecules.

10. Once the living matter of the cell becomes modified to the extent that new biophores have been produced by reduplication, or, more exactly, growth, that modification is apt to persist and this long after the agent which caused the modification in the first place has ceased to act. The only valid explanation of these facts is that, while at first the specific dissociation products of the substance causing the modification were built into the side-chains and biophores, once these biophores or other molecules of living matter have assumed a particular constitution, they possess the power of attracting to themselves, and of building up into side-chains and new molecules, other and simpler ions in such proportion that from them they synthesize components of the side-chains and rings identical to the dissociation products of the substance which primarily brought about the modification.

Adaptation to Physical Alterations in Environment.—Thus far we have, for simplicity sake, taken into consideration only modifications in the cell produced by "foodstuffs." It will already have been determined by the reader that under this term is to be included everything capable of providing ions which can be seized upon by the living molecules and incorporated into side-chains or utilized for growth. The term is useful as implying this idea, but it must be kept in mind that under it we include a large variety of substances—toxins and other poisons, for example—which ordinarily do not enter into our conception of "food." Our argument, in short, holds for all the adaptations in response to change of a chemical nature in the environment of the cell, with one possible exception, namely, that there may be substances absorbed or diffused into the cell which do not directly afford ions to be taken up by the molecules of living matter, but which break up matter already present in the cell, thus indirectly affording ions capable of utilization. This possible exception does not invalidate our main argument. It affords, indeed, a connecting link whereby to attach another series of phenomena, namely, the adaptations to physical, as distinguished from chemical, changes in environment. Changes in temperature, light, vibrations, do not introduce new ions into the cell from without; they tend, however, to modify the dissociation of the matter already within the cell, nuclear, cytoplasmic, and paraplasmic, and modifying the number and relative abundance of the different orders of free ions, they in a similar indirect manner must bring about change in the constitution of the biophoric molecular complex.

We possess, indeed, accurate observations upon the capacity of the lower forms of life to adapt themselves to temperature changes. The

earliest were those of Dallinger,[1] who by a very gradual increase in th temperature of the water in which they lived, extending over sever months, accustomed infusoria, normally killed by a temperature 25° C. to endure a temperature of 70° C. Davenport and Castle[2] hav shown that tadpoles reared from the egg and kept at 15° C. for a mont pass into heat rigor at a temperature of 40.3° C., whereas those reare at 24° to 25° C. do not manifest heat rigor until 43.5° C. is attained.

From a general biological point of view these data regarding ind vidual and cellular adaptation are of the very highest importance, an our conception of the means whereby it is brought about, afford th necessary key to an understanding of variation, its origin and limit tions, and through this to the process of evolution. We shall have t refer to these matters to some slight extent in later chapters. Her we would only lay stress upon the fact that cellular structure is th expression of the chemical constitution of the cells, that histologic alteration presupposes modification in the arrangement and intimat constitution of the molecules of living matter, and lastly, that for th modifications to be more than merely transient the biophores or con trolling molecules of living matter must have undergone alteration.

From a pathological point of view the data are of equal importance We shall see that disease is two-sided. We have, on the one side, t regard the noxæ, or influences acting from without, setting up disturb ances in cell activities; on the other side, the reactions on the part c the cells induced by such noxæ. And these reactions all come unde the heading of adaptations to changed conditions. It is, perhaps more correct to speak of these reactions as "tending to adapt," for tim and again the adaptation is far from perfect. But in all the reactiv processes we can recognize the existence and action of the same basa principles which are to be made out governing the microbe whe its environment is altered—when a new sugar is introduced into it pabulum, and it proceeds to become modified, owing to the presence c that sugar and its dissociation products, with the result that the suga becomes utilized as a foodstuff, and with this the microbe not merel accustoms itself to, but takes advantage of, the changed condition These considerations lead us to another possible definition of disease *i. e.*, that "it is the expression of a reaction on the part of the cells t injurious agencies," just as the normal processes in the body are reaction to normal stimuli.

[1] Jour. Roy. Micr. Soc., 3: 1880: 1.
[2] Arch. f. Entwick. Mech., 2: 1895: 227.

CHAPTER X.

CELL AND TISSUE DIFFERENTIATION—INDIVIDUAL DEVELOPMENT.

MERELY to describe in outline the embryogeny of one of the higher vertebrates would demand more space than can here be afforded; we must take it for granted that the reader is familiar with the general details of the process. For our present purposes all that is necessary is to lay down that by successive division and redivision a single cell—the fertilized ovum—gives rise to all the cells which form the tissues and parts of the multicellular animal; that in the earlier periods of embryonic life the cells, the result of this division, show little sign of differentiation, but as development proceeds, differentiation becomes more and more marked in a larger and larger number of the cells, until at birth the separate organs, or almost all of them, are formed of constituent cells recognizably different from those of other organs, even if the full differentiation of the same is not completed until some considerable time later. In other words, with progressive segmentation we pass gradually from the undifferentiated, or apparently undifferentiated, ovum to the most highly differentiated cells of the various tissues.

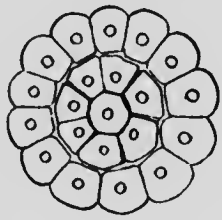
What we have now to consider is the means whereby this differentiation has been brought about, and this, again, not merely as an academic quest, but because in various states of disease we encounter extensive alterations in the characters and appearances of the cell of affected areas, and a knowledge of the laws governing the normal process of cell differentiation is essential for a comprehension of the abnormal processes. And here, at the outset, we would ask the reader for the time being to dismiss from his mind all thoughts of the modifications induced by the sexual fusion of the germ cells. These modifications are of a different order, and will be discussed in a subsequent chapter. The existence of parthenogenesis—of the development of individuals from non-fertilized ova—and the data gained from the abundant experiments on development initiated by physical and chemical means without spermatozoic fertilization, which we owe, in the first place, to Jacques Loeb,[1] prove that tissue differentiation is primarily independent of fertilization. For the present it will simplify matters to leave out of account the meaning and influence of this process.

[1] For a fuller study of these observations and of vital phenomena in general the reader may be recommended to Loeb's most interesting and suggestive lectures on the Dynamics of Living Matter, Columbia University Biological Series, New York, 1906.

Let us, in the first place, recall what we said (p. 34) regarding our conception of the multicellular individual, namely, that this is to be regarded, not as a colony of individual unit cells, which have become and remained united for mutual benefit, but as a unit mass of living matter which, by increasing the surface presented to the external medium, has continued to remain a unit in spite of growth and increase in volume, and has preserved the due proportion between surface and mass through the agency of nuclear, followed by cell, division, the component cells in general being not wholly isolated, but remaining connected by cytoplasmic bridges.

1. In such a process, with continued nuclear division and distribution of the biophoric material into the constituent cells, inevitably that material is subjected to different influences. Just as in the free-swimming unicellular organs we note that a differentiation presents itself between the external and the internal cytoplasmic substance—the former being directly acted upon by the surrounding medium and becoming modified into the denser ectoplasm—so, to take the simplest

FIG. 25



case that presents itself, in the even division of a spherical cell into a spherical cluster of cells, it must inevitably happen that those cells which are superficial are exposed to conditions distinct from the conditions acting upon the cells of the interior of the mass. And, remembering what has been said in the preceding chapter regarding the capacity of living matter to adapt itself, it is obvious that through adaptation the biophoric matter of the superficial cell layer will become modified, as compared with that of the deeper cell mass; and this modification in the constitution of the living cell substance will show itself in structural differentiation.

We gain, that is, our simplest and most natural explanation of cell differentiation by regarding it as *primarily* the result of adaptation to modified environment.

2. Accepting this as the primary cause of cell differentiation in the unicellular organism, it follows that if there be two primordial cells possessing biophoric matter of identical constitution, and these each, under like conditions of environment, undergo conversion (growth and division) into a multicellular mass, then the component cells will undergo like differentiation. This, incidentally, is a basal law of heredity proper.

3. If, on the contrary, the composition of the biophoric material in two such primordial cells varies, then, although these be subjected to like environment, the cells resulting from their division will be affected diversely by that environment, and cell differentiation in the two resultant multicellular organisms, even if along the same lines, will nevertheless be distinct.

Granted the existence of living material after the order of biophores (as being at basis a chemical compound, however complex), and of adaptation, these must be our three primary postulates. And cell differentiation in the multicellular organism is to be regarded as essentially the outcome of relative position in a complex of cells derived from one common biophoric material of particular constitution, subjected to the influence of a particular environment; that biophoric material becoming modified according to the influences brought to bear upon it in the different areas of the cell mass.

EPIGENESIS AND PREFORMATION.

This primarily. But a halt must be made. Are we justified in regarding the biophoric material of the ovum as "common," *i. e.*, as constituted of an aggregation of molecules of like order? There is the possibility that (even in the parthenogenetic ovum) the biophoric material is not homogeneous, but is composed of molecules of different orders, and that it is the mode of distribution of these diverse molecules that determines cell differentiation. Here, in short, we have to take sides in a controversy that has waged for close on a century and a half, now one party, now the other, appearing to gain the upper hand—the controversy between the upholders of *epigenesis* and *preformation*, respectively. Although with the progress of time and with fuller knowledge the field of battle has altered its position, the point at issue is essentially the same.

Before anything was known regarding the stages of development of the individual or of embryological histology, what may be termed the natural view held sway, and this was accepted by Aristotle and supported by Harvey as the result of his naked-eye studies of the developing hen's egg. The ovum in its earliest stage was seen to possess no internal structure that by the wildest imagination could be regarded as a minute edition of the future animal. No likeness could be made out between the germinal disk and primitive streak and the future chick. The natural view, therefore, was that the individual developed by the successive transformations of a germinal substance which originally was without form and without parts.

Only in the middle of the eighteenth century was this view called in question. Bonnet[1] recognized in the developing ovum an unfolding or "evolution" of invisible small parts. These parts, he held, are

[1] Considerations sur les corps organisés, Amsterdam, 1762.

present in the ovum from the first; are preformed. The ovum contains a "miniature model," as he unfortunately termed it, of the perfect animal—a model which he was careful to say is not exactly like the perfect animal, but consisted of "elementary parts" only. Bonnet had not observed the earlier stages of the chick. Caspar von Wolff[1] had, and saw clearly that the fertilized egg, as it proceeded to develop into the chick embryo, exhibited nothing that could be regarded as a "miniature model." He actively opposed Bonnet's doctrine of preformation.[2] The simple egg substance became modified under the action of its inherent formative power until, through continual new formations, and transformations more and more complex, the perfect animal was developed. And for a long period Wolff's "epigenesis" was the accepted doctrine, and this even after the development of studies of the cell showed that the ovum was by no means the simple substance which Wolff held it to be, and after the doctrine of vitalism rendered the conception of an inherent formative force unacceptable. For, on the whole, the successive discoveries of the embryologist favored Wolff's view. The morula and blastula stages of the embryo, the formation of the three germ layers, can only in an indirect way be dragged in to support the preformation theory.

Neither doctrine, as originally enunciated, is valid in the light of our present knowledge, but still the contest continues, and has, by Weismann,[3] been brought down to the biophores.

"Two fundamental assumptions," he states, "present themselves, and these can be related to every conception of germ plasm. . . . Either we may think of the id[4] as made up of similar or of different kinds of parts, none of which has any constant relation to the parts of the perfect animal, or we think of it as composed of a mass of different parts, each of which bears a relation to a particular part of the perfect animal, and so, to some extent, represents its primary constituents. The assumption of a germ plasm composed of similar parts, which has been made, for instance, by Herbert Spencer, may be called the modern form of epigenesis, while the other assumption is the modern form of the (preformation) theory. The former theory can only explain development as induced by the influence of external conditions—temperature, air, water, gravity, position of parts—upon the chemical components of the germ plasm which are everywhere uniformly mingled, and it makes no difference whether this uniform germ plasm is thought of as composed of many different kinds of parts, so long as these parts are mingled uniformly to make a germ plasm and bear no relation to definite parts of the developing animal." We have quoted this *in extenso* because it

[1] Theoria Generationis, 1759.

[2] We use this term in place of Bonnet's own "evolutio," so as to prevent a very possible confusion.

[3] The Evolution Theory. Translated (and that into clear and excellent English) by J. Arthur Thomson, London. Arnold, 1904, vol. 1, pp. 350 et seq.

[4] The unit mass of biophores, or, according to Weismann's terminology, of nuclear chromatin, capable of giving origin to the complete individual.

states so accurately the conditions of the problem. Are we to regard the biophores present in the ovum of a given species as potentially of equal value, so that if in the process of cell division the biophore which finds itself in a nerve cell will have undergone those changes which convert it into a neuronic biophore; if, on the contrary, it has passed into a liver cell, the successive changes it has undergone in growth and multiplication have modified it into an hepatic biophore? Or, on the contrary, are we to suppose that the biophores present in the ovum are most varied in their constitution—that there preëxist in it biophores of the neuronic, hepatic, muscular, osseous, connective tissue, germ cell, and other types (the list could be lengthened prodigiously) which in the process of segmentation of the ovum are sorted out and distributed into the cells which form the *anlagen*, or basis of the different specific organs and tissue cells, and, entering these cells, control, or, more exactly, cause the differentiation of the same?

The point, it will be seen, is one of great importance, since our views not merely of tissue and cell differentiation, but of the broader subjects of evolution and heredity, materially depend upon which theory we accept. Weismann upholds stremuously the preformation theory, and as his views are widely quoted, it is necessary to inquire into his arguments.

Ontogeny (the development of the individual), he states, is not an isolated phenomenon, which can be interpreted without reference to the whole evolution of the living world, for it is most intimately associated with this, being, indeed, a piece of it. *Ontogeny must be explained in harmony with phylogeny* (the evolution of the race), *and on the same principles.* The assumption of a germ plasm without primary constituents, or of a completely homogeneous germ plasm, is irreconcilable with this, for it contradicts certain facts of inheritance and variation.

We take it that what Weismann means by this broad and rather vague pronouncement is that, to afford an example, if the lepidopterous insect, before attaining full development, has to pass through the caterpillar and chrysalis stages, this can only be explained by the preformation theory; that epigenesis is unable to explain the metamorphoses; that the effect of environment, merely, on the germ substance of the lepidopterous ovum would render the intermediate stages unnecessary, would cut them out, and would remove the manifold indications which individual development affords of the evolution of the race. We freely admit that, as a matter of fact, ontogeny affords most valuable indications as to phylogeny—that it is an abbreviated phylogeny, but how greatly abbreviated those who currently repeat this dictum are apt to slur over. The human embryo is at no period a pure worm, a perfect fish, a simple saurian; certain characteristic features only at certain stages are capable of explanation by the one theory alone—the theory that these features are reminiscences of the phylogeny. The retention of these features does not, however, demand the existence of *determinants*, *i. e.*, of biophores or groups of biophores of special constitution having the particular function of developing these par-

ticular features of special biophores which have descended unchanged from the annelid, fish, or saurian stage of existence; it can be explained more simply by the supposition that all the properties of the cells of the different tissues are the result of modifications of one common biophoric matter, these modifications being impressed upon that matter by the successive influences that have acted upon the cells in the course of development. From which it follows that we may regard it as essential that the cells which are ultimately to form certain organs shall have passed (or their progenitors shall have passed) through certain stages, in order that the contained biophores may undergo a particular line of modification. When the same result can be attained by a "short cut," this is done; whence it happens that the ontogeny does not by any means represent the full phylogeny. A very little knowledge of embryology furnishes abundant examples of these short cuts and of cases in which, in closely allied species, development is abbreviated by widely different "short cuts."

This argument, then, against epigenesis—if we understand Weismann's argument aright—is not unanswerable. His next appears, *prima facie*, to be more convincing. The existence, he urges, of a white lock of hair through several generations can only depend ultimately on a divergently constituted part of the germ plasm, which can only affect the one spot on the head and alter it, if it is itself different from what is usual. "On this account I call it the *determinant* of the relevant skin spot or hair group." In a germ plasm without primary constituents the variation could only depend on a uniform variation of all the parts, for the parts are either alike among themselves or, at any rate, have the same value for every part of the finished organism. How could an animal differing only in one minute part arise from a germ plasm which has varied in all its parts? There are five well-marked variations of the Indian species of butterfly, *Kallima paralecta*, in which the variation is in the markings on the under surface of the wing, *while the upper surface is alike in all.* How is this to be explained by the epigenetic theory? If each individual variation of the species depended on a variation of the whole germ plasm, the wood *Kallima* would soon bear no resemblance to its ancestral form, the meadow species. There must be primary constituents in the germ plasm, that is, vital units whose variation occasions the variation of definite parts of the organism, and of these alone.

As a consequence, Weismann has elaborated a scheme of inheritance in which the biophores (which he regards as supramolecular rather than molecular—as aggregates of molecules) are combined to form determinants or biophoric groups, each of which controls or determines the structure and function of one particular cell area of the body, and he assumes further that these determinants are combined into *ids*, each id containing the full complement of determinants necessary to give origin to the complete individual—numbers of these ids arranged serially are regarded as being present in the "idants" or "loops" of the wreath or aster of the nucleus of the ovum—the separate ids being

conveyed to the ovum from different ancestors, and according to the ids which thus happen to pass into a particular ovum, so does one or other group of determinants derived from different ancestors come to gain control in the development of the individual. But of this more anon. We mention this here solely in order to give an idea of the relative size of these determinants as demanded by Weismann.

We could bring several arguments to bear against this chain of reasoning of Weismann's; could inquire, in the first place, whether Weismann is justified in assuming that where two varieties of a species exhibit *to the naked eye* only one single morphological point of differentiation, that is, the only difference between them—whether more careful study would not demonstrate numerous concomitant variations not merely morphological, but functional also. We could quote the recent remarkable and extensive studies of Max Standfüss upon the experimental production of variation in butterflies, demonstrating that quite an extensive group of varieties which hitherto have been regarded as essentially due to difference in constitution of the germ substance—of the biophores of the germ cells—are due to the action of environment upon the germ substance, variation in the temperature to which the fertilized ova are subjected during the course of development sufficing to bring about an extraordinary variation in the coloration and marking of the eventual butterfly, a given temperature leading with striking constancy to a particular result. One single consideration, however, suffices to demolish the whole of Weismann's theory—the consideration, namely, that it is a physical impossibility that the id could contain all the requisite determinants; they could not be compressed into the space afforded, even were they atoms and not, as he demands, collections of biophores, and these biophores not merely molecules of proteid nature and relatively great size, but collections of the same. We have already called attention to this *reductio ad absurdum* of Weismann's theory.[1] It is based upon Lord Kelvin's most ingenious and physically exact demonstration of the size of the molecule of water—exact, that is, so far as it affords the limits. Weismann[2] freely admits, regarding determinants, that "in the higher multicellular organisms, as, for instance, in most arthropods, the number must be very high, reaching many thousands, if not hundreds of thousands, for in them almost everything in the body is specialized and must have varied through independent variations in the germ." And to make his image of these determinants quite clear, he adds: "In multicellular organisms I should be inclined to picture the determinants as a group of biophores which are bound together by internal forces to form a higher vital unity. This determinant must live as a whole, that is, assimilate, grow, and multiply by division, like every vital unit, and its biophores must be individually variable, so that the separate parts of a cell controlled by them may also be capable of transmissible variation.

[1] Adami, Inheritance and Disease, Osler's System of Medicine, vol. I.

[2] Loc. cit., p. 370.

If the diameter of the largest possible bubble blown from a known amount of water be accurately measured, it is a matter of simple mathematics to determine the surface area, and from the surface area to determine the thickness of the film which that amount of water has expanded. This Lord Kelvin did. It is obvious, further, that *at its thinnest* such a film could consist of merely a single layer of molecules, and, conversely, that the diameter of an individual molecule of water *could not be greater than* the thickness of the film. Nor, on the other hand, could it be much less. Working along these lines, he arrived at the conclusion that in a line 1 μ (one one-thousandth of a millimeter) in length there could only be about 300 molecules of water. The smallest body we can study under the one-twelfth immersion lens has a diameter of about half this length, namely, about 0.5 μ,[1] and this is about the diameter of the chromosomes in the nuclei of certain cells undergoing mitosis (*e. g.*, those of the salamander), which Weismann regards as representing his ids. For comparison we may state that these chromosomes are distinctly smaller than the Pyococcus aureus. Across the diameter of such a chromosome or id there could, therefore, be stretched in series only about 150 molecules of water.

But now the molecules of living matter are admitted to be of proteid nature—or, if not proteid, even more complex—and protein molecules, according to all observations, are, even the simplest of them, vastly larger than the molecules of water. As already stated, the simplest protamines, like sturin, are given the formula of $C_{30}H_{69}N_{19}O_9$; and hemoglobin, which is not one of the most complex, has the formula $C_{68}H_{1098}N_{211}O_{240}FeS_2$. The molecular weight of the ordinary proteid is estimated, roughly, at about 15,000. While, therefore, 150 molecules of water could occupy a line 0.5 μ long, the number of proteid molecules occupying this space must be very small; indeed, as indicated by other considerations also, it is clear that some protein molecules closely approach the limit of visibility—if, indeed, by the recently discovered "ultramicroscopic" methods we are not able to see them.

If, then, the biophores are, according to Weismann's conception, not simple molecules of proteid type, but aggregations of the same, the determinants composed of aggregations of biophores should be recognizable under the highest powers of the microscope, and the id formed in the higher animals, of thousands and tens of thousands of biophores, must inevitably be a body of from thirty to three hundred times the diameter of the determinant—so large, that is, that if it existed, it must have been recognized from the moment the nucleus of the cell was first observed—and if, as Weismann supposes, the nucleus of the ovum contains hundreds of ids derived from numerous ancestors, that nucleus would fill the whole field of the microscope! Needless to say, this is not the case; nor, we may add, does the coarseness of the nuclear structure vary materially according to the complexity of the

[1] According to Abbé, from physical considerations 0.2μ is the ultimate limit of visibility by the compound microscope as at present developed.

animal. Physically, therefore, Weismann's conception is an impossibility, and, as Weismann has carried this conception of preformation to its logical outcome, it follows that, in demonstrating the impossibility of his theory, we simultaneously destroy all less fully developed theories of preformation.

Determinants, in Weismann's sense, cannot exist, and we must accept (with reservations, to be noted when we come to discuss the fertilized ovum) the alternative theory of epigenesis—the view that there exists primarily a single biophoric substance which in its growth and distribution to the various cells of the developing animal is subjected to varying influences whereby it becomes modified, and whereby the cells governed by it come to assume diverse functions and diverse structure. There is a preformation, but of the common biophoric substance alone: this must differ in the different species. And there is an evolution, or unfolding, but the nature of this unfolding is of this order, that, given growth and cell division, the biophoric material subjected to a particular environment inevitably undergoes a definite series of transformations; and the different orders of cells, tissue, and organs are the result of the diversity of influences acting upon the one common biophoric material of the ovum.

So far, let it be remembered, we have studiously kept out of consideration the facts of fertilization. It has seemed to us that we could make our statement of first principles clearer by neglecting them for the time being. Now we have reached the point at which they can no longer be neglected, for, obviously, in the gamogenetic individual—the individual resulting from the union of the male and female germ cells—there is not a common biophoric substance; in them, at the moment of fertilization, at least, there are biophores of two orders, and it may be of many more, for, the parents being unlike, the biophores which controlled their growth must presumably have been unlike, and the same is true of all the ancestry. How, then, can we combine the conception of epigenesis from a common biophoric material (minus determinants, in Weismann's sense) with this necessary existence in the fertilized ovum of biophores of different constitutions? This we shall discuss in the next chapter.

THE MOSAIC THEORY.

But before leaving this portion of our subject there is a somewhat weighty objection to the theory of epigenesis which cannot be passed over in silence. The more carefully we study the earliest stages of segmentation of the ovum in the various forms of life the more clearly we recognize that, after the first or second division, the blastomeres or resultant segmentation cells, begin to show signs of differentiation. In other words, cells *apparently subjected to identical environment* exhibit structural differentiation.

This point was emphasized strongly by Weismann in some of his

earlier writings, and has been more particularly studied (1888) b Roux, of Breslau. The ovum in its earliest stages segments first alon one median plane into two cells (or blastomeres), then each of thes subdivides along a plane at right angles to the former, a four-cell stag being produced, and subsequently an eight, sixteen, thirty-two ce stage, etc. In certain most interesting observations upon the germinati frog's eggs, Roux[1] showed that by destroying one or other of the blasto meres in their earliest stages he could produce monsters of defect, on or other region of the body being undeveloped according to the ce destroyed. If, in the four-cell stage, for example, one of the blastomere be destroyed by means of a heated needle, a frog may develop wanting on entire quarter of the body. The conclusion appears obvious that in th segmentation of the ovum, with the first division the determinants fro one-half of the body pass into one of the primary blastomeres, those fo the other half into the other; and that when these two divide, the deter minants for the front half of the right side pass into the right anterio blastomere, for the hinder half of the left side into the left posterio blastomere, and soon. And more particularly from these observation be developed what has been termed the "mosaic theory" of development that "the development of the frog gastrula and of the embryo forme from it is, from the second cleavage onward, a mosaic work, consistin of at least four vertical independently developing pieces;" organization that is, precedes cell formation.

But in the course of these observations Roux himself was the first t note that, where he destroyed one of the cells in the two-cell stage instead of gaining a half embryo (unilateral), he might gain a whol though dwarfed, individual; and later, Driesch[2] conducted a mos suggestive series of experiments. Taking the eggs of the sea urch in the two- and four-cell stages, he was able, by shaking, to separate th cells, each of which gave rise not to half and quarter embryos, but t entire, though dwarfed, larval forms. E. B. Wilson[3] obtained eve more striking results with amphioxus eggs, while, not to mention severa other confirmatory observations, Zoja,[4] in certain jelly-fish (medusa obtained perfect embryos, though correspondingly dwarfed, from th separated blastomeres of the sixteen-cell stage.

We shall have later to point out how these observations throw ligh upon the development of certain twins and double monsters. Wha we have to indicate here is that they absolutely contradict the mosai theory. They show that in the earliest stages, and the same, we ma presume, is the case in the later stages, the division of the cell—th ovum—and its nucleus is into similar parts. The daughter chromo somes are of equal value qualitatively and quantitatively.

But how are these facts to be reconciled with the opposed facts o

[1] Virchow's Archiv, 114: 1888; see also Anatom. Hefte, February, 1893.

[2] Zeitsch. f. wissensch. Zoölogie, 53: 1892.

[3] Jour. of Morphology, 8: 1893.

[4] Arch. f. Entwickelungsmechanik., 1 and 2: 1895.

Roux? This has been solved by Morgan.[1] He has shown that in the frog's eggs, if, after the destruction of one blastomere, the other be allowed to remain in its normal position, a half embryo develops, conformable with Roux's observations; if, on the other hand, following the action of gravity, it becomes inverted, it most frequently gives rise to a whole dwarf, although in some of his experiments, even under these conditions, the half embryo developed. Wilson has obtained similar results with amphioxus eggs. Through these and allied observations, it has been determined that the different components of the ovum assume naturally particular relations, the one to the other. This is largely a mechanical matter. Thus, in the frog's egg the stored food material, yolk or deutoplasm, is heavier, and sinks, while the lighter nucleus and cytoplasm rise, and so far, it would seem, from purely mechanical causes there is developed a *polarity* in the ovum. Similarly the pigment in the frog's egg collects, or is developed, at the upper pole —the part exposed to the greater amount of light. Thus we have indications that in the very earliest stages the fertilized egg obtains polarity; or, otherwise, that the different constituents—nucleus, cytoplasm, and paraplasm (deutoplasm)—take on a definite arrangement, which in itself determines to a large extent the subsequent course of cell division; if this arrangement be disturbed, then that subsequent course is liable to alteration. We can, that is, given these data, harmonize apparently contradictory facts, and, what is more, can from them gain an understanding of how it may come to pass that without determinants there may be potential cell differentiation in the very earliest stages of the segmenting eggs. Briefly, while the nuclear biophores are to be regarded as the controlling agents in the cell, their activity is determined by the surrounding cytoplasm and deutoplasm, and the relations of these three again are determined by physical agencies.

This controversy is still raging regarding the "mosaic theory," or, more definitely, regarding prearrangement of blastomeric constituents prior to segmentation and the meaning of the same. The reader will find a fuller discussion in Professor Wilson's work on the cell. It will be seen that our conclusions very largely agree with his. Here we must call attention to the fact that there are certain fertilized eggs whose separated blastomeres cannot be brought to form complete dwarf individuals, but always—under the conditions of experiment—develop into partial larvæ. Nevertheless, these cases cannot be adduced in favor of determinants. The separated blastomere of the four-cell stage of the gasteropod *Ilyanassa*, for example, contains biophoric matter which, under normal conditions, would eventually give rise to germ cells, *i. e.*, to cells capable of giving origin to whole individuals. This notwithstanding the blastomere only develops into a quarter larva. The matter capable of developing the whole individual is present; there must, however, be some arrangement, some mutual relationship of biophores, cytoplasm, and paraplasm which inhibits the full devel-

[1] Anat. Anzeiger, 10: 1895: No. 19.

opment. Modifying Driesch's[1] conclusion, we may say: the relative position of a blastomere in the whole agglomeration of blastomeres, coupled with the relation of the parts in that blastomere, determine in general what develops from it; if these relationships be changed, it gives rise to something different; to this extent "the prospective value of the blastomere is a function of position"- ..cting upon biophoric constitution.

This power of single cells to produce the entire body ' general, limited to the earliest cleavage products, with the one p'.a.ment exception of the germinal blastomeres—cells that can be distinguished or followed back to a very early period in the embryo—which are destined to give rise to the germ cells. In certain of the lower multicellular animals there are indications that the body cells in general retain this property, as again in certain plants—the trite examples are the *Hydra* and the *Begonia*; but even in these it is at least questionable whether a single cell has this capacity. In these cases we are unable by experiment to isolate a single cell, and when the removed portion is below a certain size no results ensue. It is therefore probable that for the reproduction of the whole individual from the body cells there must be present representatives of the different germ layers—a collection of ce'ls rather than a single cell. In the higher animals, at least, a distinction between germ cells and somatic cells is very marked, and it may be laid down as a general principle that *the more pronounced the differentiation of a cell, the less its capacity, not merely to reproduce the individual, but also to reproduce itself.* In these higher animals, judging from the data regarding homologous twins and multiple births, and more particularly from Spemann's experiments upon the eggs of the newt, not beyond the gastrula period are we able to divide the embryo so that each half gives rise to the whole individual. With the development of the primary germ layers the constitution of the biophoric material has already become so modified that epiblast cells give rise to epiblastic structures only, hypoblast to hypoblastic. The apparent exceptions to this law we shall discuss in the chapter on Metaplasia. It is the existence of this law that permits us to classify the new growths or tumors. (See Chapter on Neoplasia.) And when we study the fully developed tissues we find that the cells which are the most highly differentiated of all, namely, the neurons, or nerve cells proper, have completely lost the power of reproduction; once fully formed, they cannot multiply. Other well-differentiated cells—muscle cells, gland cells, and even squamous epithelium—have retained the power of reproduction, but gland cells can only give origin to gland cells, muscle cells to muscle cells, epithelium to epithelium, and when fully developed they can only multiply after undergoing a preliminary "Ent-differenzierung," or undifferentiation, reverting to a simpler, less differentiated stage. The developed muscle cell, before it can multiply, loses its striation, reverts to a more embryonic type, its nuclei multiply, and each becomes surrounded by apparently undifferentiated protoplasm; the gland cells, to a large extent, lose their

[1] Studien, IV, Zeitsch. f. wissensch. Zoölogie, 55: 1893: 39.

specific granules and paraplasmic matter, the cell body swells and stains poorly; the squamous epithelial cell becomes swollen and more rounded, its nucleus more prominent, its cogwheel-like processes unrecognizable. We shall describe these changes more fully when treating of the subject of tissue regeneration. The more fully we study the differentiated tissues of the body the more it is brought home to us that the fully developed and differentiated cell, as such, exhibits little active multiplication, and that to a very large extent under normal conditions the renewal of cells worn out by use is brought about by the presence and reproductive activity of "*mother cells*," of cells, that is, present in the tissue in a relatively undifferentiated form, or, as we are accustomed to term it, of embryonic type.

For instance, where the skin has been irritated, we find that even well out in the stratum corneum certain cells are swollen as above indicated, and show stages of mitosis. The normal skin does not present evidences of multiplication in these regions; in it the constant loss of surface cells is made up by the mother cells forming the deepest Malpighian layer of the epidermis. This, as every student knows, is a palisade layer of small, simple cells with deep-staining nuclei. These are present throughout life; they never become converted into squamous cells; they exhibit mitotic figures and multiply, and it is their daughter cells given off toward the exterior which, as they pass farther and farther away from the nutrient basis, undergo successive modifications, until they become completely keratinized. There are similar mother cells for cartilage (perichondrium), bone (periosteum, osteoblasts), mucous membranes, and their gland follicles, lymph nodes, etc. In voluntary striated muscle it is probable that the so-called muscle spindles have a like function; in the heart muscle, as pointed out by MacCallum, there exists a layer immediately beneath the endocardium of this mother-cell type;[1] in the brain and nerve centres we have indications that, with destruction of the neurons, certain of the less differentiated neuroglia cells can undergo differentiation and development into neurons.

It is, in short, only the lowest and simplest of tissues that can impartially either perform function or multiply, and even here we note that *Entdifferenzierung* precedes multiplication. The simple connective-tissue cell, with attenuated nucleus and scarce visible cell body, swells prior to multiplication, its nucleus becomes spindle-shaped and deep staining, it gains a recognizable cytoplasmic body, it becomes identical with the spindle cell of developing connective tissue.

How are we to explain these facts in the terms of the biophore concept already laid down? Our conception of the biophores, it will be remembered, is that these primary molecules of living matter have, within relatively wide limits, the capacity of adaptation, *i. e.*, with modified environment undergo structural modification. These facts indicate

[1] The remarkable observations of Tawara in Aschoff's laboratory upon the "Reizleitung system" (Jena, Fischer, 1906) render it urgent that these observations be repeated, to determine the distinction between such cells and those connected with the bundles of His and the conducting system of the heart.

that, with active growth of the fertilized ovum and coincident mu
cation of the biophores, the modifications undergone may be so
siderable that the first cleavage products possess biophores
retain all the properties possessed by the biophores of the ovum
so, like the ovum, are capable of giving rise—if the blastomer
separated—to complete individuals; if they be not separated,
through the interaction of the cells and the polarity of the cell ma
portions only of the simple individual. Rapidly as the cells mu
and the cell mass grows in extent, the biophores contained in eac
become modified. According to their environment, so do the
stuffs assimilated vary, and the groups of ions seized upon and att
to the biophores exhibit variation, with resultant modification i
constitution of the new biophores, until these become so specialize
they give rise to biophores capable only of determining the char
of special orders of cells, incapable of giving origin to all the ord
cells present in the organism. And, as this process continues, ev
ally the elaboration of the biophores in adaptation to particular
tionships and particular function becomes so extreme, their consti
so elaborate, that the capacity to deduplicate, *i. e.*, to multiply, is
the cells containing these elaborated biophores cannot multiply; or i
be more correct to say that the biophores still possess the power of
plication, but this is inhibited by the extreme differentiation o
cytoplasm.

Reverting to what we have written regarding cell energy (p. 8
will be realized that the immediate reaction to external stimul
the performance of function is exerted through the cytoplasm
this is to be regarded as intermediary between the biophores an
external medium; that the performance of function demands disc
of energy on the part of the cell, while, contrariwise, growth dem
storage of energy. From these considerations it follows that the
pronounced the differentiation of the cytoplasm the more is th
prepared to expend the energy acquired from assimilated food
in the performance of function rather in growth. In other word
greater the cytoplasmic differentiation the less the capacity o
biophores to initiate growth and cell multiplication. That this is
strongly supported by the phenomenon of Ent-differenzierung
described; or, concisely, the change from the functional to the vege
type of cell is accompanied by a loss and using up of the cytopl
structures elaborated for the due performance of function in respo
external stimuli.

We cannot sufficiently emphasize this antagonism betwee
katabiotic and bioplastic activities of the cell. It may not be abs
within certain narrow limits, as already indicated (p. 86), the two
surely co-exist; but these limits appear soon to be overpast, an
more the cell prepares itself for the performance of special fu
the less becomes its vegetative activity.

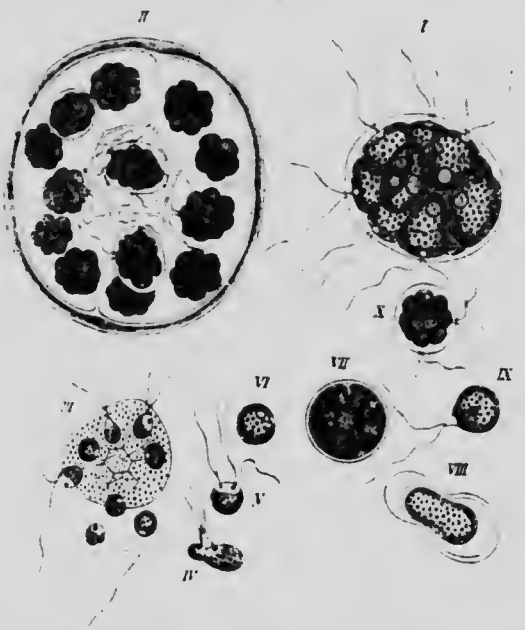
In our study of tumors it will be seen how important is the beari
these considerations upon our grasp of the essential nature of neop

CHAPTER XI.

FERTILIZATION.

Two facts in themselves indicate that sexual conjugation and fertilization, the result of that conjugation, essential as they have become for the continuation of the bulk of living species, are nevertheless of secondary import, or at least not primordial: the facts, namely, that growth, adaptation and cell differentiation can proceed in animals

FIG. 26

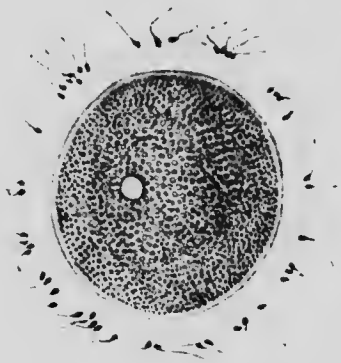


Development of the colonial flagellated Infusorian Pandorina morum, to show conjugation of like sexual cells. *I*, ordinary colony formed of sixteen like cells (persistence of morula stage of embryo of higher forms); *II*, similar colony in which each cell has developed into a daughter colony of sixteen cells; *III*, colony like *I*, in which the cells are escaping from the gelatinous envelope for purposes of conjugation; *IV*, *V*, conjugation of two like individual cells; *VI* to *X*, subsequent stages leading up to development of a cell mass as in *I*. (After Pringsheim.)

developed parthenogenetically, and that in the lowest forms of life long successions of generations have been followed without signs of conjugation being detected; so that we may with security state that in these sexual conjugation does not occur. For these reasons, difficult as

at times it has been, we have, to this point, studiously refrained from considering these processes and their results. Their study introduces a new and complex order of phenomena, which best is taken into account after everything not directly due to sexual differentiation has been passed in review.

Fig. 27



Egg of an Echinoderm with surrounding spermatozoa to show differentiation in size of invasive male, and yolk containing female germ cells. (Korschelt and Heider.)

Here we shall not discuss the significance of that differentiation nor the meaning of fertilization. We will provisionally accept the light afforded by Maupas' observations[1] upon long series of parthenogenetic generations of the infusorian *Stylonychia pustulata*, confirmed as they have been by Calkin's recent most painstaking studies upon long generations of *Paramæcium*, that fertilization is essentially a means of biophoric rejuvenation. Later, we may have a few words to say upon what rejuvenation implies. Indeed, our treatment of the whole of what has now become a very considerable branch of biological research must be brief and eclectic. We can but select those data and general conclusions which lead us forward toward, and supply us with, a foundation for the study of heredity.

Thus, in passing, we may note that the simplest type of conjugation found among *unicellular* forms of life is that of fusion of two wholly similar individuals; that among the *multicellular* forms, whether of animals or plants, we find similarly, low down in the scale, that little differentiation is to be made out between the male and female germ cells, but very soon this differentiation shows itself, so that the one cell —the male or invasive element—becomes motile, to the end that, being attracted, it may actively move toward and penetrate the more passive female element—passive, because it contains in its cytoplasmic meshes a store of foodstuff or yolk, necessary for the active growth which follows fertilization. Of such store material the male element, or spermatozoon, shows the veriest trace; it comes to consist of little beyond nucleus, centrosome, and actively motile tail or flagellum. The disproportion in size of the two elements involved in the act of fertilization becomes thus singularly great.

From a very early period of development of the individual the germ cells, destined to give rise to either ova or spermatozoa, are marked off from the somatic cells, destined to give rise to the tissues of the body in general. In certain insects they have been traced back and recognized at the blastula stage; in the nematode worm, *Ascaris*, Boveri

[1] Archives de Zoologie, 2d series, 7: 1889.

has succeeded in tracing the differentiation back to the results of the first segmentation of the ovum—to the two-cell stage. Not to enter into details of modes of differentiation of the two orders of cells, which vary considerably in different forms of life, we may, with very slight alteration in wording, follow Professor Wilson, and lay down that the difference between the germ and the somatic cells is, that the former retain the sum total of the egg chromatin handed down to them from the parents, whereas, by one or other process, the somatic cells retain only a portion of the same. Following back the descent of cells destined to be germ cells, we find that the series is uniformly rich in chromatin—that there is no primary casting out or reduction; in somatic cells preliminary reduction does occur. "The original nuclear constitution of the fertilized cell is transmitted, as by a law of primogeniture, only to one daughter cell, and by this again to one, and so on, while in the other daughter cells the chromatin in part degenerates, in part is transformed, so that all the descendants of these side branches receive small reduced nuclei."[1] In conformity with what we have already stated regarding the nature of biophoric material, we would suggest that the *somatic blastomeres receive, not so much a reduced amount of chromatin, as a chromatin of modified constitution.*

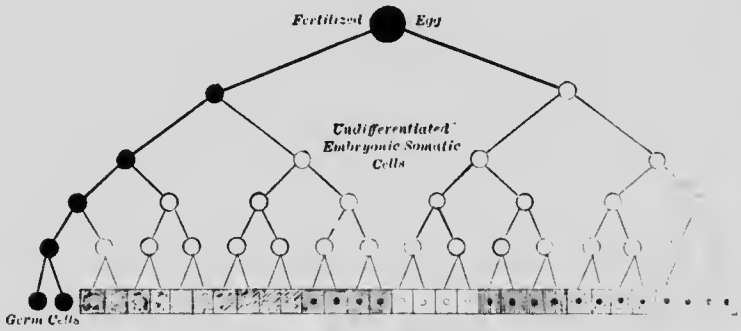
As already hinted, it is still an open question how far the nuclear chromatin is to be regarded as identical with biophoric matter; from the fact that chromatin (stainable material) may disappear from view entirely at certain stages of cell activity in certain of the lower forms, there are those who regard this not as the active living substance, but as a first product of the activity of the same. On the other hand, this loss of staining power has received what is at least a plausible explanation. The more acid the character of the chromatin the greater its affinity for basic dyes, such as hematoxylin. The greater the proportion of unsatisfied nucleic acid in the nucleus, the more intense its staining properties. The intense stain taken on by nuclei prior to mitosis indicates thus a heaping up of bodies of the nature of nucleic acid; if later, as the nucleus breaks up during the process of mitosis the staining power diminishes greatly, this suggests that the nucleic acid becomes combined with (possibly) proteid matter to form nucleoproteids, the compound losing its strongly acid properties. We are agreed that there is the closest possible relationship between the nuclear biophores and chromatin, and that a permanent reduction in the amount of the latter is the expression of a reduction in the amount of the former. Fig. 28 expresses graphically this relationship in descent of the germ cells to the rest of the organism.

In general it would seem that the primordial germ cells are sexually indifferent; the sex of the individual is not predetermined at the moment of fertilization, and the germ cells in the early embryo are potentially either male or female; that, in short, the transformation into the male germ cells (spermatozoa) or the female (ova) is not due to inherent predisposition, but is a reaction to external stimuli.

[1] Boveri: Merkel and Bonnet's Ergebnisse, 1: 1891: 437.

We state this as a probability, for while the bulk of the evidence so far accumulated favors this view, and experiments on lepidoptera, hymenoptera, and amphibia show that the nutrition of the embryo very largely determine the eventual sex, there are cases—the rotifers, for example—in which sex is predetermined *ab ovo*, the eggs being of two sizes, the larger producing females, the smaller males. It may be that here, as in the preceding chapter, in our discussion of the mosaic theory, we shall have to admit the combined action of internal and external cell relationships, and that, to solve the problem, experiments must be undertaken not only upon the nutrition of the embryo, but also upon the nutrition of the parents prior to maturation of the sexual elements—that eggs rich or poor in yolk may afford primordial germ cells rich or poor in foodstuffs, and so tending to give origin, other things being equal, to either female or male elements.[1]

FIG. 28



Schema of germ and somatic cell differentiation. (After Klebs.)

We have pointed out that the primordial germ cells differ from the somatic cells in that they undergo no primary reduction in their chromatin. We have now to point out that a most remarkable feature of the adult germ cells, the immediate precursors of the ova and spermatozoa—the oocytes and spermatocytes, as we may term them—is that in the process of maturation they exhibit a *terminal* reduction.

If we study the mitotic figures in the growing tissues of multicellular individuals, we discover that, with one exception, which we shall have to deal with in studying tumor formation, these exhibit in the aster stage a number of chromosomes or loops of chromatin which is constant for the particular species, and is always even, always a multiple of two. Thus it is 2 in one variety of *Ascaris*, 4 in certain worms, 16 in man, 18 in the sea urchin, 168 in the phyllopod *Artemia*.

In all cases so far studied the mature ovum and the spermatozoon contain or exhibit just one-half the number characteristic of the somatic

[1] The reader will find an interesting and authoritative discussion of these matters in Geddes and Thompson, in the Evolution of Sex. International Science Series.

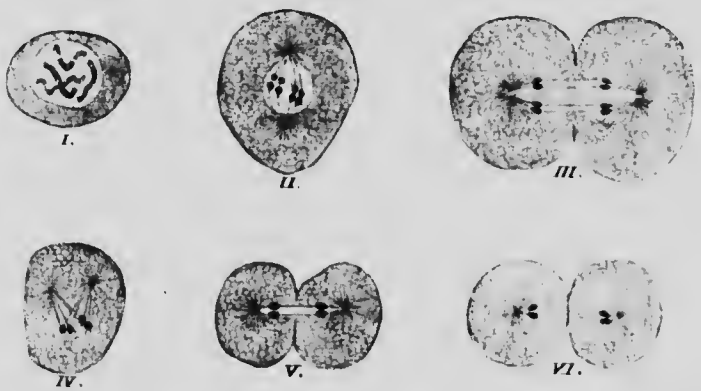
cells of the particular species. The mature ovum and the spermatozoon receive and contain half the number of chromosomes characteristic of the previous generations of germ cells and the somatic cells as a body.

The method of reduction varies in the two sexes, varies also to some extent in different species. The following account gives the stages common in all multicellular organisms, whether animal or plant, omitting details.

SPERMATOGENESIS: THE MATURATION OF THE SPERMATOZOON.

The primordial male germ cells give origin to *spermatogonia*, cells which divide and redivide, with the ordinary number of chromosomes, until, with adolescence, these cease dividing, attain a considerable size, and become known as *primary spermatocytes*. Each divides into two, giving rise to *secondary spermatocytes;* each of these again into two *spermatozoa*. Thus each primary spermatocyte produces four spermatozoa.

FIG. 29

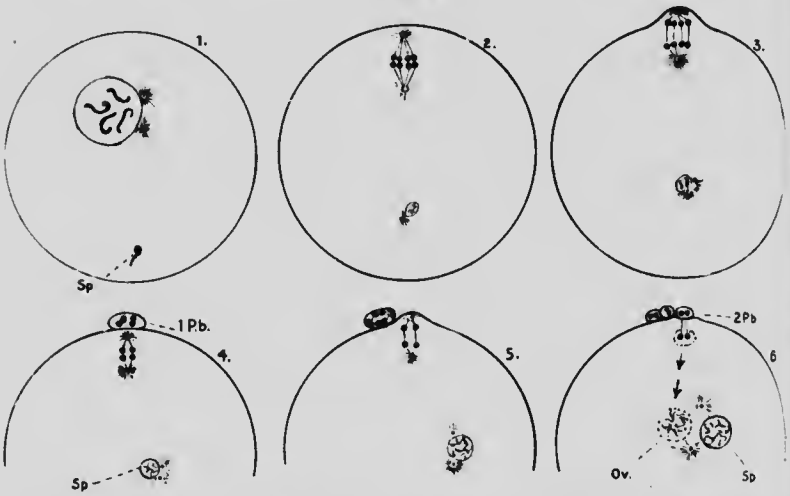


The stages of spermatogenis in *Ascaris megalocephala bivalens*. *I* spermatogonium, with four chromosomes (the normal number for the cells of this species); *II*, primary spermatocyte with two *tetrads;* *III*, primary spermatocyte undergoing division into two secondary spermatocytes, each with two *dyads;* *IV*, secondary spermatocyte; *V*, secondary spermatocyte undergoing division into two spermatozoa, each with two *monads;* *VI*, two young spermatozoa, each bearing two monads. (After A. Brauer.)

Following now the chromosomes, this may be stated: In the ordinary cell prior to division each chromosome splits longitudinally into two, and one of each pair thus formed passes into each daughter cell, which thus comes to possess the same number of chromosomes as did the parent cell. If the parent cell in the monaster stage exhibits eight chromosomes, each aster in the diaster stage is composed of eight members. But now in the primary spermatocyte—supposing, for convenience, that in the species studied the number of chromosomes in the ordinary cell be four—preparatory to the development of the

secondary spermatocytes (or mother sperm cells) two *tetrads* appear in place of eight chromosomes. Each tetrad is a quadruple mass or series of chromatin granules; each of the four parts of which the tetrad is composed is, as we shall point out, the equivalent of a chromosome. This first stage is thus in reality a false reduction; instead of being a reduction process, it is the very reverse. Although there are only half as many tetrads as there are normally chromosomes, these tetrads together contain not four but eight potential chromosomes.

FIG. 30



The stages of reduction in the ovum and formation of polar bodies. Diagram based upon Boveri's observations on the maturation of the ovum of *Ascaris megalocephala bivalens*. 1, entrance of spermatozoon into ovum; 2, formation of two tetrads in place of four chromosomes; 3, first division: formation of two pairs of dyads; 4, expulsion of 1st polar body (1 *P. b.*) containing two dyads; 5, second division of nucleus of ovum, and division of nucleus of 1st polar body: formation in each of two pairs of monads; 6, expulsion of 2d polar body and division of 1st polar body: ovum and each polar body provided with two monads. The arrows, pointing to *Ov.*, indicate subsequent enlargement of the nucleus of ovum and conversion of the two monads into a chromatin network similar to that developed in *Sp.*, the nucleus of the spermatozoon.

With the formation of the spindle each tetrad undergoes halving and each daughter cell (mother sperm cell) receives two *dyads* (or sets of two chromatin masses), and when rapidly the nucleus of the mother sperm cell undergoes division prior to the formation of the two spermatozoa, each dyad in its turn becomes halved. Thus the spermatozoon, or its nucleus, receives two monads, or single chromatin masses. When the spermatozoon gains entry into the ovum, each of these monads enlarges and becomes a typical chromosome, undistinguishable in character from the chromosomes of the nucleus of the ovum.

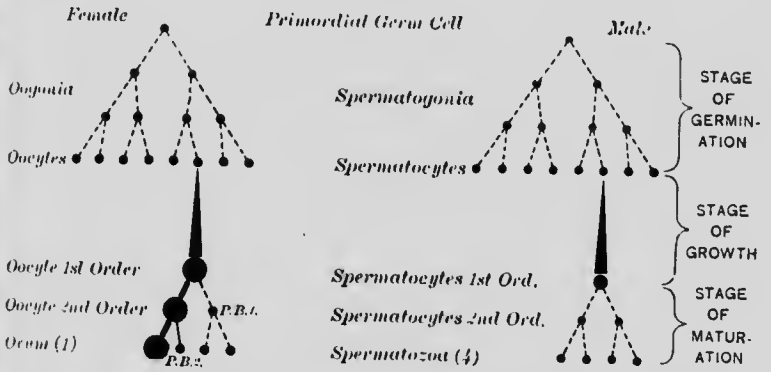
Or, briefly, by this remarkable process the spermatozoon comes to possess one-half the number of chromosomes peculiar to the cells of the species.

OOGENESIS: THE MATURATION OF THE OVUM.

A process, strictly parallel in intent, occurs in the maturation of the ovum, although so different in appearance are the stages that it was some little time before observers realized that they had to deal with like phenomena. We owe more particularly to Oscar Hertwig the demonstration of the identity of the two processes.

Like the spermatozoa, the ova are descended from the primordial germ cells, whose descendants in the ovary are termed oogonia, each germ cell dividing with the usual number of chromosomes, in general until the final stage. The differences now are these: that whereas, all the four cells derived from the primary spermatocyte become active spermatozoa, only one of the four cells descended from the corresponding oocyte becomes functional. The other three are degenerate and

FIG. 31



Schema of comparative descent of ovum and spermatozoa. The dotted lines indicate successive cell generations, the continuous lines connect successive stages of one cell. (Modified from Boveri.)

cast out as *polar bodies*—minute cells, with nucleus and cytoplasm, apparently functionless. Secondly, the period at which the process occurs is different; in general, the formation of these polar bodies either does not begin, or is not completed, until after the spermatozoon has entered the ovum (oocyte), and thirdly, and most perplexing of all, the process is conducted in such a way that all the stages happen *within* the body of the one cell, the oocyte. The polar bodies are intracellular formations. What was the oocyte undergoes nuclear changes and eventual reduction in its chromosomes and emerges as the mature ovum.

There is, however, and this prior to the formation of the first polar body, the same appearance of tetrads. These undergo division, whereby both the oocyte and the first polar body become endowed with dyads—half as many dyads as the ordinary cells of the species

possess chromosomes. And next, both the first polar body and the *nucleus of the oocyte* undergo division, the dyads separating into monads. The first polar body in this way gives origin to two polar bodies, each possessing half as many monads as the ordinary cells possess chromosomes. Similarly, the nucleus of the oocyte halves and gives off again a polar body (making three altogether). In this way the nucleus of the ovum and the third polar body also contain half as many monads as the ordinary cells contain chromosomes. The monads of the nucleus of the ovum prior to fusion with the nuclear matter of the spermatozoon develop into typical chromosomes.

Conclusions.—Even leaving out the details (some of which, as, for example, the assumption of a ring shape by the chromosomes prior to the formation of the tetrads, may be of great significance), this is an extraordinary history. It is, nevertheless, one that has been confirmed by a large number of independent observers in connection with a great number of species both of animals and plants. What is the meaning of every step we have honestly to confess that we not know. But certain conclusions are almost self-evident:

1. We are forced to see that what is in its essence the same process occurs in the maturation of both the male and the female elements. From the fact that the process obtains in all multicellular organisms examined, whether animal or plant, it is clearly of fundamental importance.

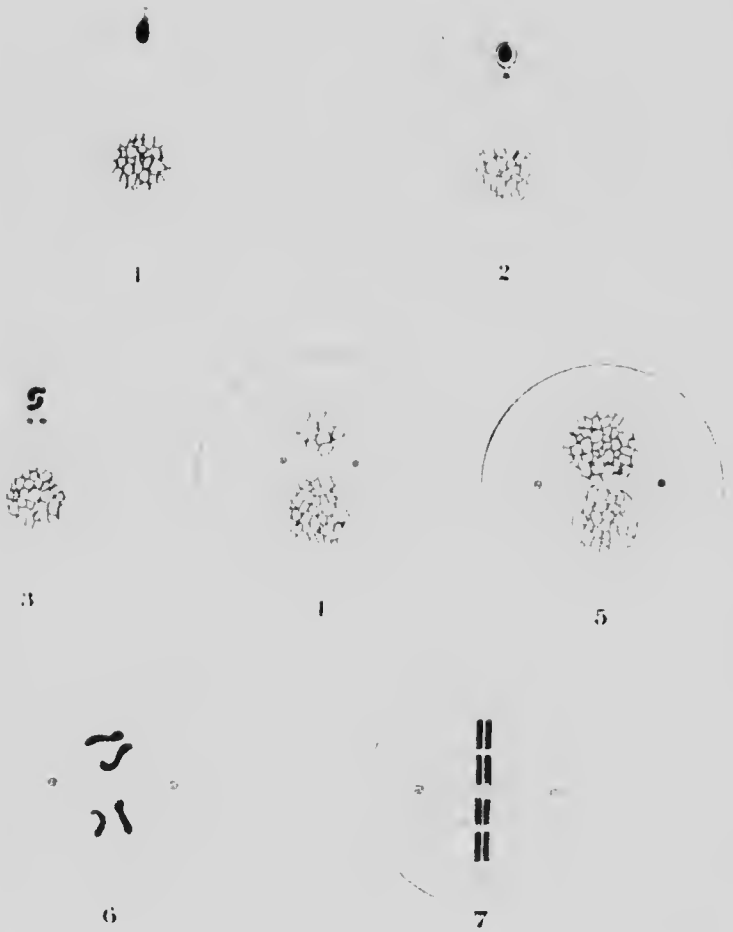
2. A feature that immediately arrests the attention is that in this process ovum and spermatozoon contribute to the fertilized ovum each one-half the number of chromosomes common to the cells of the particular species; so that the fertilized ovum, that is, the new individual, begins life with the normal number of chromosomes instead of double the number, which would be the case did spermatocyte and oocyte give rise to sperm and ovum by the usual methods of mitosis.

3. What is the significance of the varying number of chromosomes in different forms of life we have no idea. We only know that in the same species varieties may exist, one of which has normally double the number of chromosomes possessed by the other.

4. There are two facts which possibly throw light upon the need for reduction prior to fertilization. One of these we have already noted—namely, that if blastomeres be shaken apart in the early phases of segmentation, they give rise to dwarf larvæ, those from the four-cell stage being little more than half the size of those from the two-cell stage, and these in their turn little more than half as large as normal larvæ. The other is that similar dwarf larvæ have been produced by fertilizing the *enucleated* ova of certain species (such larvæ thus possess only the paternal chromosomes). Obviously, for due metabolism and growth to the normal size, there must exist a very precise quantitative relationship between chromatin and cytoplasm. This reduction on the part of both ovum and spermatozoon preserves that precise relationship.

5. An equally striking feature is that, leaving out of consideration

PLATE III



Fertilization.

1. Entry of spermatozoon into ovum. 2. Loss of tail of spermatozoon; its mid-piece becomes the centrosome of the fertilized cell. 3. Division of centrosome. 4 and 5. Chromatin both of ovum and spermatozoon converted into a network; the two moieties gain approximately equal size. 6. Chromatin of both becomes arranged into chromosomes (one-half of the number in each variety that is usual in the cells of the species). 7. Formation of spindle; division of chromosomes partition of chromosomes derived from the two parents in equal number between the two future cells (blastomeres).

the "accessory chromosome,"[1] these chromosomes are contributed to the new individual equally by both parents. These are, in fact, the one organ or component of the fertilized ovum and new individual, which is an identical contribution on the part of the two parents. We have seen what curiously elaborate methods have been developed to ensure their equality.

6. Equally striking and equally important is that, so far as we can determine, following the development of the new individual, it is evident that the same care is taken to ensure that the chromosomes from both parents are distributed equally into each daughter cell, so that each cell of the various tissues of the adult is influenced by chromosomes derived from both parents. We do not say that chromosomes of paternal and maternal origin are of equal value. Everything indicates that is not the case; that now one, now the other, is the more potent; or, indeed, that in particular properties the one may be the more potent, in others the other. But histologically, or structurally, we cannot but recognize in these processes of fertilization and development a most marvellous mechanism tending to ensure equal opportunities to both paternal and maternal chromosomes to influence the progeny.

7. Nay, more, we cannot but be led to the conclusion that in the chromosomes which become converted into the chromatin network of the functioning cell there must be contained the active controlling living matter of the cell—the biophoric matter. If we admit—as from everyday observation we are compelled to admit—that the properties or characteristics from both parents are conveyed to the offspring, and this variously in different members of the same family, we are equally compelled to admit that the chromosomes are the one component of the fertilized ovum capable of bringing about these results. The cytoplasm of the beginning individual is derived in the main from the mother, the centrosome from the father; the chromosomes are the one component contributed equally by both parents.

In short, in these chromosomes of the spermatozoon and ovum and their subsequent distribution we have the anatomical basis of heredity. So far as it is determined and modified by sex, descent is dependent upon them, and no theory of descent can be considered adequate which does not take them into account. What is of direct interest to us, as students of disease, is that, following this line of thought to its legitimate conclusion, it is obvious that the inheritance of morbid states must be through the chromosomes, must be limited to conditions which are capable of affecting the biophores of the germ cells.

It is when we come to inquire into the earlier stages of maturation, the formation of tetrads, the causes leading thereto, and the processes of division of the tetrads, that so far no one theory has been brought forward which satisfies all the variations in the process; certainly the facts so far recorded fit in with no one theory of preformation, of ids, determinants, and the like. Now we find the tetrads divided along one

[1] Vide p. 257.

plane, now along that at right angles to it. Studying the details of the process in various species, we are most strongly reminded of the slight differences in the technique of different assayers seeking to gain a perfect admixture of all parts of a given ore, in order that from a sample an ounce or less in weight they may estimate with accuracy the amount of precious metal in a ton of the material. To see such an assayer grind, and then shake, and roll, and mix the ground ore, smooth it out, cut into four parts, select two of the four diagonally opposite, and discard the other two, mix these thoroughly together and again divide, and continue the process until, finally, the amount is obtained just sufficient for melting in a small crucible, is curiously suggestive of what we see happening in these germ cells. In our opinion the most we can conclude is that here we have methods tending to ensure that the ovum and the spermatozoon receive each a well-admixed sample of the biophores contained in the germ cells. For, as we have already indicated (p. 115), and must now proceed to consider, while denying the existence of determinants, we have to recognize that biophores of more than one order are present in each germ cell, and that inheritance is largely governed by the proportion of biophores of the different orders gaining entrance into the fertilized ovum.

CHAPTER XII.

A RÉSUME: THE BIOPHORIC THEORY.

It will be well at the present point to pause and, looking backward, survey the road that we have travelled up to the present point, that we may see how far our quest has led us, and this because our present position gives entrance, to continue the metaphor, into the domain of heredity, and it is useful before entering this difficult territory to recall the path leading thereto. The present chapter will thus constitute a *résumé* of the conclusions reached in the preceding chapters. We may characterize it as summing up (to this point) the biophoric theory of living matter.

We have seen, in the first place, that all the phenomena that we regard as vital are manifestations of energy, and, as such, are bound up with matter, necessitating changes in the relationship of the molecules of the same. And what is more, that they are the attributes of a particular order of nitrogen and carbon containing bodies. We may speak of the molecules of this living matter as biophores, and, while still ignorant of their exact constitution, a study of metabolism leads us to regard them as "ring" formations, composed each of a ring of radicals, the component radicals having free affinities which are capable of being satisfied by the attachment of groups of free ions from the surrounding medium whereby "*side-chains*" are built up (synthesis).

These side-chains are capable of detachment (dissociation) when, through alteration in the surrounding medium, ions are present in the same which exert greater attraction. By this means the biophores again become unsatisfied. Further, the side-chains themselves are to be regarded as unsatisfied bodies, able to build up like side-chain bodies in series. It is this unsatisfied nature or constitution of the side-chain bodies (and of the biophores) that permits them to act as *enzymes*. In short, it is this condition of persistent unsatisfaction that distinguishes living from dead matter, and that underlies all the processes of assimilation and dissimilation.

We have seen, further, that, given molecules of this nature, the side chains attracted, and so the constitution of the biophores *in toto*, must very largely depend on the surrounding medium. The entrance of free ions of other natures into that medium, and alterations in the relative proportions of the ions there present, will lead to the building up of modified side-chains, and, as in the process of growth (polymerization) such side-chains, or some of them, must be utilized in the formation of new central molecular rings, so alteration in environment, if continued, is apt to lead to alteration in the essential constitution of

the biophores. So long as the environment remains unchanged, so long the basal constitution of the biophores remains unaltered; modify the environment, and, provided the modification be not so extreme as to arrest the series of ionic interchanges, the molecular constitution of the biophores becomes modified. It is property of the biophores that is the basis of *variation*, *adaptation*, and *evolution*.

We have equally to recognize the co-existence of another property in the biophores, that of fixity of constitution, inherent in the relationship of the constituent atoms and radicals the one to the other. The biophores, that is, are to be regarded as built up according to a particular (geometrical) arrangement. It is this arrangement which prevents the indiscriminate linking of ions and grouping of radicals from the surrounding medium and necessitates that, if unsuitable ions do become attached and the constitution thus interfered with, the compound loses its special properties; the biophore becomes "dead" matter. There are thus certain definite limits to modification, and these determine *heredity* in the narrower sense.

A study of the histology, physiology, and embryology of [illegible] renders it evident that the biophores are contained in the [illegible] that they are intimately associated with the chromatin. The [illegible] at the main bulk of (dead) nuclear chromatin is formed of nucleoproteids leads us to the conclusion that, although the biophores cannot be regarded as essentially nucleoproteids (for nucleoproteids, as such, have not by any means all the attributes of living matter), nevertheless the main component radicals of nucleoproteids must be contained in the biophores; or, otherwise, that the chemical changes which bring about the death of the biophores convert them largely into nucleoproteids.

The extent of growth of the unit mass of biophores is determined by two factors: (1) The extent of surface of the same in contact with the intermediate medium (cytoplasm) in relation to the mass, and (2) the extent of the surface of the cytoplasm exposed to the external medium relative to its mass. These relationships determine the size of the cell. We must regard the multicellular organism not as a colony of individual cells, which have primarily united for mutual protection, but as an adaptation, or means, whereby continued growth of the biophoric matter is most economically ensured, with due retention of the above relationship of surface to mass. When this mass of biophoric matter passes the optimum the above relationship is preserved by nuclear division (with coincident increase in biophoric surface exposed to the cytoplasm), followed by cytoplasmic division (with like increase in cytoplasmic surface exposed to the external medium). In this multicellular organism the cytoplasmic division is in general incomplete, cytoplasmic bridges uniting related cells. With each segmentation of a cell, following upon biophoric growth, there is equal division of the biophores between the daughter cells.

The formation of multicellular masses renders it inevitable that all the cells of the mass are not exposed to an identical environment, and

brings about alterations in the biophores controlling cells subjected to different environment. It is to this effect of modified environment acting upon biophoric material of a common order, and to this adaptation of the biophores to such altered environment, that we must attribute tissue *differentiation*. Alteration in the biophores effects alteration in the cytoplasm and histological and functional modification of the entire cell. It is physically impossible for the ovum and its nucleus to contain determinants or specific biophores for the various tissues and the localized variations in those tissues which characterize the various species.

In the process of differentiation the constitution of the biophores in the different orders of cells undergoes progressive modification of such a nature that those controlling the main mass of cells of the body (the *somatic cells*), while capable of growth, *i. e.*, of polymerizing identical biophores, and so of giving rise to cells of like nature, become incapable of giving rise under any conditions to the complete organism. They may, at most, exhibit an incomplete reversion to a simpler, less differentiated state. Those most highly differentiated lose even the power of reproducing cells of like nature. The power of reproducing the individual has become restricted to a group of cells (the *germ cells*), which, so long as they remain integral portions of the parent organism, present a minimum of differentiation. In these, presumably, the biophores undergo minimal modification. They are characterized histologically by showing no primary reduction in their chromatin in the process of successive division.

In all multicellular organisms (and in unicellular, save the lowest forms) the species is continued and the specific living matter propagated, if not in every successive generation, at least ultimately, by conjugation and fertilization. Sex has been developed, and fertilization is the process of fusion of the male (invasive) with the female (receptive) germ cell. The process is essentially one of combination of equal amounts (or numbers) of biophores from the two parental germ cells to constitute the nucleus of the new individual. Prior to the act a remarkable series of changes occurs in the germ cells involved, changes which would seem to have for their object to supply to the eventual ovum and spermatozoon an admixture or selection of the biophores present in the parental germ cells and to reduce the number of the same, so that the proportion present in the fertilized ovum is identical, relative to the cytoplasm of the same, with that of the unaltered germ cells of the parents, or, more exactly, in the ovum from which these gained development.

CHAPTER XIII.

INHERITANCE.

We come now to consider the problems of heredity, by which, speaking strictly, we mean the conveyance to the offspring of the properties of the parents and of the parental stock, so that familial, racial, and specific characters are passed onward from generation to generation. Were inheritance pure, did the child absolutely reproduce the parent, were all the members of one family and stock identical in form and characters—as identical as are crystals of the same salt—or were they born identical, and did they owe individual differences purely to the diverse influences to which each individual becomes subjected after birth, the problem before us would be relatively simple. But this is far from being the case. Interwoven with *heredity* there is *variation*, and this not of one but of two, if not of three, orders. We see, in the first place, that influences from without modify the individual. It is a matter of familiar knowledge that the soldier, the sailor, the professional musician, the undertaker, assume pronounced types; they have become modified by their course of life. In man and mammals we can subdivide these *modifications* (as some would term them, in contradistinction to inherited variations, or variations proper) into those acquired during intra-uterine and during postnatal existence. In the second place, from the fact that the individual is the result of *amphimixis*, of the fusion and intermixture of germ plasm from two parents who are not themselves identical, and whose germ plasms are not identical, it follows that the individual is not identical with either parent. This, again, is a matter of familiar knowledge: the child, while resembling the parents, now more the one, now more the other, is identical with neither. If the general tendency of successive acts of amphimixis is by the mingling of diverse germ plasms to produce intermediate grades, to maintain the mean, and so preserve the type, it clearly at the same time necessitates that each individual varies from either parent. And, thirdly, the study of the progeny of one pair of parents demonstrates to us that the interaction of the parental germ plasms, or—to preserve our terminology—of the germinal biophores in successive acts of fertilization, induces variation. No two children of the same parentage are born identical; no two fish, even of the same spawning (in which thousands of ova and millions of spermatozoa are matured at the same time), though these, admittedly, more nearly approach identity. As we shall have to point out, not only have we to recognize variation in the orders of biophores supplied by each parent to ovum and spermatozoon, respectively, but also we are forced to the conclusion

that during the course of the individual life of the parent individual, biophores are liable to undergo a certain amount of modification of their constitution. Indeed, if we do not accept this capacity on the part of the biophores to undergo modification, the facts of variation become incomprehensible.

Our study thus is not one of heredity pure and simple, but of the interaction of heredity and variation, and obviously, with so many factors to take into account and to analyze, the study is most complicated. Keeping in mind that here we are engaged upon an introduction to pathology, with particular reference to the principles underlying the same, the sense of proportion demands that our treatment be relatively brief. In almost every work upon general pathology with which we are acquainted the subject is dismissed in a brief paragraph or two. This we regard as a grave omission. It demands fuller treatment, and this because the physician, in his study of the individual case, is constantly brought to ask himself how far a given condition is an individual acquirement, how far it depends upon a vice of organization and is the outcome of inheritance; or, again, is himself asked to advise whether one or other condition of the parent, or would-be parent, is liable to influence the prospective offspring. And what is more, as we hope to show in later chapters, a broad grasp of the principles of heredity aids us materially in comprehending not a few pathological conditions, while, conversely, a knowledge of data acquired by the pathologist aids us equally in determining what are those principles.

While we are not blind to the virtue of according to the student a knowledge of diverse opinions and opposing theories, we believe that the better teaching is, where possible, to inculcate definite views, as also to afford a thoughtful presentation of the data upon which one theory is based rather than a didactic epitome of many. And as we are already upon record as having definite views upon this subject of heredity,[1] and more particularly have based our theory upon pathological data; as, further, that theory conforms to and continues the considerations brought forward in the preceding chapters, we shall here limit ourselves largely to a presentation of that theory, although, at the same time, we shall endeavor, as already stated, to indicate to the reader in passing what are the other theories and what their salient points.

THE DIFFERENT FORMS OF INHERITANCE (*i. e.*, HEREDITY PLUS VARIATION).

We may, in the first place, make a classification of the properties exhibited by the individual. These are:

1. Individual, *i. e.*, properties peculiar to the individual, and not recognizably inherited from either parent or from any ancestor.

[1] British Medical Journal, 1901: i, June 1; and article "Inheritance and Disease." Osler's Modern Medicine, 1: 1906.

2. Parental, *i. e.*, properties possessed by and peculiar to one or other parent and obviously inherited from that parent.

3. Familial, *i. e.*, properties possessed by and peculiar to the family of one or other parent.

4. Racial and stock properties: characters common to a particular stock.[1]

5. Specific or ex specie, *i. e.*, properties peculiar to the species, those, for instance, distinguishing the human individual from the ape.

6. Class, *i. e.*, properties peculiar to the class: those distinguishing man from animals that are not mammals.

And we can continue the classification yet farther to ordinal distinctions, peculiar to the particular order, *i. e.*, distinguishing man as a vertebrate from the invertebrates, and even to those distinguishing man as an animal from plant forms.

Studying these various orders of inheritance in man alone, the various departures from type, one prominent fact makes itself evident, namely, that the most basal features are those which are most firmly impressed on the individual—a fact which, in itself, is one of the strongest evidences in favor of evolution and against special acts of creation. Vertebrate characters are more firmly impressed and more constant than mammalian, mammalian than human, human than racial, racial than familial. In other words, a study of variation in its broadest aspects confirms the view already indicated of the progressive building up of the biophores in the course of the evolution of the different species. The facts are in harmony with the view that the original molecules of living matter were of relatively very simple constitution, becoming progressively more elaborate and complicated, not by loss of that original constitution, but by the addition of side-chains, those side-chains becoming successively integral portions of the more complex molecule. Under like conditions of environment, the same epigenetic series of transformations of these biophores must occur; polymerization, growth, and reproduction of these complex molecules is, with favorable changes in environment, still permissible, but new side-chains are either added to, or replace, those previously present. Following out this line of thought, it is seen that ontogeny becomes an epitome of phylogeny, not as a matter of mere historical survival, but as an epigenetic necessity. For the biophores controlling and giving rise to a given tissue or part of

[1] Our terminology is here a little indefinite; we speak indifferently, for instance, of the *human race* and of *races of mankind*, thereby meaning two different things. Of the human *species* we recognize several subspecies: Indo-European, Mongol, Australasian, etc., and of each of these several *races*, of the Indo-European for instance, the Teutonic, the Celtic, etc., and of each of these races several stocks. Thus, among those of Teutonic descent the Anglo-Saxon differs in certain recognizable particulars from the North German, the North German from the South German. Some of these differences are doubtless due to the fact that the stocks are not pure, that at one or other period there has been extensive intermarriage with individuals of other stocks, but some at least are independent of this cause, as witness the differences that already show themselves between the Anglo-Saxons who have remained in England and those whose ancestors migrated to North America or Australia.

the body to be able to order the particular structure of that part, they must have a particular chemical or physical constitution. To gain that constitution the original common biophores of the fertilized ovum must in growth and distribution to the different organs pass through a particular series of chemical changes. To exhibit these successive changes they must be subjected to one particular series of alterations in environment. In ontogeny, therefore, and the development of the individual, the cells and the contained biophores reproduce the conditions undergone by the race in its evolution—this being essential for the due production of the specialized biophores of the different tissues. Where, in this process, conditions are such that the same reaction and end result may be attained by one step in place of two or more, the ontogenetic process is correspondingly abbreviated, and to this extent the ontogeny fails to reproduce the phylogeny. This, in brief, is what is known as the Recapitulation Theory, and our conception of its meaning.[1]

Racial Inheritance.—It is unnecessary to detail examples of hereditary properties older than racial, for the reader can easily call these to mind. And, as regards racial and stock inheritance, the same is largely true. Everyone is familiar with, for example, the differences in the form and structure of the individual hairs and the amount and nature of the cutaneous pigment in the different races of mankind, and has some knowledge of the differences in stature and in the conformation of the skull in the same. It may be of value from a pathological point of view to recall yet other differences, functional in nature and co-existent with these histological variations, which the morphologist is naturally apt to overlook. We refer to differences in reactive power toward various pathogenic agents, microbic and non-microbic. These we find well marked in the different races of domestic animals. Thus, the native cattle of Japan and the buffel, or native cattle of Austro-Hungary, are much more insusceptible to tuberculosis than are ordinary European and American breeds, and one race of Algerian sheep is highly refractory to anthrax, a disease to which sheep in general are peculiarly susceptible. Between the races and stocks of mankind many such differences have been noted. Those of European descent and Malaysians subjected to the same conditions react very differently toward plague and beriberi. Both, it is true, are susceptible, but a far smaller proportion of Europeans exposed become victims to these diseases, and a far smaller proportion of those taking the diseases succumb. The reverse would seem to be the case as between those of European descent and negroes in regard to yellow fever; here it is the Europeans that are far more susceptible, while, contrariwise, negroes and American Indians and native races in general are more susceptible to tuberculosis than are "white men" under conditions of civilization.

So, also, with non-microbic diseases. Those of the Hebrew race are more prone to certain nervous affections and to diabetes than are the

[1] See more particularly Hurst, Natural Science, 6: 1895. It is also laid down at length by Reid, The Principles of Heredity, London, Chapman and Hall, 1905, without however, any clear recognition of the underlying causes.

surrounding Gentile population; the French more subject to hystero-epilepsy; the English to gout; the inhabitants of North America of European descent to dyspepsia and disorders of dentition.

And these finer distinctions even exhibit themselves in the almost indescribable *nuances* of character. It is not necessary to quote Shakespeare or Sir Thomas Brown on these matters; one has but to "walk the wards" of any large metropolitan hospital and observe how those of different nationalities bear themselves under conditions of disease, to become convinced of these pronounced underlying variations.

It may be argued that the differences are purely or in the main the result of differences in mode of life and general surroundings. But this is exactly our point: it is the various grades of variations in environment that are essential causes of these differences, from the pronounced distinctions in cutaneous pigment down to national gout and national dyspepsia.

This, however, may be said, that a study of these finer differences between the races and stocks of mankind throws doubt upon the argument of Weismann and other morphologists, based upon single morphological variations—that these demonstrate the existence of determinants. We find that such impalpable variations as occur between different stocks of the same race of mankind—morphological variations so slight that we can scarce measure them by instrumental means—are constantly accompanied by functional variation; or, otherwise, that a change in one slight direction affects not a single part, but the whole organism; while, conversely, change of any one part which produces no obvious morphological alteration has nevertheless an influence upon the body as a whole.

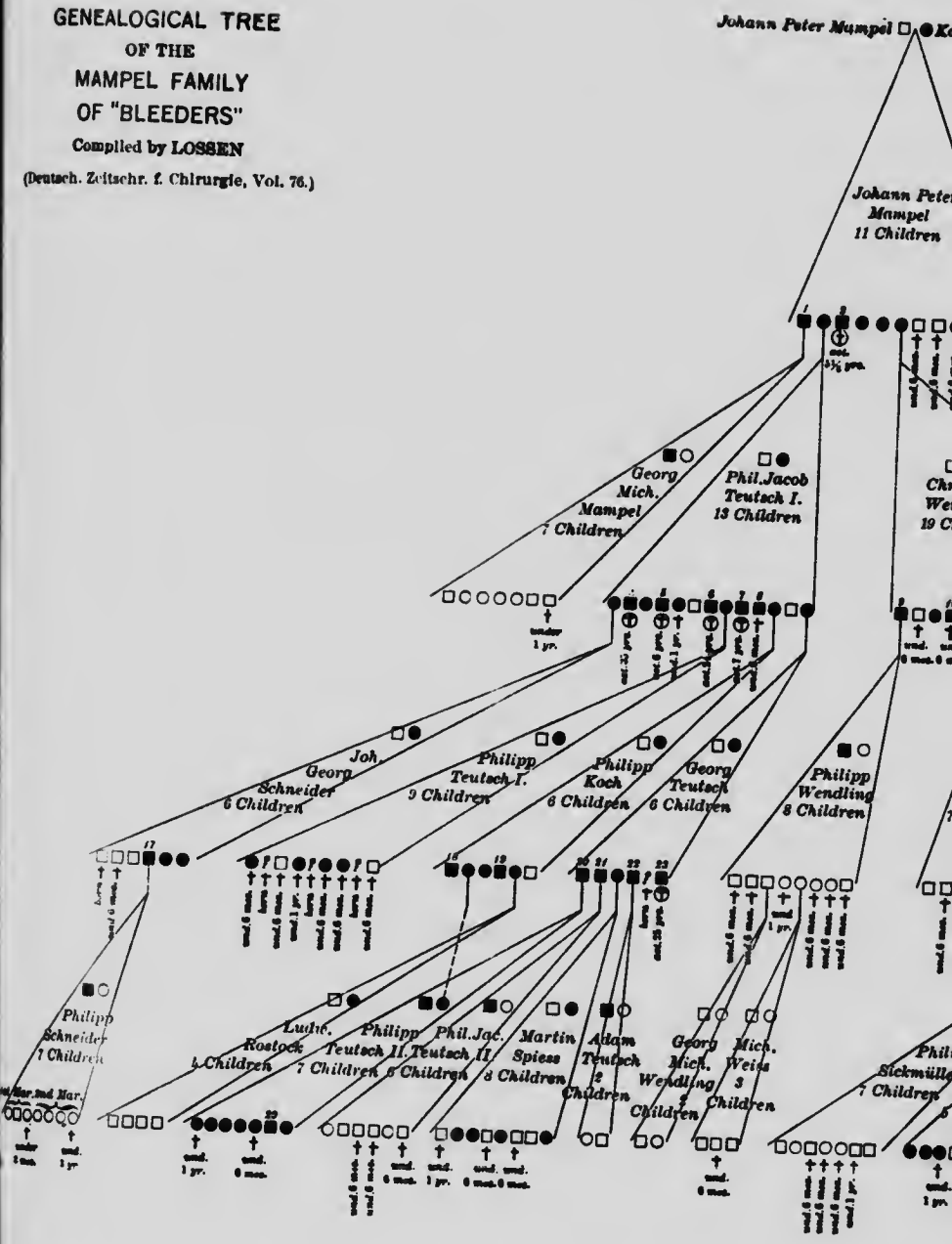
Familial Inheritance.—It is a well-known fact of the same order that not merely is there a certain likeness between the members of one family, but that certain traits peculiar to a family present themselves generation after generation with remarkable persistence—stature and length of limb, shape of some special part, as, for example, the "Hapsburg lip," which has characterized the present reigning House of Spain for so many centuries; actual malformations, like accessory digits, which have, in certain cases, been traced back for close upon three centuries; morbid conditions or tendencies to the same (diatheses), such as albinism (deficiency of cutaneous pigment), Daltonism (color blindness), hemophilia (liability to excessive hemorrhage as the result of relatively insignificant injury), nervous disorders; or, again, traits of character and tricks of expression. And all this we note in the absence of interbreeding—marriage of cousins, for example—which we might reasonably expect to intensify such family peculiarities, and in spite of the continual introduction of "new blood" into the family by marriage with members of other families not presenting these particular features; so that we are forced to recognize the possession of what we may term *dominant* properties by the germ plasm or biophores of particular strains, whereby, in amphimixis, these biophores assert themselves in one or other direction, overshadowing the effects of the conjoined biophores.

PLATE I

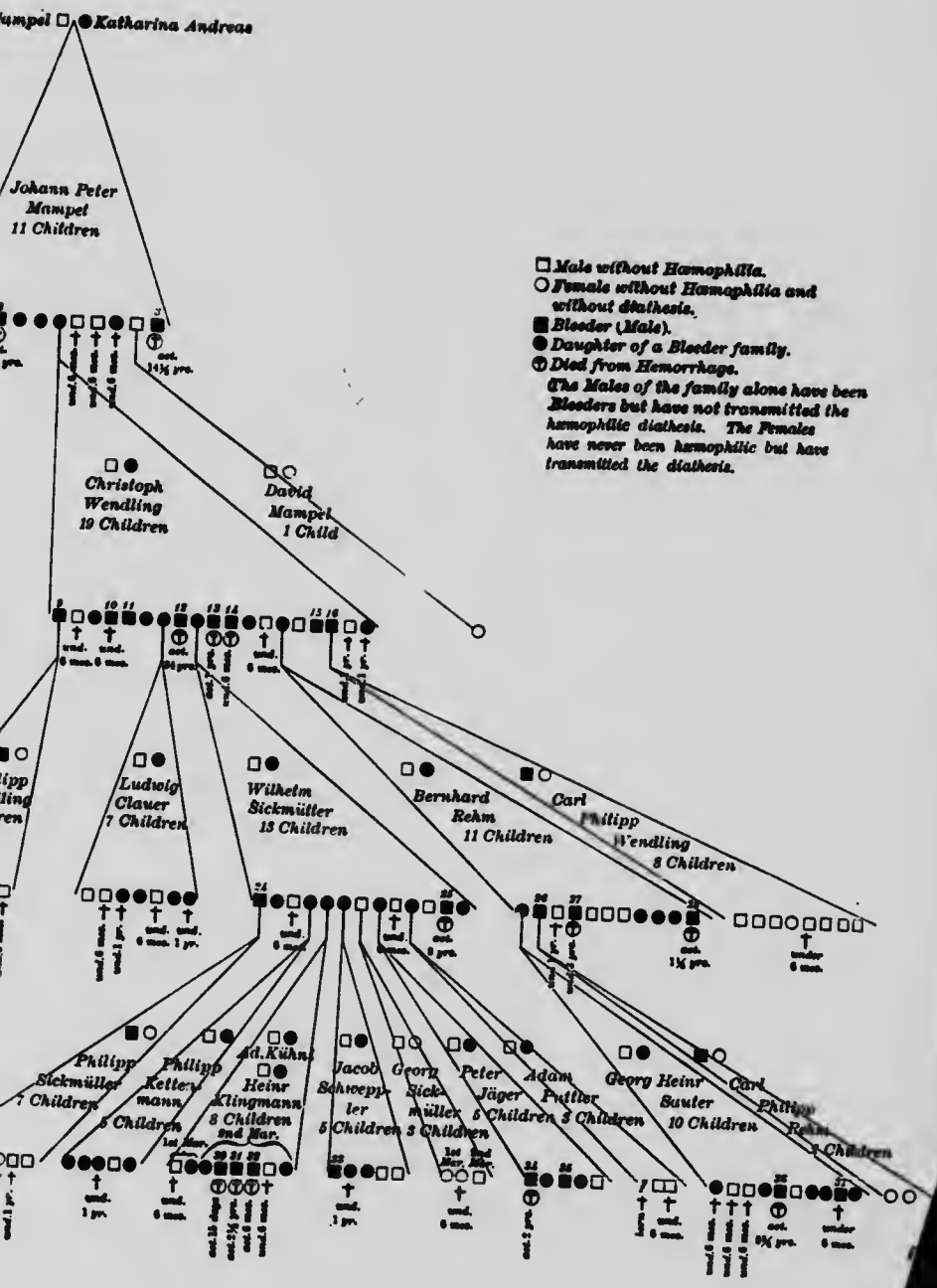
GENEALOGICAL TREE
OF THE
MAMPEL FAMILY
OF "BLEEDERS"

Compiled by LOSSEN

(Deutsch. Zeitschr. f. Chirurgie, Vol. 76.)



LATE IV


Katharina Andreas
Johann Peter Mampel 11 Children
Male without Hæmophilia.
Female without Hæmophilia and without diathesis.
Bleeder (Male).
Daughter of a Bleeder family.
Died from Hemorrhage.
The Males of the family alone have been Bleeders but have not transmitted the hæmophilic diathesis. The Females have never been hæmophilic but have transmitted the diathesis.
Christoph Wendling 19 Children
David Mampel 1 Child
Ludwig Clauer 7 Children
Wilhelm Sickmüller 13 Children
Bernhard Rehm 11 Children
Carl Philipp Wendling 8 Children
Philipp Sickmüller 7 Children
Philipp Kettenmann 5 Children
Ad. Kühn
Heinr Klingmann 8 Children 2nd Mar.
Jacob Schweppler 5 Children
Georg Sickmüller 3 Children
Peter Jäger 6 Children
Adam Pfeiffer 3 Children
Georg Heinr Sauter 10 Children
Carl Philipp Rehm 3 Children

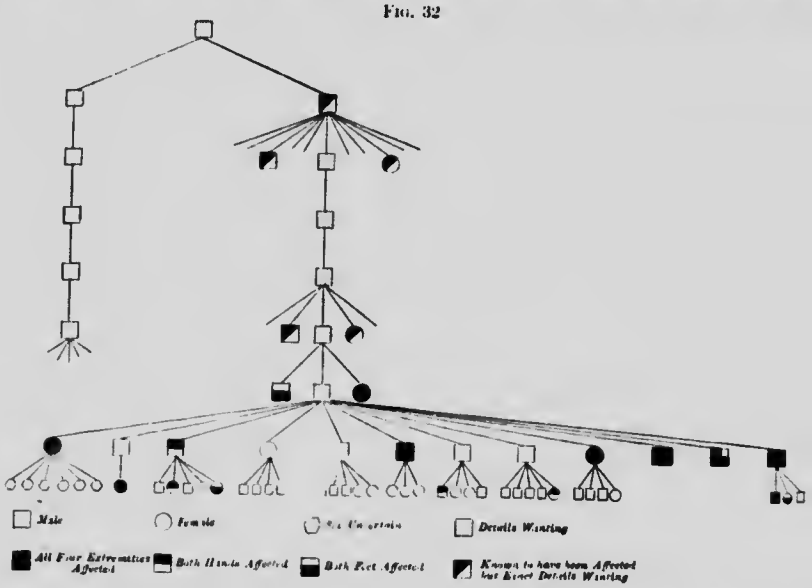
A study of family inheritance reveals other remarkable features. Thus, there are certain characteristics which affect male and female members of the family alike, others which appear in the one sex only, although they are conveyed by the other. The daughter of a gouty family may, throughout her life, be free from gouty manifestations, and her daughter also, but her male children may exhibit gout at or before attaining middle age. This interrupted descent is most pronounced in the case of hemophilia; in this the female members of the family are rarely "bleeders," but they give birth to sons who are. Irrespective of sex, also, we encounter frequent cases in which one or other member of a family exhibits peculiarities not present in the parents, but well marked in one or other grandparent, or even in a great-grandparent. This reproduction of features, absent from the parents but present in a preceding generation, is termed *atavism*. It has, as we shall note presently, to be distinguished from *reversion*.

In case after case the existence of this atavism renders it difficult, if not impossible, to trace a family peculiarity to its origin—a case of polydactylism (supernumerary digits), for instance, occurs in a family whose members are otherwise provided with the normal number of fingers and toes. To determine whether this is a wholly new appearance in the family, or merely the breaking out again of a dormant tendency, demands an extensive knowledge of lateral as well as of direct lines of descent. A man must have two parents, and may have —if there has been no inbreeding—four grandparents, eight great-grandparents, sixteen great-great-grandparents; thus, an intimate knowledge of at least sixteen family histories is requisite; such knowledge is notoriously hard to gain, especially where blemishes are concerned. Such difference must have made itself manifest in some one particular generation, must have had an origin. We have to turn to the smaller animals, with rapidly recurring generations, to throw light upon this point, and even with these have to breed for several generations and preserve exact records.

I owe to an old student a remarkable case of the hereditary transmission of family defects, which well illustrates many of the points here referred to. In 1620 two brothers landed from England and settled at Woburn, Massachusetts, and these, according to family history, married two sisters. The family and the descendants of the one brother have since then shown no abnormality; in the children of the other brother, N. N., himself, according to tradition, polydactylous, polydactylism presented itself. He had ten sons, whose descendants are now scattered through North America. For the next two generations it was dormant, or at least there are no records of its existence. In the direct line of my informant it has indeed been dormant for three generations. His great-grandfather was free, though other members of that generation were affected; his grandfather was also free, as was his father, although an uncle and aunt were affected. Of his father's twelve children, eight were affected, the condition being for the first time complete in himself. By complete is here meant that not only did the condition

affect all his members, so that he had six fingers and six toes, but all the accessory digits were perfectly formed. What is more, his young son has them all perfectly complete. Another characteristic of the family history is that, whereas the daughters of the family may show the effect, it tends to die out with them; their children have normal digits. In this way, according to our patriarchal method of determining the family, the defect tends to remain familial, descending only through the males. The potency of the "blood" of this family is, in other respects, strongly pronounced; there is a succession of large families, and the different members exhibit a great family likeness, so great that my informant could salute a stranger travelling in the West, "Good morning, Mr. X," and have him return the salute, "Good morning, Mr. X.," with the further remark: "I see you have the family sign

FIG. 32



(referring to his six fingers). I do not possess it, but my father did, and so does one of my eight children." And, on inquiry, the consinship between the two was found to be at least beyond the third degree of removal. The following exhibits the genealogy of my informant's branch of the family:

A careful inquiry made by my friend, Dr. Brockbank, of Manchester, has succeeded in bringing to light a family of the same name in England, two members of which migrated to America in or about 1620, and in this at least one member of the present generation exhibits polydactylism. It is evident, therefore, that the tendency to polydactylism *must* date back to the generation preceding the *emigrès* of 1620, and *may* have originated much earlier. There are, indeed, indications that the tendency may be traceable back to earlier than 1500.

CHAPTER XIV.

PARENTAL AND INDIVIDUAL INHERITANCE.

STRICTLY speaking, every property possessed by the individual which is not and cannot be ascribed to intra-uterine and postnatal *acquirement* is the individual inheritance of the individual. It has reached him through the parental germ plasms. Specific (*ex specie*), racial, and familial traits become the property of the individual. But here we would deal with those features which, peculiar to one or other parent, reappear in the offspring; and again, those which, not observable in either parent but present in the offspring, can only be ascribed to the interaction of the two parental plasms. What has once been inherited may be conveyed to a subsequent generation.

A little consideration shows that these two conditions as here defined are practically identical, and must be considered together. Considering these together and studying the various grades of inheritance, we find that these may be classified as follows:

1. **Blended Inheritance.**—As regards the majority of properties, this must be regarded as the most usual type. The offspring, that is, tends in the main to exhibit a blend of the paternal and maternal features, intermediate between those presented by either parent. In general, that is, we observe an equality of influence on the part of the respective germ plasms, and that the tendency of fertilization is to preserve the mean and perpetuate the type.

2. **Particulate Inheritance.**—There are, however, many exceptions to this law of blended inheritance, nor have we as yet determined adequately what it is that determines these. All that we can say is that we are forced to recognize that, in respect to certain properties possessed by the parents, we have to note an incapacity to blend; they are antagonistic. First and foremost among these is the series of associated sexual properties; the offspring of most animals must be either male or female. Anything of the nature of coincident equal development of both sets of sexual organs is found incompatible with perfect function of either, and is an attribute of imperfect organization. We see the same in many properties which we may regard as of subsidiary importance. When one parent has brown eyes, the other blue, the children have either blue or brown eyes, rarely those of an intermediate color. And what is more, as between alternative antagonistic properties, in a given mating one of the two is apt to be *dominant*.

MENDEL'S LAW.

This was well shown in the remarkable observations of the Austrian monk, Mendel,[1] upon hybridization, *i. e.*, upon the cross-fertilization of well-marked varieties of certain flowers, notably of the pea: observations which, neglected for long years, have of late been widely confirmed, by zoologists as well as by botanists. If two well-differentiated varieties of such a plant as the pea be selected and grown, varieties presenting when grown pure constant differences, differing in such particulars as position of the flowers on the stem (either axial or terminal), length of stem (whether markedly long-stemmed or markedly short-stemmed), character of the seed pods (either inflated or constricted between each seed and its fellow), seed coat (whether smooth or wrinkled), and if these be cross-fertilized, the pollen of the one variety being employed to fertilize the ova of the other, it is found that the hybrids which result manifest these antagonistic properties according to a very definite law. One of each pair of properties is dominant, *i. e.*, present, in these "bastards" of the first generation, overwhelming in them wholly or mainly the corresponding character present in the other parent. Thus, if we hybridize a red-flowered pea with a white-flowering species, the first set of hybrids will have red flowers, and in this respect be indistinguishable from the red-flowered parent. In this respect they will show no relationship to the white-flowered parent. Red color of flower here is dominant, white recessive, and this irrespective[2] whether the pollen of the red-flowered variety be employed to fertilize the white-flowered, or *vice versa*. Almost always it is the progressive characteristic which is dominant. In this case, for example, red color of flowers is the positive acquirement; white color is latency, or loss of this acquirement. It is the positive acquirements—color, hairiness, presence of starch in seeds, etc.—characterizing the species as a whole, that are dominant; absence of these, that are recessive.

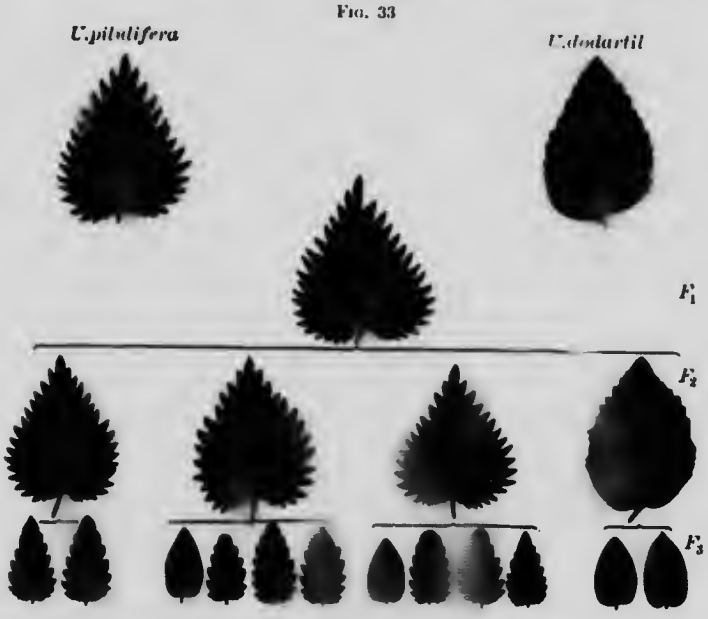
But while this is the case, it does not mean that the characters of the other parent are completely thrown out; the recessive character is only latent. In other words, from what we know of nuclear division and distribution of parental chromosomes in the cells, biophores derived from both parents are conveyed to all the cells of the individual, only as regards any particular feature, those from one source may be more active than those from the other. This is surely the case with the germ cells, as pointed out by Mendel.

[1] Verhandl. d. Natur. Vereines in Brunn, 1866, reprinted by Göbel in "Flora" 89: 1901: 364, and translated by W. Bateson in "Mendel's Principles of Heredity: A Defence," Cambridge Univ. Press, 1902. De Vries, who rediscovered Mendel, gives a singularly clear account in his "Species and Varieties," Chicago, 1906, lecture 10.

[2] In the main, Heider (Ueber Vererbungsgesetze, Berlin, Borntrager, 1905) gives some exceptions among plants, in which differences are noted. There are peculiarities in the development of the plant ovum (not seen in the animal) which help to explain this.

Pens have this advantage, that they are capable under ordinary conditions of self-fertilization, and so the disturbing effects of cross-fertilization with pollen from other sources can be prevented. If, now, the offspring of this *bastard* first generation be grown and brought to flower, in their characteristics they are found to follow closely a numerical rule; the recessive character reappears in one quarter of this second generation, and if the flowers of this one-quarter be allowed to self-fertilize themselves, the subsequent generations show constantly the recessive character; the dominant is wholly cast out. As regards this one feature of flower color, for example, one can, after bastardization, regain a white-

FIG. 33



...af characters of hybrids of *Urtica pilulifera* and *U. dodartii* (Correns): F_1, of first hybrid ...ration; F_2 and F_3, of second and third ... fertilizations. The dentate character of the leaf ...edge is seen to be a dominant property.

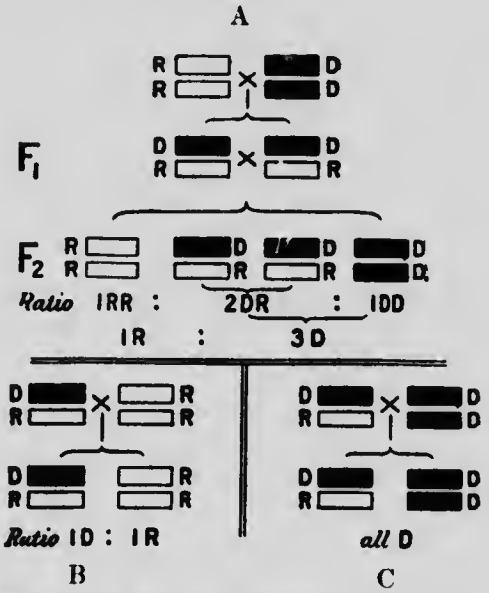
colored variety. As regards the other three quarters, they, it is found, divide themselves into two orders: One of the three quarters consists of purely dominant plants, and subsequent generations grown from these remain purely dominant always, for example, have red flowers. The other two quarters, or one-half of the whole number of this second generation, have the properties of the first generation of hybrids; they are hybrids, and in each subsequent generation they give rise to the same proportion of pure dominants, hybrids, and pure recessives, namely, one-quarter that are found to be pure dominants, one-half hybrids, and one-quarter pure recessives.

The action of this law is perhaps, best grasped from the accompany-

ing figure, afforded by Correns, giving the character of the leaves in successive generations of hybrids of two species of nettles, *Urtica pilulifera*, a species with strongly toothed or dentate leaves, and *Urtica dodartii*, which has leaves with almost uninterrupted edges. Mathematically expressed, if we designate the dominant character as D, and the recessive character as R, the proportions of the different types of hybrids evolved is represented by the formula n(D + 2DR + R); or, more exactly, n(DD + 2DR + RR).

We use the DD and the RR to indicate that each individual ovum of the pure dominant and recessive types receives the same number of biophores as do the hybrid ova.

FIG. 34



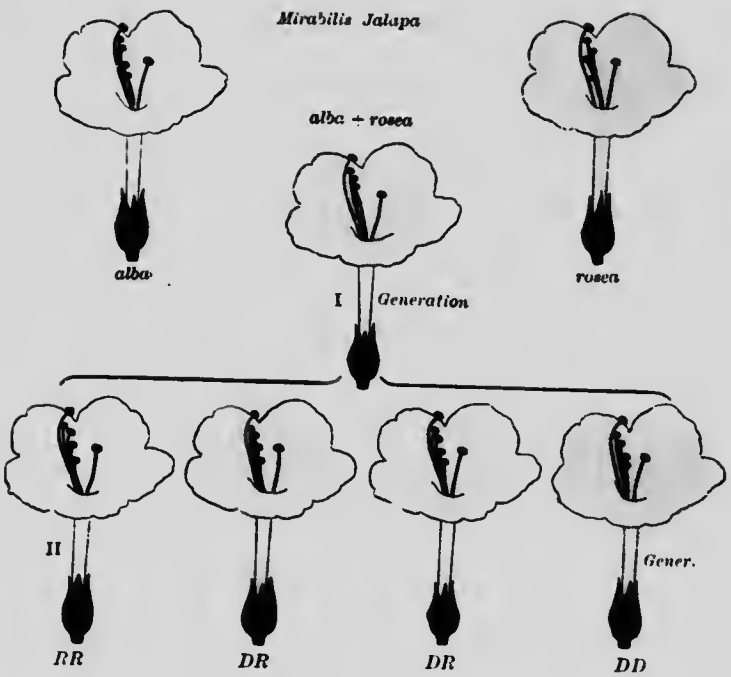
Schema of Mendel's law for a single pair of "antagonistic" properties: *A*, the results of hybridization of a pure dominant (D) with a pure recessive (R) form; *B*, the results of crossing a hybrid with a recessive form (50 per cent. of progeny pure recessive, 50 per cent. hybrid, but apparently dominant); *C*, the result of crossing a hybrid with a dominant form, all apparently dominant (but 50 per cent. pure, 50, hybrid). (Bateson.)

If further generations be grown and self-fertilized, it is found that plants of the DD type always produce DD offspring; plants of the RR type always produce RR offspring; plants of the DR type constantly give the different types of offspring the proportion of n(DD + 2DR + RR).

The Limitations of Mendel's Law.—It must, however, be borne in mind that the law is not universal.

1. It deals only with that class of cases in which we encounter an acquirement on the part of one group of members of a species mated with a *varietal* deficiency on the part of other members, and this varietal deficiency is not to be regarded so much as an absence of a particular

PLATE V


Mirabilis Jalapa
alba + rosea
alba
rosea
I Generation
II
Gener.
RR
DR
DR
DD

property, as a lying latent of the same: the phenomenon, that is, is not strictly the result of interaction of opposed properties.

2. Where in the hybrid the one property dominates, it does not drive the other out; the other is latent through the whole existence of the hybrid, and at times, under suitable conditions, may show itself.

Thus, as de Vries points out, the hybrid between the blue *Veronica longifolia* and its white variety has flowers with blue corolla; here and there among 1000 or more of the hybrids a completely white spike may be noted, or a side branch with white flowers, or one side of a spike may be blue, the other white. Bud varieties may show themselves, that is, with the recessive property in the ascendancy. It is there all the time, as shown by the subsequent generations, and now some influence has rendered it the more active in certain cells. Here possibly we have an insight into the nature of mosaic inheritance.

3. At times the coincident influences of both dominant and recessive unity is recognizable; in other words, we have indications of apparent blending rather than of particulate inheritance, indications that the one form passes into the other, as shown in the accompanying figure from Correns of the result of hybridizing two varieties of *Mirabilis jalapa, rosea* and *alba*. All the flowers of the first generation are of a lighter pink color than those of the dominant parent, although in the second generation the formula works out obviously into DD + 2DR + RR.[1]

4. The law is of no avail in connection with hybridizations between *distinct species*. As is well known, it is only between species that are closely allied that such hybridization has any result, and then the offspring tends to be infertile. There are, nevertheless, cases in which a somewhat fertile progeny results, more particularly among plants. As de Vries points out, the conditions here are different; in the Mendelian cases we deal truly with pairs of conditions; the species and its variety differ in the presence or latency of a given property. Different species may, it is true, if allied, have many properties in common. Their difference lies in the fact that one has an acquirement in one or other direction (or, it may be, several) which is wholly unrepresented in the other; as a result the mating is incomplete and unbalanced, one or more units are introduced by the one germ substance for which the other introduces nothing that corresponds. If hybrids are produced under these circumstances, then, as de Vries has demonstrated experimentally:

(*a*) Different types are produced according as to whether the male element of the one parent, A, is used to fertilize the ovum of B, or *vice versa*.

[1] Bateson affords an equally striking instance. The *blue* Andalusian fowl is a hybrid of the DR type, produced by mating a dominant black Andalusian with a recessive white splashed with black. Breeders have striven in vain to raise a pure strain of the blue variety; mating two blue birds gives progeny in the proportion 1 black, 2 blue, 1 white splashed with black; mating black with splashed white gives a *first* generation all blue.

(*b*) The hybrids yield very little seed, whereas Mendelian hybrids are as fertile as the parental stocks.

(*c*) Self-fertilized, they remain true to type and constant: there is no segregation or reversion to either parental form.

(*d*) All the individuals of each generation are alike.

Here, it will be seen, we have a wholly different condition of affairs. As de Vries well points out, up to the present there has been a great vagueness as to what constitutes a species, what a variety. Here hybridization would appear capable of affording an answer in any given case; while, conversely, cases which do not conform to the Mendelian law may be explained as demonstrating that the one or the other parent exhibits a specific and not a varietal difference from the other; in other words, that the point of difference between the two is not a retrogression, but a positive acquirement.

The Mendelian Law for Multiple Pairs of Features.—When the individuals of the two Mendelian varieties thus hybridized differ in several pairs of features, the result, though following strictly the same law in respect to any one particular pair of features, becomes much more complicated. For two pairs of features, Ab and aB (Aa representing one pair of features, Bb the other, the capital letters representing the dominant feature of each pair), respectively, while in the first generation all the individuals will be of the AB type (the dominant features prevailing), in the second there will be sixteen possible combinations between germ cells carrying the different admixtures of these properties, and of these sixteen possible combinations, externally, 12 will show the dominant A, 12 the dominant B character, 9 will show both dominant characters combined, 3 only will present the recessive *a* character, 3 the recessive *b* character, and 1 only will show both recessive characters (ab). For these and greater numbers of pairs of opposed characters (n), the law is that there will be $2^n \times {}^n$ possible combinations, 2^n forms which are externally different, and 3^n which, from the internal constitution of their germ cells, will produce different orders of descendants. To show this in algebraic form, illustrating the different possible combinations, AB.AB, ABaB . . . to ab. ab, would occupy more space than perhaps the subject demands. Those who would follow it may be referred to Bateson's work.[1] Two important points are deducible from a mathematical study of these possible combinations between germ cells of different characters, and have been amply proved in practice: (1) That when the species crossed differ in two pairs of characters, one-sixteenth of the second and subsequent generations is liable to reproduce in a pure form the ancestral features of one or other of the original parent species, and by proper mating may be propagated, showing no trace of the *mésalliance* (as regards these two characteristics): and (2) that another one-sixteenth exhibits permanently the combination of the dominant character of the one species with the recessive character of the other—whereby,

[1] Bateson, loc. cit. See also Brit. Med. Jour., 1906: ii: 61.

through proper self-fertilization or inbreeding, a new race or subspecies may be developed which retains this particular combination of features. This, for breeding purposes, is a matter of the very highest importance; already, by carrying out these indications and selecting advantageous features in two different species of plants, it has been found possible to develop species combining the two; as, for example, to obtain a new variety of wheat combining the rich yield of the English variety with the good flowering and early ripening qualities of the Manitoba wheat. It is along these lines of selection and appropriate mating that during the past centuries blindly, and with numerous failures, our breeders have developed the various pure breeds of domestic cattle; and that, in more recent years, Burbank has attained such marvellous developments in the practical production of improved varieties of fruits and flowers.

Unfortunately, with the human species we can so far hope to obtain little of practical benefit along these lines, nevertheless the abundant studies of the last few years have thrown some little light upon human pathology. In the first place, it has to be noted that this law, shown to be of wide application among plants, has, where tested, been found to apply also to animals. Coutagne[1] has proved it for silkworms; Lang[2] has shown that it holds in snails; Bateson[3] with fowls; Cuenot,[4] Darbishire[5] and G. M. Allen[6] in mice; Castle,[7] Woods,[8] Hurst,[9] and Schuster[10] in rabbits and guinea-pigs.

In man himself it is known that there occur such opposed pairs of characters; thus, where one parent has brown eyes, the other blue, the children do not have eyes of intermediate color, but either brown or blue. Davenport[11] and Hurst[12] have independently shown that there are two orders of eyes, the blue and hazel group with pigment only in the back of the iris, the browns, greens, "ringed" and spotted group with pigment also in front: this latter is the dominant, the former the recessive type. Study of long series of different matings in man shows a very close conformity to Mendel's law. Dark hair also, though not to such a marked extent, tends to be dominant over flaxen; but, confessedly, it is difficult to make accurate observations where each successive marriage introduces such widely different "blood." We can recall one other definite observation made upon man, namely, that of Castle.[13]

[1] Bull. Scient. d. l. France et l. Belgique, 37: 1902.
[2] Festschr. f. E. Haeckel, 1904: 439.
[3] Repts. to Evolution Committee, Roy. Soc., 1: 1902, and 2: 1905.
[4] Arch. de Zoöl. Exp., Notes et Revues, 1902: 27, and 1903: 33.
[5] Biometrika, 3: 1904.
[6] Proc. Amer. Acad. of Arts and Sciences, 40: 1904.
[7] Carnegie Institution Reports, Washington, No. 23: 1905.
[8] Biometrika, 2: 1903: 299.
[9] Jour. of Linnean Soc. Zool., 29: 1905.
[10] Biometrika, 4: 1905: 1.
[11] Science, 26: 1907: 589
[12] Proc. Roy. Soc. B., 80: 1908: 85.
[13] Science, N. S., 17: 1903: No. 419.

Albinos occasionally present themselves among negroes—individuals, that is, devoid of cutaneous pigment. As might be expected from what we have already said (p. 148), such loss of pigment, being a loss of a character, a retrogression, is recessive, and not dominant. Castle[1] and Bateson[2] have, independently, suggested that sexual characters come under Mendel's law—that male and female properties are antagonistic, one or other presenting itself, while the other lies dormant, to show itself in a later generation. This cannot as yet be regarded as determined, but true it is that there are combinations of sets of characters which are combined in descent. The case already noted (p. 146) of polydactylism, conveyed along the male line,[3] and the opposite conveyance of hemophilia through the female (although the female herself may show little tendency to manifest the condition), are instances in point.

GALTON'S LAW.

Before leaving the subject it is necessary to refer to another which, for a time, was regarded as antagonistic to Mendel's law, but now has been shown by Darbishire[4] and Correns to be another, though perhaps less satisfactory, expression of the same—less satisfactory in that it expresses the source of the effects in a given generation rather than an analysis of the same. It was held that blended and antagonistic inheritance were opposed, and that this law dealt only with the former. As we have pointed out, the two are not opposed, but various transitions are to be recognized, and, as a matter of fact, Francis Galton,[5] who established his law upon a very extensive analysis of the coat color of Basset hounds, truly employed a pair of particular features. The law, as determined by him, is to the effect that in the composition of the individual the two parents contribute the half of the total (or each one-quarter), the four grandparents one-quarter (or each one-sixteenth), and so on. According to this law, the series $\frac{1}{2} + \frac{1}{4} + \frac{1}{8} + \frac{1}{16} = 1$; i. *e.*, it equals the total inheritance. Karl Pearson, a strong adherent of Galton's methods, from a study of other sets of features (the color of the eyes in man and the color of the hair in horses—both, again, Mendelian or antagonistic properties), arrived at slightly different results, giving the grandparents and earlier generations somewhat greater influence. Without discussing the matter in detail, it may be pointed out that if we cross a Mendelian bastard (first generation) with the recessive parent, we get 50 per cent. of the offspring taking purely after that parent, the offspring being constant in feature, and 50 per cent. presenting the dominant feature, but truly bastards, this offspring dividing up according to the Mendelian formula.

[1] Contrib. from the Zoöl. Lab., Harvard, 40: 1903: No. 4.

[2] Address to Zoölogical Section, British Assoc., Cambridge, 1904.

[3] This is by no means constantly the case with this particular abnormality.

[4] Proc. Manchester Lit. and Phil. Soc., 49: 1905

[5] Proc. Royal Soc., London, 1897.

If the cross be made with the dominant ekler, all the offspring are of the dominant type: 50 per cent. of them are pure dominants, the other 50 per cent. hybrids (Fig. 34 *B* and *C*). These figures fit in, it will be seen, with Galton's law. The law, so far as we can see, fits a restricted series of cases, and does not, it seems to us, lead to practical application in the same way as do the Mendelian principles.

3. **Mosaic Inheritance.**—In this form, strictly speaking, in certain cells and cell groups the paternal influence is dominant; in others of the same order, the maternal. Such is best seen in connection with surface coloration, where the parents have been of different color, the result being a streaking or dabbling with the two colors without blending of the same; we obtain the effect (distantly, it is true) of a mosaic work. The condition is on the whole infrequent, and particularly so in man. The only examples that we can recall which would seem to come under this category are those rare ones in which the eyes are of a different color—and, possibly, the still rarer condition, in which the internal sexual organs on the one side are male, on the other female. It is a form of inheritance that has been little studied, which nevertheless has to be recognized, and may, indeed, color effects apart, be much more widespread than is generally held; for, passing beyond individual organs or tissues, we must realize that the individual is not in certain organs and tissues to reproduce the properties and peculiarities of the one parent; in others, those characteristic of the other, and this is but mosaic inheritance on a larger scale. Regarded thus, recognizing that biophores from both parents pass equally into all the cells of the body, multiplying as the cells multiply, it is not difficult to imagine that where those are relatively equally balanced, in certain environments the one order will be dominant, in others the other order.

4. **Atavism.**—As originally employed, all reversionary conditions —the appearance in a given generation of traits not present in the parent but characteristic of previous generations—were included under the one term atavism (*atavus*, a grandfather). It is needful, however, to make a distinction between familial reversion, or atavism proper, and racial or ex specie reversion, with the appearance of properties characteristic of an earlier stage in the phylogeny. We shall use the term atavism for the former, phylogenetic reversion for the latter.

Such atavistic inheritance—the inheritance by a child of properties not manifest in either parent, but present in the grandfather or some relatively recent ancestor—is seen to fall in with Mendel's law. That law and the observations on which it is based demonstrate that a condition may remain latent through several generations, to reappear eventually in a definite proportion of the members of a stock. We gain also an understanding of *collateral* inheritance, *i. e.*, of possession of properties corresponding with those of members of collateral branches of the family—uncles, aunts, or distant cousins, and unlike those of the parents.

So, also, looking to the future, we see that all the progeny of an indi-

vidual exhibiting one or other inherited taint need not of necessity exhibit that taint, although some are likely to do so, while, if both parents vary in the same direction, the probability becomes very great. Further, if either parent come from an unsound stock, though not individually presenting the stigmata of the family taint, these may reappear in subsequent generations, being merely recessive. This may seem, and is, vague. It may be possible, when these principles become more firmly established and family histories more fully recorded, to state the probabilities of the inheritance of one or other condition.

5. **Reversionary Inheritance.**—A clear distinction is to be drawn between this and *atavistic inheritance*. In the latter we have the manifestation of properties present potentially in the germ plasm, though unable, owing to certain conditions, to manifest themselves fully in the body of the individual parent, while able to do this in the body of the offspring; those properties may be either favorable or unfavorable. In reversionary inheritance, we have *always* a return in the offspring to a *lower type*—a development which is incomplete, not reaching the standard of the type, but only attaining to a stage characteristic of an earlier period in the development of the species, whether affecting the body as a whole or more especially some particular system, such as the nervous system.

It is by no means easy in a large proportion of cases to determine whether reversionary traits present in an individual are truly inherited or merely acquired. A child is born microcephalic, for example, and with simian physiognomy, or possesses indications of persistent gill clefts, recalling earlier stages of evolution. Arrests of development of these orders may be due to no primary defect of the parental germ plasm, but to disturbance affecting the fœtus *in utero*. Nor can we always determine with precision which order of events we have to deal with. Yet in certain cases we can have no doubt that we deal with undoubted reversion, brought about either by defect in the germ plasm of one or both parents or by the interaction of dissimilar germ plasms.

Darwin's Experiment.—The classical example of the latter method of inducing reversion is afforded by Charles Darwin's[1] well-known observations upon the effects of crossing a barb-fantail female pigeon with a barb-spot male, from which cross there developed a "bird hardly distinguishable from the wild Shetland species" (of blue-rock pigeon, *Columba livia*). The Columba livia is the ordinary wild pigeon, common over a large portion of the northern hemisphere; everything indicates that from it during the course of long centuries, and by artificial selection the extraordinarily divergent varieties of tame pigeons have been developed. Similar results have more recently been obtained by Ewart.[2] Crossing an absolutely white fantail, with thirty feathers in its tail, with an owl-archangel hybrid (the "owl" a powdered blue pigeon, with short beak, the "archangel" copper-colored, with well-developed

[1] Animals and Plants under Domestication, 1: 204

[2] The Penycuik Experiments, 1899: 26.

crest), he obtained a bird almost identical in measurements with the blue-rock, while in color and markings it showed complete reversion to the checkered blue-rock of India, and, like that, had only twelve tail-feathers. History indicates that the cult and culture of the domestic pigeon began in the East, and, like the crow—and like man—the wild pigeon shows variation in different regions of the earth's surface.

Here, obviously, by crossing widely separated varieties of a species, we obtain not the domination of the characteristics of one or the other, but a reversion to an earlier type. We occasionally encounter in man instances apparently of the same nature, in which parents, each of sound constitution and each well developed, but coming of widely distinct stocks, have a series of children who, in bodily constitution and mental growth, are distinctly of lower type.

Familial Degeneration.—More often, however, in man we encounter cases in which reversion is to be ascribed not to antagonism of the germ plasms, but to defect in the same, defect which, as we shall point out, is to be regarded as primarily brought about by toxic influences telling upon and modifying the constitution of the parental germ cells. Such are the class which nowadays, though we do not wholly like the term, it is the custom to describe as *degenerates*—the progeny of those leading vicious lives. The typical degenerate is of poor bodily development, brain smaller than the normal, with convolutions less abundant and less fully formed, of degraded physiognomy, little capacity for sustained attention or for prolonged thought, cunning rather than intelligent, deficient in moral sense—in all these points resembling the lower, less-developed races of our species. No one studying a well-marked example of this order can fail to be impressed by the reversion to a lower type. The fortunate tendency is for families of this type to deteriorate in successive generations, for the latter members of this heritage of misery to exhibit idiocy, non-viable children, monstrous births, still-births, and so on, so that by the third or fourth generation the sins of the father have told so surely that the stock dies out.

6. **Diathetic Reversion.**—What must be regarded as a slighter grade of the reversionary process is still more frequently encountered—conditions in which one or other system does not attain full development, and in which the incomplete development descends from one generation to the other. We have already laid down that where the environment is unfavorable, conditions of latest development are those most easily lost; those of oldest phylogenetic acquirement are most firmly retained. The widest and latest evolved distinction between man and the other animals is the development of the higher nervous centres in the former. It is noteworthy how relatively unstable and various in their development are these centres; no other tissues of the organism vary so greatly in their functional capacity. This capacity, it is true, cannot easily be measured, but the variation is well indicated by certain figures from Cambridge University.[1] There they afford the

[1] For these I am indebted to my friend John Greaves, Esq., M.A., Christ's College.

students the option of taking either the ordinary or the honors course, and the better-trained men, who select the latter, have the choice of no less than eight triposes, or honor examinations, in different subjects, from mathematics and theology to Indian languages and agriculture, to work at for three years. The choice is thus singularly wide. The most celebrated of these tripos courses is that in mathematics; it draws the best men from all over Great Britain. The questions given range over a wide area, and the papers are set and marked not by one, but by several mathematicians of distinction, the candidates being in each paper given a choice of more questions than it is possible to cover in the time.

The examination, we repeat, is not compulsory; all who enter have had a mathematical training and a *penchant* for the subject. The following figures give (1) the maximum marks obtainable were every question answered and every problem worked out on each of the eight days the examination lasts, the average being struck for two successive recent years; (2) the mean of the marks obtained by the highest candidates (Senior Wrangler) in the successive years; (3) the mean mark of the two lowest candidates to obtain first class honors; (4) the mean mark of the "Wooden Spoon" in those two years, *i. e.*, of the last candidate to be granted a "pass."

AVERAGE OF TWO ORDINARY YEARS, CAMBRIDGE MATHEMATICAL TRIPOS.

	Maximum marks obtainable.	Maximum obtained Senior Wrangler.	Lowest Wrangler.	Wooden Spoon
Total examination	4873	1896	942	190
First four days only	1486	787	477	170

Mr. Greaves has afforded also the figures for the first four days only, as the papers on these days cover what may be termed ordinary mathematics, and the ordinary man often has little knowledge of the advanced mathematics of the last four days. The mean "Wooden Spoon" secured only 20 marks in the second, advanced part of the Tripos, out of a possible 3400 or so). Even in these routine mathematical subjects the first man secures close upon five times as many marks as the last, whereas in the total examination he scores nearly ten times as many. There is, indeed, the memory of a Tripos in which the Senior Wrangler (now a member of His Majesty's Ministry) secured twice as many marks as the second on the list (now a university professor of worldwide reputation).

It is difficult to imagine the difference in the development of the associated centres for calculation, figures, expression, and writing between the Senior Wrangler and the "Wooden Spoon" (the lowest on the pass list)—and also between the latter and the born idiot.

While here, again, mental development may be arrested by intrauterine or postnatal influences, and that mental power is capable of great development by proper training, it is abundantly evident that mental capacity in the main is a matter of inheritance. We possess

much evidence that imperfections of the higher centres and mental instability of various grades are markedly liable to descend; cases, indeed, are on record in which certain grades have shown themselves in the same family for two centuries and more. Marriage with those of good mental state reduces the liability, intermarriage of members of the same neurotic family is seen most markedly to increase the liability. In some cases the descent is *homeomorphic:* in others, *heteromorphic.* The former type would seem to indicate the inheritance of some particular anatomical imperfection, or the subjection of the members of successive generations of the weak-headed to like strains, producing like results; the latter is nowadays accepted as indicating a general imperfection of development of the higher centres. For some years, so long as they are not subjected to strain, these reversionary individuals may show little departure from normal; subjected to some particular strain—alcohol, syphilis, or other infectious disease, anxiety, religious emotion, or intense mental activity of other nature—and the brain gives way in one or other direction, according as the strain falls on one or other centre. Thus, the mother may have religious mania, the son become an epileptic or victim of general paralysis, and his son be an imbecile.

Yet another recent and special acquirement of man, as distinct from nearly related animals, is his power of resistance against, and of susceptibility toward, sundry infectious diseases. These powers also vary considerably, and, like mental capacity and deficiency in the same, are largely a matter of inheritance. Indeed, a lack of resistance toward infection frequently accompanies mental weakness—as it accompanies the more pronounced reversionary degenerations—rendering the children weakly and liable easily to succumb to childish ailments. Just as we noted that certain neuroses are distinctly inherited, so do we observe specific inheritance of susceptibility to one or another infectious agency. We have called attention to this in the different races of mankind; we observe it also in particular families: this family is particularly susceptible to tuberculosis, that to scarlet fever. What is still a matter of debate is whether an infectious disease affecting an individual under any conditions renders the offspring either more or less susceptible to that disease.

7. **Cumulative Inheritance.**—It occasionally happens that the blend, instead of showing a given property to an extent intermediate between what the two parents exhibit, shows this more pronounced than does either parent; there is, as it were, a summation rather than a mean product. Examples of this order are not frequent, nevertheless they do occur. Thus, Mendel noted that the hybrids of certain peas, short-stemmed and long-stemmed, respectively, developed constantly a much greater length of stem than either parent form, or than the pure progeny of the longer stemmed subspecies. Nor can the cases properly belonging to this class be ascribed to atavism. The conditions leading to cumulative inheritance are, so far, wholly undetermined, but its existence throws some light upon the condition next to be studied.

8. **Spontaneous Variation; Mutation.**—So far we have had to deal with conditions present in the ancestors and conveyed to the individual, or failing to be so conveyed; there is yet another condition to be taken into consideration, namely, the appearances in the offspring of conditions and relationships which are new to the stock. These we speak of *spontaneous variations*. Of such, numerous examples in animals and plants have been collected together by Bateson;[1] the most easily grasped examples of the conditions occur in flowering plants. The tulip, for example, is a plant having a six-partite arrangement of organs, well seen in the flower. Now, occasionally in a bed or field of these plants flowers are to be encountered showing a four or five-partite arrangement. The trefoil, or shamrock, and the clover, have tripartite leaves; careful search in certain localities frequently afford leaves which are quadripartite, five-partite, and, very rarely, six-partite. Everything is opposed to the belief that the Liliaceæ, to which the tulip belongs, are descended from a four- or five-partite ancestry, or that the shamrock had originally cruciform leaves. Or otherwise, in this and numerous similar instances, reversion is incapable of affording an explanation.

The frequent existence of these spontaneous variations has not been sufficiently recognized in man. By hook or by crook, anomalies of excess, supernumerary fingers, toes, vertebræ, ribs, teeth, breasts, hair, etc., have one and all been attributed to reversion or atavism, so called, no matter how far back, or how far off the probable line of descent, it is necessary to travel to find a form possessed of the condition—of seven digits, for example. Thus, take the case of supernumerary mammary glands. In mammals possessing several pairs, these are arranged in a row on either side of the ventral median line, either over the abdomen alone or stretching well over the thorax. The number of pairs is in relationship to the number of young brought forth—from one pair in man to five pairs in the sow.

Now in man it is not so very rare to have the presence of one or more accessory mammæ—generally so small as to attract little notice, and less inconvenience, but sometimes large and well developed. These are situated, whether paired or unpaired, at some point or points along converging lines stretching, roughly, from the region of the axillary angles toward the symphysis pubis. Their position along these lines strongly suggests reversion toward the condition of a many-breasted ancestry. But, in the first place, what positive knowledge have we of such many-breasted ancestors in the direct line of human descent; and, in the second, how are we to account for those cases in which the supernumerary mamma is situated—as it may be—on the back of the shoulder, or the buttock—regions never the site of mammæ in the lower animals?

And why, to continue this line of argument, do we not find the greatest number of mammæ in the very lowest mammalian forms? The ornitho-

[1] Materials for the Study of Variation. London, Macmillan, 1894.

rhynchus possesses only one pair. Atavism will not explain the progressive increase in number as we proceed upward along the line of ascent of certain species of mammal. Spontaneous variation, with subsequent inheritance of a favorable variation, must have occurred in them to produce the result, and if it has occurred in the one order of cases, it is simpler to invoke it to explain the other set, and this the more easily when we recall that the mammary glands are not totally new organs, but, strictly speaking, are collections of hypertrophied and modified sebaceous (or some would say sudoriparous) glands, of glands scattered all over the mammalian integument. It is true that more than one embryologist has called attention to the existence of a ridge—the mammary ridge—extending bilaterally in the fœtus in the position of the mammary line already referred to; but in no mammal do mammæ present themselves normally along the whole length of this ridge, and when variations do occur the existence of this ridge does not make them any less spontaneous.

Regarded thus, the more we consider the subject the greater appear to be the number of cases of spontaneous variation.

It may, indeed, in general be laid down that when a condition is progressive, or when on the contrary, it appears to be regressive, but is isolated and unaccompanied by other indications of regression and incomplete development, then the indications are that we deal with spontaneous variation rather than with reversion. We would thus equally include in this class cases of polydactylism and bradydactylism (shortness of certain phalanges), supernumerary vertebræ, as well as reduction in the number of the same, supernumerary and deficient ribs.

Once these occur, they have a tendency to be inherited. We have already referred to the case of inheritance of polydactylism.

Closely allied, and apparently due to the action of the same causes, are certain conditions of defect, which nevertheless cannot be attributed to reversion, they reproduce no stage in the previous history of the race, and these, too, are singularly liable to be inherited; such are *articular laxity* (with liability to spontaneous dislocation of various joints), *ichthyosis* (with peculiar modification of the growth of the epidermis, so that the cells produced abundantly do not scale off, but accumulate to form thick masses or scales over the body), *hemophilia* (with its peculiar instability of the vascular system, rendering hemorrhage liable to occur upon the slightest provocation, and with inheritance not direct but through the female, who herself does not show the affection). Possibly in this class is to be included *Daltonism*, or color blindness, in which, while we have no evidence that the formation of the eye is modified, the individual is unable to recognize certain colors.[1] So, also, several observers have noted that certain *tumor formations*, such as the development of multiple lipomas (fatty tumors), enchon-

[1] A letter from Mr. Bateson, received while this chapter was passing through the press, affords evidence that Daltonism must be regarded as varietal and subject to Mendel's law.

dromas (cartilaginous), and exostoses all tend to be inherited. All tumors proper, it may be noted, are progressive in type; as to how far they are to be regarded as primarily the result of spontaneous variation will be discussed later.

This may be noted that the spontaneous variation, even when liable to be inherited, is not necessarily useful. There is some evidence that if its development be correlated to that of some useful property, a useless or apparently useless variation may become a specific character. Thus, Bland-Sutton[1] calls attention to the callosity on the inner side of the foreleg of the horse as a probable example of correlated inheritance. That area of cornification of the epithelium is not possessed by other species, and its existence, save on this supposition, is an enigma.

Of late years the distinguished Belgian botanist de Vries[2] has thrown considerable light upon the appearance of this spontaneous variation. Cultivating the plant *Œnothera lamarckiana* (one of the evening primroses) for some fifteen years, he noted the appearance from time to time of individuals which definitely varied from the parents. These appeared suddenly in growths of large numbers of young plants which, as a mass, did not depart from the parent stock; and, what is more, these "mutations," as he terms them, were true to seed. Thus in 1895—to quote an instance—there appeared the relatively huge *Œnothera gigas*. There had been no gradual variation leading up to it; the appearance was sudden, and, subjected to self-fertilization, this single plant afforded seeds giving origin to several hundreds of the *gigas* type. Here, at a bound, a new species was seen to develop, and de Vries lays down very decidedly that new species are not brought about by the accumulation of small individual variations, but in nature and during the course of the artificial culture of plants there appear occasionally, if not periodically, individuals manifesting changes so pronounced from the beginning, and these so distinctly heritable, that one has to regard these individuals and their descendants as constituting a new species. He holds, indeed, that in all cases evolution is of this discontinuous type. These mutations, it will be seen, are what we have considered as spontaneous variations. With this view I cannot but agree. To quote Jacques Loeb:[3] "If the determinants are comparable to a series of compounds, *e. g.*, of alcohols, there is no more a transition possible between two species separated by a difference in only one determinant than there is a transition possible between two neighboring alcohols of the same series."

It will be seen from the following chapter that with this view of Loeb we must largely agree.

What is the cause of these spontaneous variations must be approached with caution. The fact already noted, that crossing of unlike races occasionally leads with certainty to offspring possessing a given property

[1] Introduction to General Pathology.

[2] Die Mutationstheorie, Versuche u. Beobachtungen, etc., Leipzig, 1: 1901

[3] The Dynamics of Living Matter, New York, Macmillan, 1906: 225.

so developed as to suggest that the development represents the sum of rather than the mean between the individual possession of the two parents, would indicate that amphimixis is immediately concerned. Nevertheless, recent botanical observations would suggest that influences brought to bear upon the parent and its germ plasm are, in some cases at least, the prime cause. Thus, Macdougal[1] notes that, taking the *Raimannia odorata*, another member of the evening primrose family, and subjecting its ovules to 10 per cent. sugar solutions and solutions of calcium nitrate (1 to 2000), definite mutants were obtained; several individuals developed from the seed were of a type wholly different from any previously seen, and their appearance could only have a direct relation to the operation.[2]

[1] Popular Science Monthly, September, 1906.

[2] "The parent was villous-hairy, the mutant entirely and absolutely glabrous; the leaves of the parent have an excessive linear growth of the marginal portions of the leaf-blades, and hence become fluted; the excess of growth in the mutant lies along the midrib, and the margins become revolute. The leaves are widely different in width, those of the mutant being much narrower. The parental type is of a marked biennial habit, and near the close of the season the internodes formed are extremely short, which has the result of forming a dense rosette; the mutant forms no rosette, by reason of the fact that the stem does not cease, or diminish its rate of, elongation, and hence presents an elongated leafy stem, which continues to enlarge as if perennial. The flowers of the mutant were closely guarded, and as soon as seeds were obtained these were planted to obtain a second generation. A few plants were obtained which in every particular conformed to the new type and exhibited no return to the parental type."

CHAPTER XV.

INHERITANCE—(CONTINUED).

THE THEORY OF INHERITANCE.

THIS enumeration of the various forms of inheritance is apt to leave the impression that the possibilities are so varied and so haphazard that it is a hopeless matter from such data to construct any theory of inheritance capable of application to all or nearly all the cases. Certain facts, however, stand out, and utilizing these, we may advance to a certain extent:

1. In the first place it is evident that, although considering any one feature, it may happen that that feature does not present itself in the immediate offspring, nevertheless the whole modern study of heredity proves convincingly that where the individual is the offspring of two members of the same species in each parent affords equivalent contributions to the offspring. These equivalent contributions of heritable material may, it is true, in one or other respect not be of equal potency; but there they are, and, contributed to the germ cells of that offspring, they may demonstrate their existence in the individuals developed from these germ cells.

This law, if we may so term it, is correlated with and evidently based upon the fact that in conjugation each parental germ cell supplies a like contribution of nuclear matter to the primordial cell of the new individual; half the chromosomes are of paternal, half of maternal origin. No other conclusion is possible than that the heritable material resides in these chromosomes.

2. If this be so, the different forms of inheritance must be related to the properties of these chromosomes and to their interaction. Our theory of inheritance must, therefore, be essentially one which deals with the chromosomes and their constituents.

3. We have already laid down that the primordial living matter of the cell is contained in the nucleus; it is this matter that must be carried over in the chromosomes. From this it follows that our theory must be expressed in terms of the biophoric molecules, and that we have to endeavor to conceive a constitution of and mode of interaction between these biophores from the two parental germ cells which will satisfy the various conditions.

4. Coming now to analyze the different forms of inheritance, we make out that a particular feature showing itself in either parent may:

(*A*) Present itself also in the offspring:

1. Dominant, wholly replacing the corresponding but divergent feature seen in the other parent.
2. Blended, this particular feature in the offspring being intermediate in character between that exhibited in the two parents.
3. In mosaic form, in certain cells the paternal in others the maternal feature being dominant.
4. Blended and excessive, the feature being more pronounced than in either parent.

(*B*) Be unrecognizable in the offspring:

1. Recessive, and replaced by corresponding feature derived from the other parent, but as such latent, capable of reappearing in later generations.
2. Absent, wholly wanting in subsequent generations, the absence being due either:
   (*a*) To casting out of an inherited condition, or
   (*b*) To the feature seen in the parent being an acquirement and not an inheritance.

5. Or, on the other hand, considering the individual, we note that as regards any particular feature or group of features there may be:

(*A*) *Normal Inheritance:* The offspring not being in this respect advanced beyond either parent, but at the same time not fallen behind.

(*B*) *Progressive Inheritance:* The offspring being advanced beyond the more advanced of the two parents and exhibiting either:

1. Excessive development of the condition or conditions already observable in one or both parents, or
2. Spontaneous variation (mutation), *i. e.*, the appearance of conditions not previously noted in either parent or either parental stock.

(*C*) *Retrogressive or Reversionary Inheritance:* The offspring reverting as regards any feature or group of features to a lower stage in the phylogeny of the species.[1]

(*D*) *Non-Inheritance:* Apparent or actual.

From this analysis one thing at least is obvious, namely, that the biophores derived from either parent are liable to retain their identity for some generations. Or, to be more accurate, that qualities conveyed by the parental biophores may be retained even if in a recessive, latent condition.

That, indeed, is clearly proved by the Mendelian studies on hybridization: after six generations or more with self-fertilization the hybrid

[1] We are acquainted with no satisfactory evidence that this class should be redivided into *recessive* and *complete*. On the contrary, it is the experience of pigeon breeders that once, by cross-breeding, the old blue color and characters of the wild pigeon reassert themselves, it is hopeless to use such birds for breeding purposes. Even when mated with birds of pure breed and dominant type it takes long to cast out the signs of such reversion.

can give origin to plants exhibiting the pure features of either the dominant or recessive ancestor. Conjugation cannot therefore be of the nature of a chemical union of the biophores from the two sources with resultant formation of a new biophoric substance. On the other hand, we cannot conclude that all the separate biophores contributed by and representing each ancestor are potentially present in the fertilized ovum. This would demand an infinite number. The existence of determinants such as Weismann conceived is, as we have pointed out, a physical impossibility, and this is equally so; were ten generations represented that would demand the presence in each chromosome of more than one thousand separate orders of biophores.

Our way, then, lies between Scylla and Charybdis. Still, between those two the cautious mariner could advance his craft and, the gods helping, could achieve through the straits. And here we would urge that our conception of the constitution of the biophore affords us a proper equipment to achieve the passage. We have, it will be remembered, been led onward to regard the biophoric molecules as composed of a central body or ring of nuclei provided with side-chains which are dissociated with greater ease. As the environment has been modified, so have the side-chains undergone modification, and as these side-chains become utilized in the polymerization of the biophoric matter and the formation of new biophores, so has there been a progressive increase in complexity of the biophoric molecule. We have pointed out how, neglecting determinants, we must regard the biophores in the somatic cells as undergoing extensive modification when their environment has become altered, whereby they have given rise to or controlled the different orders of cells in the different tissues (p. 114). As regards the germ cells, their biophores must similarly be influenced, for it is upon their modification that the whole evolution of living forms has depended. Clearly the biophores of the human ovum are vastly more complicated than those of the amœba, or, again, than those of the lowest multicellular organism of the line of man's ascent, and yet the progressive elaboration of the soma or body throughout the course of the ascent has been the outcome of the germ plasm and the biophores of the same within ovary and testis.

6. There are two, or three, possible causes for the progressive variations of multicellular organisms: the mingling of germ plasms in conjugation (amphimixis), the effect of environment on the respective germ plasms, and the effect of both of these combined. The first of these was strenuously upheld for long by Weismann as the controlling cause, but he was compelled to admit that the second must also be in action. In regard to this second cause, we have demonstrated that it is clearly in action in unicellular organisms which do not conjugate, as also in the somatic cells of the highest multicellular forms of life (p. 105); it is illogical to deny its action upon the germ cells of the same. Not to waste time by taking part in what has been an angry discussion, we are prepared to accept the third course—to admit that both the action of external agencies and amphimixis are factors in variation, retrogressive as well as progressive.

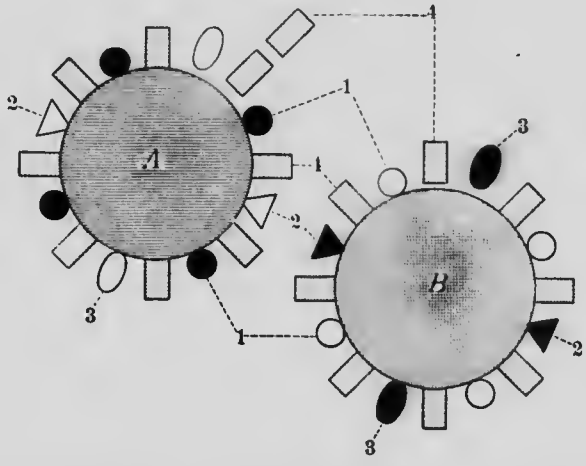
7. Granting this, and admitting that through the action of both causes it comes to pass that the germinal biophores in no two members of the same species are absolutely alike in constitution, what must we conceive to be their action upon each other when, through conjugation, biophores of two orders come together in the same cell, the fertilized ovum?

The facts of inheritance, and what we know regarding its histological basis entirely refute the hypothesis that the biophoric molecules as a whole undergo chemical union. We may, however, conceive these, in the first place, as lying side by side in a common cytoplasm or, to be more exact, nuclear sap, in the process of assimilation attracting ions in the surrounding medium, building these up into side-chains of different orders. Of these side-chains, some of them are identical—common, that is, to the molecules of both sets of biophores—some, on the other hand, of unlike constitution, so that certain side-chains having corresponding position or attachments in the two sets of parental biophores are dissimilar. As demonstrated by studies upon immunity, we regard such side-chains as detachable and apt to be detached, that is, to be developed in excess, and then, becoming loose, passing into the surrounding cytoplasm. Again, as we have pointed out (p. 83), we must regard growth and increase in the number of biophores as brought about, in the first instance, by the building up of nuclei or side-chain matter, this matter attracting other matter in due order, so that gradually new rings are constituted—new biophores. If these views be correct, then, when molecules of closely allied constitution and properties are growing side by side, what is there in this process to determine that side-chain matter, which has been liberated under the influence of the one set of biophores and has become detached, does not become attracted to and built up into the substance of the "growing" biophores of the other set? I cannot but hold that under these conditions—that is, conditions under which we have compound molecules of very similar structure becoming built up side by side—this must inevitably occur in a common fluid medium. Whenever a greater affinity exists between the components of one growing biophore and certain side-chain nuclei developed under the influence of the molecules of the other set of biophores, then these nuclei will be apt to be built into, to become an integral part of, the new biophores, to the exclusion of the corresponding nuclei—those proper to the original molecules. In short, there will be, physically speaking, a contest between the two orders of growing biophores and, to a certain degree, a selection or rearrangement of constituent nuclei. This rearrangement in the simplest case will result in an interchange of constituent parts; in other cases, may result in side-chain material derived from one parental biophore, and possessing powerful affinities to the growing biophores of both orders, becoming built up into both sets, to the exclusion of corresponding but weaker side-chains (so that these become wholly cast out), and with this the properties determined by their presence disappear in the next generation. In other cases, again, we can premise an interaction between certain side-chain groups

derived from the two parental biophores, the resultants of this interaction becoming built up into the growing biophores, this interaction having as a result either an exaltation or a depression of parental character, or, again, leading to the production of mutation.

Granted, that is, that in its broad lines we have come to realize the mode of constitution of the proteidogenous molecule, that we are justified in assuming that the biophoric or living molecules partake of similar constitution, and that our conception of growth is that which must be accepted, then under these conditions growth, in a common medium, of biophoric molecules of two orders, alike in general constitution but differing in certain of their component chemical nuclei, must result in a certain amount of interchange of those nuclei. Two sets of biophores may still be traced in the blastomeres, in germ cells, and other cells

FIG. 35



Schema of mode of interaction of two biophoric molecules in a common cell sap: *A*, of maternal; *B*, of paternal origin. 1, 2, 3, allelomorphic side-chains, which, when liberated into the cell sap, will be attracted to the biophore exercising the strongest affinity; 4, side-chains common to both molecules, built up indifferently into either.

derived from the fertilized ovum; two sets each derived by direct physical descent from the original paternal and maternal biophores and chromosomes respectively, but the members of each of these while building up into their structure material assimilated by their legitimate progenitors, attract for purposes of growth allelomorphic[1] matter formed similarly by the other. By this method, apart wholly from what may be regarded as external influences acting upon the germ cells during their existence within the organism of the individual, it must come to pass that through

[1] Bateson employs this term in connection with Mendelism, to indicate the corresponding or antagonistic property, either dominant or recessive, the two allelomorphs forming a "pair."

conjugation the biophores giving rise to a new individual are not identical with those of either parent, and that each comes to lose certain properties which belonged to the biophores of the one, and gain some belonging to the biophores of the other. If this be so, then we can picture that in the process of reduction and casting out of biophoric material in the development both of the oocyte and of the spermatocyte, *while there are delivered to the ovum molecules of living matter which in direct descent have been derived from one parent only, those molecules may convey to the ovum constitution and properties which have been derived from both parents.* In this way, without any increase in the number of determinants or ids, by this chemical modification of biophores, a constant number of such biophoric molecules may become the bearers of properties derived from a long series of ancestors.

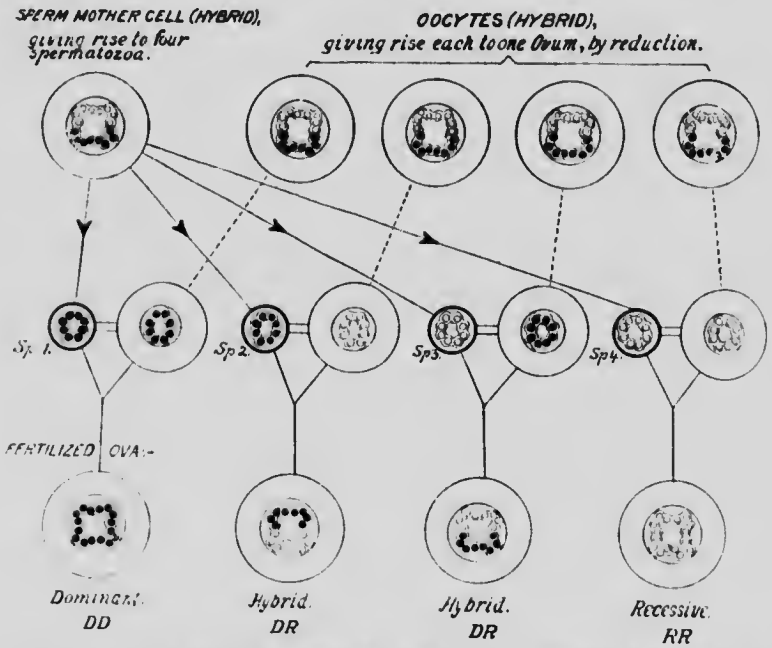
We purposely do not here consider all the different types of inheritance, for this is not a full treatise on the subject. We have taken up forms that are sufficiently wide apart to show that this biophoric theory is capable of elucidating their occurrence. It appears to us to have the great advantage of explaining how hereditary characters may be conveyed through a relatively small number of molecules of highly complex organization; how those molecules can in the course of amphimixis undergo modification through interaction; how they can become modified through the action both of amphimixis and of environment; how similarly they may undergo retrogressive changes and lose certain properties under the same influences.

8. With reference to the action of environment on the germinal biophores it is still necessary that something be said, but our treatment of the subject of amphimixis will not be complete without reference to the remarkable reduction process which precedes fertilization. The mode of that reduction we have already described (p. 131 et seq.). We have seen that in the process of maturation of the ovum three-quarters of the chromatin present in the penultimate stage of the process is cast out (the three polar bodies), one-quarter only being retained, and that similarly the spermatozoon is developed from one-quarter of the nuclear matter of the primary spermatocyte. As shown by the abundant recent studies on Mendelism, the results of this reduction may be very remarkable; certain properties may at a single conjugation be thrown out so completely that they do not reappear in subsequent generations.

During the very first process of reduction in a hybrid a property or properties derived from the one parent may thus be thrown out; and yet when the parents had differed in several particulars, at this same moment properties derived from the other parent may likewise disappear. And as in such hybridization there may be as many as a score of properties in which the two parents had been contrasted—size, color of flower, position of flowers, shape of leaf, hairiness of leaves, shape of seed, etc. the process of sorting prior to this casting out, if we regard these qualities as conveyed by distinct ids or determinants, is beyond conception. It demands so exact a localization in each chromosome of the particular determinants, and at the same time so precise a distri-

bution of the determinants for the various properties, that by no possible means have we been able to visualize what is supposed to happen. By the biophoric concept this casting-out process is, we think, comprehensible, namely, as already stated, we can imagine that during the sojourn together of the parental biophores in the germ cells of the new individual, from the moment of fusion of the parental germ plasms to give rise to that individual up to the maturation of his or her germ cells,

FIG. 36



Schema to illustrate Mendel's law regarding the second hybrid generation as regards a single pair of features; as also to illustrate the effects of reduction of the chromosomes in oogenesis and spermatogenesis.

Each germ cell (first row) is originally provided with chromosomes of paternal (black) and of maternal origin (white). The existence of the law demands that in the process of reduction the ovum and the spermatozoon (second row) become provided with chromosomes (and biophores) that are of either paternal or of maternal descent, but not of both; although as above noted the biophores may in their growth and development have attracted side-chains formed primarily by the opposed order of biophores, to the exclusion of those originally belonging to them.

there is an interaction and interchange between the side-chains to whose presence is due these contrasted features, and this of such a nature that the newly developed biophores, descended, let us say, from the biophores of the female parent, have not the identical composition of those parental biophores. In the process of growth and formation there has been, as it were, a selective process. Owing to greater affinities, they have attracted and built unto themselves certain side-chains derived from the paternal biophores, and from merely attracting them in the first

place have come to form them actively. According to our conception, that is, a side-chain, to whatever central ring it is attached, tends to attract ions and radicals of a particular order to itself, so as to reproduce itself in series. This interchange depending upon chemical affinities will not be universal, affecting all the side-chains of both paternal and maternal biophores; the newly formed biophores will present an admixture of the two orders; they will occupy definite positions in the nuclear thread and in the chromosomes derived from that thread.

Thus it will happen that in the process of reduction, as indicated by the studies upon hybridization, the maturing ovum, or the spermatozoon, may come to contain biophores purely of paternal or purely of maternal origin.[1] The accompanying diagram indicates what we conceive to be the process (Fig. 40).

Along these lines we believe it is possible to conceive the conveyance of a limited number of biophores in the germ cells from generation to generation, those biophores under favorable conditions gaining through amphimixis accretions to their properties, under unfavorable conditions becoming shorn of certain properties, and as a result the individuals developing from these germ cells may show either progressive evolution or devolution. To apply these considerations to the facts of hybridization, etc., and thereby exemplify the mode of action of Mendel's law would be altogether beyond the scope of the present work.

THE INHERITANCE OF ACQUIRED CHARACTERS.

The above considerations upon amphimixis and its influence in causing the offspring to vary from either parent accept tacitly, it will be seen, the fact that there is variation between the two germ cells which enter into conjugation, but throw no light upon the primary cause of that variation. It is impossible to arrive at any other conclusion than that variation originates primarily in the action of modified environment upon the labile bioplasm. Nay, more, as we shall have to point out, such action of environment upon the germ cells during the course of their existence in the parent cannot be regarded as non-existent, though there are those who deny it; for upon its existence hangs the solution of the question whether any order of characters acquired by the parents in the course of their life can be conveyed to the offspring, and we cannot close our treatment of heredity without taking side in this ancient controversy.

To what extent, if any, can acquired characters be inherited?

Before answering this it will be well to classify the characters which may be acquired; first, we may divide them into the progressive acquire-

[1] So far as we can see, there are no indications that a given germ cell contains, for example, three-quarters of the grand paternal and one-quarter of the grand maternal. The rule appears to be that there is exclusive representation or it may also be equal, the one series lying latent; although there are difficulties in connection with this latter conception. This in itself indicates that the number of biophores gaining entrance is relatively small.

ments and the regressive. Among the former come the increased use of parts, with improved functional activity of the same, swifter response to reflex or other nervous stimulus, and to these we must add acquired immunity to disease. Among the latter, mutilations and loss of parts; arrested development of parts, and abnormalities brought about by disturbances during development, whether the influence causing these have told upon the organism during intrauterine existence, or after birth during the period of postnatal growth; atrophy of tissues through disease, both in childhood and more particularly during adult life; retrogressive changes in the tissues brought about by disease or more broadly by intoxications of various orders. For we recognize more and more clearly, not merely that bacteria and the larger parasites produce their deleterious effects upon the organism at large almost entirely through the agency of the toxins which they elaborate, but also that disturbances of very many orders which lead to continued depressed or perverted function of one organ lead thereby to either heaping up in the system of the deleterious substances which should be acted upon by that organ, or to modified internal secretions of the same, and so secondarily to poisoning of other tissues. These subjects will be dealt with more fully in the subsequent chapters upon Intoxication, Infection, and the Internal Secretions. Lastly, there may here, under protest, be included the legendary maternal impressions, because these are popularly and loosely held to come under the heading of acquired conditions.

1. **Maternal Impressions.**—We will deal with these first. If a mother while bearing her child has been frightened by a toad jumping toward her unexpectedly, and subsequently brings forth an anencephalous, toad-like monster, it must, *imprimis*, be advanced that the mother has not acquired that toad. None of the cases on record (and American medical literature a few decades back abounded in them) are in any sense instances of acquirement of a condition by the parent which is reproduced in the child. In the second place, if now the nervous theory be adopted and it be urged that a pronounced shock or stimulus referred by the parent to one area of her person is reproduced in a like area on the person of the child, it has to be pointed out that the child *in utero* is a separate individual, unconnected with the maternal nervous system; and, thirdly, with the rarest exceptions the fright or profound influence noted by the mother are stated to occur *in the later months of pregnancy*, when the different organs and parts of the fœtus are already not merely laid down, but advanced in development, and we know that monstrosities and abnormalities date most often from the very earliest period of fœtal life. All these tales are at the most examples of coincidence, where they are not the bizarre product of the female imagination.[1]

2. **Use Acquirements.**—Of acquirements in the strict sense of the word there is a complete lack of evidence that "use acquirements" are trans-

[1] See McMurrich, The Physician and Surgeon (Ann Arbor), for an interesting study of the subject.

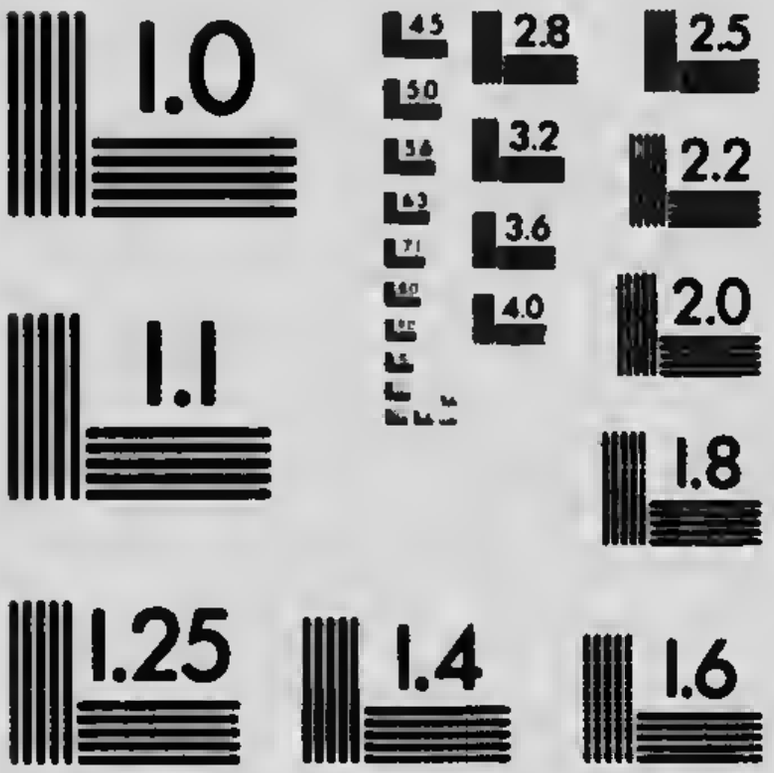
mitted. The blacksmith's son has not larger biceps than has the ordinary individual, nor with our knowledge of the relations of the germ cells to the rest of the organism, can we conceive why he should have. The utmost we can accept is that if the blacksmith has by exercise kept his system in excellent coordination, his germ cells will benefit thereby and his progeny be sound and generally well developed. But that one particular muscle or group of muscles should be picked out for progressive advance cannot be grasped. Confusion is here apt to arise between preëminent qualities that are inherited—the results in the first place of fortunate amphimixis—and such use acquirements. A great composer, for example may have descendants with musicianly qualities above the normal: we have the Bach family, and more recently the three generations of Strauss, of waltz fame. In mental ability may be mentioned the Cecil and Sheridan families, the Darwin and Wedgwood group; but in no one of these cases have we the slightest evidence that the peculiar ability was acquired in the first place. More often than not the great genius has mediocre descendants; more often than this, none at all.

3. **Acquired Immunity.**—The evidence so far is against this becoming inherited. The latest extensive observations—those of Lustig[1]—upon fowls rendered highly immune to abrin showed, indeed, indications of the reverse, the chickens in some cases being more susceptible to the special poison than were ordinary chickens of like age. For such observations mammals are ill adapted, or if employed the males alone should be immunized, for if the females be immunized there is the possibility, not to say the likelihood, that the antitoxins which have been developed in the mother may be conveyed to the offspring both through the placenta and through the milk, whereby some grade of passive immunity is liable to manifest itself. We shall, however, revert to this matter shortly.

[1] Ctbl. f. Pathol., 15: 1904: 210. While this work has been passing through the press there have appeared the observations of Couradi (Ctbl. f. Bakt., Abt. I, Originale, 46: 1908: 139), upon the transmission of acquired immunity to rabies in the dog. He found that the offspring of a dog which had been immunized to this disease for three and one-half years, and a bitch immunized for five months showed very definite increased immunity, even to the most severe form of inoculation (intradural). Four of the six puppies survived doses of the virus which killed the controls in eight to ten days, and the two that succumbed did so only after lengthened periods of incubation. There have been not a few investigations along these lines with the infectious diseases, in general with negative or discordant results, or without adequate recognition of the conditions demanded for the proper carrying out of the experiments. Even here we deal with but one litter, and it might be objected that the immunity was of intra-uterine acquirement, from the blood of the immunized mother. To afford absolute proof, in mammals, of the transmission of acquired immunity it is essential to immunize the male parent alone, and that through a series of successive generations, and what is to be expected under these conditions is a Mendelian inheritance, certain of the progeny being immune, the others not.

MICROCOPY RESOLUTION TEST CHART

(ANSI and ISO TEST CHART No. 2)



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4. **Mutilations and Loss of Parts.**—It is a commonplace that the man who has lost an arm or a leg does not beget one-armed or one-legged children, but, on the contrary, offspring having the proper equipment of well-formed limbs. There is, it may be stated, no satisfactory recent case on record in which loss of a part by either parent has led to the offspring being minus that part. Weismann[1] cut the tails off successive generations of mice as soon as they were born; the twenty-second generation showed tails of perfect formation and normal length. We have the trite example of the Jews who have been circumcised religiously since the days of Abraham and in whom the boy children have still to be circumcised.[2] Here again, as in connection with overdevelopment of one or other region of the body, it is not unlikely that the loss of a limb or important organ may have influence on the bodily health, and so tell—in this case deleteriously—on the nutrition of the germ cells, but such influence must be general and not specific, leading to arrested development of one special organ or part in the embryo.

5. **Arrested Development of Parts Due to Intra-uterine Disturbance.**—We have been able to collect very little evidence under this heading, and the subject deserves fuller attention than has been given to it. Certain of these arrests are so extensive, as, for example, conditions of anencephaly due to amniotic pressure or adhesions, that life is arrested, and others not so severe must undoubtedly lead to general malnutrition, which must tell in a general way upon the germ cells. The difficulty before us consists, as we shall have further to point out in discussing abnormalities, in determining in very many instances whether a given arrest is inherent, due to the imperfect constitution of the embryo, or of external causation, brought about by intra-uterine conditions. But so far as we can see, a local arrest of development of definitely intra-uterine causation is not inherited. The earliest disturbance of development at all consonant with continued life—namely, the production of *monochorial* twins (from separation of the first two blastomeres)—does not lead to the offspring also producing twins, nor did the Siamese twins produce other than normal offspring; and cases are on record of individuals born without limbs, apparently from intra-uterine amputation, being the sires of well-formed families.

6. **Disuse Atrophy.**—The same considerations must apply to this order of cases, so far as regards any individual organ. As regards the organism as a whole, it is the experience of breeders that the greatest fertility is associated with moderate exercise; that lack of exercise plus obesity tend toward sterility, and it is noticeable that the hard-worked wife of the poor curate has her quiver full and overflowing, whereas the millionaire's

[1] The Evolution Theory, 2: 190, 66.

[2] It has been objected that a definite percentage of modern Jews are born with short foreskin, naturally circumcised. But so are "Gentiles," and it has not been shown that the percentage is greater. As I have pointed out elsewhere, although in different regions of the world circumcision is a religious rite, it must have been originated primarily from the observation that in hot climates those "naturally circumcised" were at a distinct advantage.

wife is apt to be childless. Clearly, therefore, there is an interaction between the soma and the germ cells, but that this is specialized, that atrophy of the muscles from disuse influences the musculature of the offspring, has not been demonstrated.

7. **Retrogressive Changes in the Tissues Due to Diverse Intoxications.**—We here encounter conditions which we are inclined to think must to a greater or less extent tell upon the offspring. In fact, we have evidence that they do, though we would hasten to add that the influence would seem to be limited. It is in investigating these conditions that the pathologist can perform yeoman service to the study of heredity. Unfortunately, so far heredity has had little interest for medical men in general, and so far the observations are few and far between; they are, however, steadily increasing in number.

Man himself is difficult to deal with. As already stated, conditions of disease and intoxication in the female must be ruled out, for the maternal influence tells not on the germ cells only, prior to fertilization, but upon the developing fœtus; and with regard to the male parent again, in most instances so many other factors have to be taken into consideration that to arrive at a sure conclusion is almost hopeless. Thus take the commonest intoxication of all—the alcoholic. The general belief—and we regard it as well founded—is that the children of the sot are as a body of lowered intelligence and vitality,[1] with unstable self-control. It is, however, next to impossible to prove this statistically, and this because:

1. If the mother be sound, her influence may be dominant upon the offspring; we must expect that a certain proportion will be of average development.

2. It is next to impossible in the majority of cases to determine whether already there be not hereditary taint in the father's family, and if there be, that this began from abuse of alcohol in a past generation—to show, in short, that alcoholism is the primary acquired condition and not the accompaniment (as apparently it often is) of retrogressive changes.

3. Alcoholism in the father, as a general rule, carries in its train home misery and poverty. The poor development of the children may largely be due to neglect and malnutrition.

Like difficulties present themselves if we attempt to study the heritage of tuberculous parentage. With syphilis, again, the fact that the father may infect the mother, and the further possibility of latent infection of the mother—and it may also be of the embryo—make it difficult to arrive at sure conclusions. Nevertheless, the frequency of stillbirths, monstrous births, and abnormalities in the children of syphilitics as compared with other children as has been noted by several observers,[2] cannot be merely a coincidence, while Mott has produced interesting data upon

[1] Thus, for example, Imbault (Thèse de Paris, 1901) found that of 100 tuberculous children, 36 per cent. were the offspring of alcoholics, 41 of tuberculous parentage. He quotes Arrivé's observations on 1506 cases of meningitis in children, that this occurs twice as often in those of alcoholic as in those of tuberculous parentage.

[2] Vide Legrain, Compt. rend. Soc. de Biol., 10 S., 2: 1895: 563.

inherited parasyphilis, and notably upon the liability of the children of syphilitics to suffer from early general paralysis, and Georghiu,[1] studying the histories of a series of monstrous births, found in almost all cases the history either of syphilis or again of some acute infection of *either parent* shortly preceding the period of conjugation. It is when we make direct observations upon the lower animals that we gain the surest indications of these effects of parental intoxication; and here some of the most instructive figures are those of Carrière[2] upon guinea-pigs. He inoculated his guinea-pigs over a period of several months with various soluble products of the tubercle bacillus, making altogether thirty separate matings in the course of two years. His results may be summed up in the following table:

	Stillborn.		Dying before 16th day.		Surviving.		Total born.
	No.	Per cent.	No.	Per cent.	No.	Per cent.	
Male and female both inoculated	13	52.0	7	28.0	5	20.0	25
Female alone inoculated . .	7	26.9	9	34.6	10	38.4	26
Male alone inoculated . . .	5	16.6	3	10.0	22	73.0	30

As might be expected, the influence of the intoxication was found greatest when both parents were subjected to the inoculation; least when the male alone was treated. But here, although there were ten matings, the average litter was only three, whereas the average litter of the healthy guinea-pig is between four and five, and of those born, 16.6 per cent. were born dead, and of the 22 who survived beyond the sixteenth day, 7 are described as weaklings. There can be no doubt from this series that a bacterial poison such as the products of the tubercle bacillus has a distinct action on the paternal germ plasm—as, indeed, on the female. Lustig's[3] figures for the results of inoculations of fowls with abrin give parallel results; and both observers found as the result that the offspring were less resistant (and not more resistant) to inoculations of the tubercle bacilli and of abrin than were control animals of the same age.

With these figures may be compared those of Constantin Paul[4] upon the effects upon the offspring of saturnine poisoning in men working in lead, the wives not being subjected to the same effects. The figures are remarkable, but notwithstanding that we have brought them forward upon several occasions no one has submitted evidence in contradiction, and such additional evidence as we have obtained is in the same direction (p. 198).

We possess thus clear evidence that substances circulating in the blood of the parent are capable of influencing the germ cells, and this not merely temporarily. In Lustig's cases the bad effects were noted months after

[1] L'Obstetrique, January, 1900: 63.

[2] Arch. d. Méd. Exp., 12: 1900: 782.

[3] Centrlbl. f. Pathol., 15: 1904: 210 and 756. Lustig, while pointing out that his series of observations prove that immunity is not conveyed, curiously enough draws no conclusions from the frequency with which he encountered monstrosities and abnormalities of various o[illegible].

[4] Arch. gén. de Méd., t5: 1860: 513.

the abrin had ceased to be given. It may be—it has been—objected that these are not cases of conditions acquired by the parent being conveyed to the offspring; the poisoned parent does not himself become a monster prior to begetting a monstrous progeny. This is quite true. It has been pointed out, again, that in all these cases we have regressive changes; the progeny tend to revert to a lower stage—as though, in the terms of our theory, the effect of the toxin had been to remove certain of the more recently acquired side-chains. This also would seem to be the case. The all-important point, however, is the demonstration that the germ cells within the ovary and testis are not inert, incapable of being acted upon by the rest of the parental organism. *If we can demonstrate that retrogressive changes are possible, then under like influences progressive changes are equally so;* if side-chains can be removed from the biophores, other side chains would seem capable of being added; so that here we have the first clear light thrown upon the mechanism whereby alteration in the environment of the individual, by telling upon his soma, may either:

1. Tell coincidently upon the germ cells.

2. Tell indirectly upon the germ cells, the modified internal secretions of one or other organ in the blood and lymph adding to or subtracting from it substances capable of acting upon the germ cells.

If the latter is demonstrable, then we are able to state definitely that the body cells themselves through their acquired conditions influence the germinal biophores.

All this is but just beginning to be realized—as it is that different toxins and nutritive substances proper in the general circulation may have a specific action on the germ causing modification in one or other direction. We have, it is true, indications that the offspring of tuberculous, syphilitic and alcoholic parentage differ somewhat in their degenerative stigmata, but these differences have not been determined experimentally.

Further researches along these lines may show that the acquired disturbances of a given organ may, through the consequent presence of abnormal cell products in the blood, influence the biophores specifically, so that under the action of different poisons the like organ in the offspring does not show the identical disturbance, but nevertheless exhibits departure from the normal. We would suggest that it is along these lines that Brown-Sequard's[1] remarkable observations upon guinea-pigs gain their explanation; observations which in our opinion have never been satisfactorily disproved, which further have been confirmed by Obersteiner[2] and others. Brown-Sequard found that by section of

[1] Researches on Epilepsy, Boston, 1857; also various papers in Jour. de Physiologie de l'homme, 1 and 3: 1858 and 1860; and in Arch. de physiol. normale et path., 1 to 4: 1868 to 1872.

[2] Obersteiner, Med. Jahrb., 1875. We quote Dietrich, Die Bedeutung d. Vererbung f. d. Pathologie, Tübingen, 1902, 14. Sir Lauder Brunton informs us that his friend, the brilliant biologist Romanes, was unable at first to gain Brown-Sequard's results, but after visiting Brown-Sequard and seeing the exact method of cerebral puncture, etc., his results were wholly confirmatory.

the sciatic and other nervous lesions in guinea-pigs he could render the parents epileptic, and that the young were liable also to epilepsy and other nervous disturbances. Obersteiner found likewise that, of thirty-two young, the offspring of guinea-pigs in which he had cut the sciatic nerve of one or both parents, 13 were healthy; 19 showed disturbances; 11 weakly; 3 paretic, more particularly in the lower extremities; 2 had epileptic fits on irritating what he refers to as epileptogenous zones, and were also paretic, soon dying; 3 showed corneal opacities and ulcers ascribed to atrophy of the fifth nerve.

If rodents are paretic, it is in the lower extremities that the paresis is most apt to show itself, thus no stress is to be laid upon the relationship between section of the sciatic nerve in the parent and paralytic manifestations in the hind limbs of the offspring. There remain two possibilities: either that the operation, setting up irritation of the higher centres, induced a general malnutrition in the parent whereby the germ cells suffered, and the nervous instability of the offspring was but the manifestation of imperfect general development; or, secondly, that the irritation of the higher centres, by modifying the internal secretion of the nerve cells, led to the presence in the blood of substances exerting a specific action upon the biophores, in consequence of which the nerve cells of the offspring were imperfectly developed. We shall not attempt to decide between these two possibilities, but they deserve mention. We would only repeat that this study of the problems of heredity in this direction is but in its infancy, and although it promises to yield most important results, results which will determine definitely the extent to which conditions acquired by the parent influence the offspring, nevertheless years of patient study are requisite before this particular field of pathology is adequately worked over. Lastly, we would add the caution that too much must not be expected. The germ cells in the ovary and testis are characterized by the long period—extending in man over many years—in which they lie latent and inert. While thus inert it is unlikely that they present very active metabolism. This very latency would seem in itself to be a preservative against parental disturbances exerting too extensive an influence upon the constitution of the contained biophores. Nevertheless, to maintain life some metabolism must proceed, and, as our examples must demonstrate, they can be influenced by parental conditions. We have, therefore, not a little confidence that results of the highest value are to be expected, results of the highest value to us as medical men, for they will establish the limits of morbid heredity, and will afford us a sure basis for determining how far the frailties of the father, or the misfortunes of the mother, affect the progeny.

SECTION II.

THE CAUSES OF DISEASE.

CHAPTER I.

INTRODUCTORY.

EVERY departure from the normal, whether in the cell, the organ, or the system in general, is a pathological condition, provided that, as indicated in the opening chapter (p. 18), we recognize that the "normal" is not an absolutely fixed point, but is the expression for the limits between which the majority of the individuals of a given species will be found to group themselves as regards any particular attribute. Such pathological conditions must, it will be seen, be of two orders: either primarily due to some constitutional defect transmitted from the parent or parents (included with which we must place the effects of imperfections in the fusion of the male and female elements at the moment of fertilization. Such effects, being associated with the actual constitution of the individual, are of internal origin and inherited); or, in the second place, they may be the result of some influence which first affects the individual after his genesis. Such conditions are of external origin and acquired. Morbid conditions, then, are to be classified into inherited and acquired.

THE USE OF THE TERM "INHERITANCE."

Much confusion has been and continues to be introduced with the discussion of the inheritance of disease, as into that of heredity in general, by a lax comprehension and use of terms. By many "inherited" and "congenital" are employed as though they were interchangeable; by others, as conveying distinct ideas; disturbances to the fœtus, for instance, and conditions of intra-uterine origin being by them regarded as congenital, but not as inherited. We hold that the latter is the correct, or at least the more satisfactory, usage, but, owing to this confusion, would recommend that the term congenital be employed as little as possible, and then with a clear understanding of what it is intended to imply.

A still greater confusion is introduced owing to the vulgar error, fostered by the legal profession, of regarding the individual as beginning existence with the moment of birth, and not until then, so that everything happening before that moment is grouped into one category; everything after, to another. The chick, so to speak, is not a chick until it breaks open the egg shell; its status, from the moment it ceases to be the expansible condition of "new-laid" egg until it emerges from the shell, is not recognized in law. But a very little reflection suffices to convince us that the individual existence of the chicken began even before the egg was laid; and what is true of the chick is equally true of the human being. *The individual begins to be the moment that fecundation is accomplished*—the moment the nuclear material of the spermatozoon fuses with the nuclear material of the ovum and "these twain become one." Compared with this event, birth is of secondary importance. The intra-uterine association of the embryo and fœtus[1] with the maternal tissues is but one of the means employed by certain species only of the animal kingdom to ensure the satisfactory nourishment of the young individual. The recognition of these facts is essential for any serious consideration of the causes of disease. To retain, in connection with man, the vulgar use of the term inheritance would be to employ a terminology having a different significance to that accorded to it by workers in other branches of biology. The biologist has no alternative but to define inheritance according to the principles here laid down, nor have we, dealing with a limited field of biology, the right to modify those terms for our own convenience. *That alone, therefore, is inherited which is the property of the individual at the moment of his becoming an individual, which is part and parcel of the paternal and maternal "germ plasm" from which he originates, or is provided by the interaction of the same.*

It is unnecessary to point out, save as a precaution, that what is a property of the individual from the moment of beginning existence need not show itself for long years—a family failing toward premature baldness not until years after puberty, or an inheritance of gouty tendencies not until after thirty-five. As the different organs and parts assume their particular conformation and properties at different periods, and do not develop *pari passu*, so must the various inherited peculiarities make their appearance at various times.

Similarly, morbid conditions—disease, injuries, malformations—may be acquired by the individual while still *in utero*, or in after life.

[1] The distinction here is that usually made, that the new individual is an embryo during the earlier stages in which the future conformation of the parts is unrecognizable; when these appear and the individual exhibits the various organs and parts laid down in the relative positions possessed in later life; when, in short, all important parts are recognizable in due position, it is a fœtus. The distinction is not a sharp one, but is of some use. Thus, the human being is regarded as an embryo until the end of the second month. Ballantyne has usefully introduced a third period, the *germinal*, preceding the embryonic, and ending with the development of the neural groove.

THE CLASSIFICATION OF MORBID STATES.

According to Period.—Inasmuch as birth is important as corresponding with the greatest change in the relationships of the individual to the external world, we may, therefore, proceed to make the following classifications of morbid conditions according to the incidence of their causation:

1. *Inherited*, due to influences affecting the ovum or the spermatozoon before or at the moment of fertilization.
2. *Acquired.*
   (1) *Antenatal*, or of intra-uterine acquirement.
   (2) *Parturient*, acquired at the time of birth before complete separation of the individual from the maternal organism.[1]
   (3) *Postnatal*, acquired after birth.

According to Cause.—This must be our primary classification, but we may approach our subject from another direction, that of causation—namely, by determining whether a given agent acts directly or indirectly in setting up morbid conditions.

The division so made is not so satisfactory as that just given, since the same agent may, according to circumstances, act in either way. Study, for example, the action of a single agent—cold. This may either lead immediately to systematic and local disturbances—to frost-bite, and even death; or indirectly, whether by lowering the vitality of the tissues, or again, by reflex nervous action, may lead to such alteration in the conditions of the circulation in the respiratory tract that the tissues there become less resistant to external agencies and afford a nidus for the growth of microbes, whereby a pneumonia is set up. Cold is the cause of disease in both cases, but in very different ways; in the first, it is the [illegible] *exciting* cause; in the second, the *predisposing* cause. It does not directly cause pneumonia; the direct exciting cause of that disease is the pneumococcus, or some other microorganism; and this, it may be [illegible], can set up the disease without of necessity the previous intervention of cold upon the lungs.

The causes, then, may again be classified into predisposing and exciting, and these are in action in connection with both antenatal and postnatal acquirements. Imperfect development of the heart, whether brought about by intra-uterine disease or by inherent imperfection of development, just as well as imperfections in the organ, the result of disease after birth, may directly induce morbid conditions causing obstruction of the circulation—morbus cœrulens (in the former case), œdema, etc.; or indirectly, through the impaired nourishment of the tissues, may render them more vulnerable and easily acted on by external agencies.

When we come to consider them more closely, we observe that inher-

[1] This is a very minor class, but has to be included, there being a few conditions which are neither antenatal nor postnatal in their acquirement.

ited conditions act in the main as indirect causes of disease. This is particularly noticeable in the finer constitutional defects, which result in the individual being more susceptible to one or other diseased state. Such *diathesis*, or specific susceptibility to a particular disease or group of diseases, is a predisposing cause. Tuberculosis, for example, is not inherited; it is a weakness of the tissues, rendering them incapable of resisting the tuberculous virus, that is inherited.

Here, however, we shall not attempt to enumerate the various predisposing causes of disease. We do but wish to emphasize the fact that, in studying individual cases, we must constantly keep before us the existence, and most often the co-existence, of the two orders of causation, and endeavor to distinguish clearly between them. The direct cause, we need not say, is all-important; nevertheless, due weight must be given to the predisposing.

At the present time it is well to emphasize this matter. Reading the works upon medicine and pathology of but a quarter of a century ago, it is impossible not to be impressed by the fulness with which, in connection with every morbid state, the possible predisposing causes are enumerated; this was inevitable. With lack of knowledge of the direct exciting cause, the known or apparent predisposing causes loom large.

With the remarkable series of discoveries of the direct causes of disease which characterized the end of the nineteenth century, it has been equally inevitable that our attention should be prominently directed to the part played by these direct causes and to the mode in which they act. It has been inevitable that, as a consequence, the study of predisposition has been relegated to a very inferior position, and, indeed, largely neglected. But already there are signs that the pendulum is swinging back—signs of a disposition to appraise these indirect causes at a higher and truer value. We see, for instance, more clearly nowadays than formerly, that the mere existence of pathogenic bacteria within the tissues is not the sole cause of infectious disease; such bacteria may pass into the lymph glands and there be destroyed. For such bacteria (in general) to be in a position to excite disease, there must coincidently be a lessened resistance on the part of the tissues, and the causes leading to this lessened resistance—the causes predisposing to infection—are being more fully studied and their importance more fully appreciated.

For the orderly consideration of the causation or etiology of disease it will be best to take up the subject according to our first scheme of classification. Following upon this we shall, in a special section, deal with the subject of predisposition.

CHAPTER II.

INHERITED MORBID CONDITIONS.

We have in the previous section laid down the general principles of inheritance, and we have there indicated what can and what cannot be inherited. It remains to apply those principles to the consideration of morbid states in man and the higher animals. And first, it will be well to emphasize what cannot be inherited:

1. *No order if mutilations, as such, can be inherited, i. e.*, while some may have a deleterious effect upon the general well-being of the offspring (this must be rare), and some even may possibly influence the development of a particular system (which must be still rarer), in no case can the identical mutilation or anatomical disturbance in the parent reproduce itself in the child. We owe the establishment of this principle more especially to Weismann, though years previously it had been laid down clearly by Francis Galton (1872), who also, it may be added, was the first to enunciate the doctrine of the continuity of the germ material.

2. *Infectious disease in the parent cannot be inherited.* There may be transmission of such from the parent to the embryo, or even in animals possessing abundant yolk and albuminous surrounding matter from the parent to the egg, but such transmission is not inheritance proper.

This is tacitly admitted by [illegible] modern writers in connection with [illegible]erculosis, but in connection [illegible]h the disease with which children are most often born infected it is s[illegible] the usual custom to speak of inherited syphilis. At the most, we may be permitted to speak of congenital syphilis, using that term as indicated on page 199, and again of inherited *parasyphilitic* lesions.

For, in the first place—although this may seem to some a refinement of logic—if inheritance be as we have defined, and as it must be, through the bioplasm, another individual living being cannot be part and parcel of the heritable material. The microbe of an infectious disease cannot be a constituent of the biophore. At most, it can be an accidental inclusion in the surrounding non-heritable matter of the cell. And in the second place, among the mammalia even this accidental inclusion is so improbable that it must be dismissed.

Such transmission can occur in lower forms of life having eggs provided with abundant food material, and we have positive e[illegible]dence of its occurrence. Thus, in the disease of silkworms known as pébrine, which now we know to be due to a microsporidian parasite (Nosema bombycis), Maillot and Pasteur noted that the eggs are infected; they nevertheless

develop, and only in the developing insect do the microbes so multiply as to cause death. Schaudinn[1] has shown the same to be the case with mosquitoes infected by Trypanosoma noctuæ (the "halteridium" of the stone owl). These parasites may pass into and be laid with the eggs, remain latent during the development of the young gnat, only becoming active when the latter is adult and begins to suck blood. Like conditions had previously been determined by Theobald Smith[2] in connection with the ticks which cause Texas fever. These, filling themselves with the blood of an infected ox, drop to the ground, there mature, and lay their eggs, and the young ties can convey the piroplasma and the disease to other cattle. And in birds the same has been definitely proved to occur. Thus, Maffucci[3] has demonstrated, and Baumgarten[4] has confirmed, that in fowls the eggs frequently convey the tubercle bacilli, and the same latency of the microbes is noted. From the eggs normal, if weakly, chicks hatch out, which at first run about and eat just like the healthy chicks, and only after some weeks emaciate and exhibit tuberculosis.

Human ova are free, or almost free, from yolk, and are relatively very small, ... r have we a single observation showing that the mammalian ovum .. phagocytic—able to take up solid particles. That the minute spermatozoa should act as carriers is still more unlikely, and the possibility that they do so has been negatived by Gärtner's[5] *reductio ad absurdum*.

The minimal number of tubercle bacilli that will set up peritoneal infection in the guinea-pig is 8; in the rabbit, 24 to 30 (Wyssokowicz). Gärtner, obtaining the seminal ejaculations from tuberculous guinea-pigs, found that only five out of the thirty ejaculations contained a sufficient number of bacilli to cause tuberculosis. Rohlff, employing the semen of men from phthisis, did not once succeed in rendering rabbits tuberculous by inoculation into the anterior chamber of the eye. From these and other observations Gärtner concluded that the semen emitted by a phthisical patient (not suffering from genital tuberculosis) does not on the average contain as many as ten bacilli.

Now on the average (Loeb) the human seminal ejaculation contains more than 226,000,000 spermatozoa. If the semen contained not 10 but 1000 bacilli, the chances that an individual spermatozoon, fertilizing the ovum, should bear with it a tubercle bacillus, and so lead to germinal infection, are as 1 to 226,000; if 1,000,000, 1 to 226. Only 1 out of about 85,000,000,000 spermatoz a has the chance of fertilizing an ovum. In short, the chance of ermatozoon conveying tuberculosis from the father to the offspring is so absurdly minute that it may be neglected.

The same considerations may be brought to bear upon fœtal *syphilis*,

[1] Arbt. a. d. Kaiserl. Gesundheitsamt., 20: 1904: pt. 3.

[2] Smith and Kilborne, Bulletin of Bureau of Animal Industry, Washington, 1893.

[3] Ztsch. f. Hyg., 11: 1892.

[4] Arb. a. d. Pathol. Inst. zu Tubingen, 1: p. 322.

[5] Ztschr. f. Hygiene, 13: 1893: 101.

in which, as must now be accepted, the Spirochæta pallida is the causative agent. That cases of syphilis in the newborn are most often of relatively late intra-uterine acquirement is rendered evident by the fact, to which Chiari has called attention—namely, that in more than 90 per cent. of infants presenting signs of syphilis, the liver is the seat of most extensive syphilitic disturbances. In the adult, in which the disease is acquired through some cutaneous infection, extensive hepatic syphilis is rare compared with the frequency of the disease. Infection through the placenta amply explains the condition in the infant; for all the blood on its way from the placenta passes through the liver, which thus is the organ first subjected to infection.

It may, in fact, be laid down that wherever there are active and specific manifestations of tuberculosis, syphilis, or other infectious disease in the newborn child, the condition is of intra-uterine acquirement, not inherited, and the conclusion is supported by the very various stages to which one may find the disease developed in the newborn.

Further support and illumination is given from Friedmann's[1] interesting series of observations. This worker injected healthy does, immediately after copulation, with a few drops of an emulsion of tubercle bacilli, and six to eight days later, killing the animals, made serial sections through the uterus, with its contained embryos, to observe the relationship of the bacilli. He discovered not a single bacillus in the mucous membrane of the vagina or uterus, but all the embryos showed within them numerous bacilli of characteristic form, and in clumps (growing). The bacilli can thus pass into the developing ovum or embryo. Other observers have noted that bacilli introduced into the uterus outside the amnion may, some days later, be found in the amniotic fluid. Whether through the placenta (from maternal infection), through the walls of the fœtal sac, or by passage into the developing ovum before that sac develops, the bacilli may infect the embryo. These various means are adequate to explain the phenomenon without calling upon the improbable infection of ovum or spermatozoon prior to fertilization.

But, if syphilis and tuberculosis themselves be not inherited, it is deserving of note that the children of syphilitic and tuberculous parentage may exhibit conditions which are derived from the infected state of the parent, and are strictly inheritances. Offspring themselves showing no signs of the active disease, may nevertheless exhibit certain stigmata—fœtal cachexia, malnutrition, senile expression, even malformations, arrested development of the bony skeleton, of the teeth (Hutchinson's teeth), etc.; children of tuberculous parentage, delicate constitutions, precocious mentality, etc. These characteristics, presumably due to the action of the toxin on the germ cells, we may refer to as *inherited parasyphilitic* or *paratuberculous lesions*. In addition to the experimental observations of Lustig and Carrière, which we have

[1] Ztschr. f. klin. Med., 43: 1901; pts. 1 and 2.

given elsewhere, bearing on this subject, we may recall the observations of Charrin and Gley, that among the offspring of rabbits immunized against diphtheria they had noticed a particular liability to definite rickets: enlarged cartilages, enteritis, pot-belly and delayed growth; whereas these appearances had been scarce noticed in their long series of other observations. Such rachitis in the rabbit may be spoken of as an inherited paradiphtherial condition.

Here, then, we have conditions in the offspring definitely inherited from the parent and due to acquired modification or disturbance of the parental germ plasm. We have not as yet determined absolutely the specific inheritance of a particular order of lesions directly associated with the action of a particular causative agent. That may be so, or it may not be. If the children of tubercuIous parents manifest a liability to tuberculosis, it has still to be proved that this is something over and above the liability to infections in general brought about by their lowered vitality, and the same may be said with regard to Carrière's and Lustig's observations upon the higher susceptibility of the progeny of immunized animals to tuberculosis and abrin poison, respectively. More observations are requisite before anything definite can be laid down upon this point. At most, the indications favor the view that there exist specific paratoxic lesions.

What is true regarding infectious diseases must to some extent hold also regarding chronic intoxications of various orders, alcoholism, plumbism, etc.

From these and the other considerations which we have discussed elsewhere it will be made out that the results of constitutional disease in either parent may be the following, according, on the one hand, to the extent of the influence of that disease, or intoxication, upon the germ plasm in that parent, and on the other, to the activity or potency of the germinal matter contributed by the other parent:

1. **Sterility.**—Sterility, the germ cells being so profoundly modified that either (*a*) they are destroyed, (*b*) their development is arrested, or (*c*) being developed they (ova or spermatozoa) are imperfect and incapable of fusing with the germ cells of the other parent.

2. **Imperfect Development of the Offspring.**—(*a*) Of such extent as to lead to intra-uterine death and abortion; (*b*) of less extent, a viable individual being produced presenting either—

   (1) Gross anatomical defects;

   (2) No gross anatomical defects, but lowered vitality, presenting itself either in the form of weakened powers of resistance against disease in general, or (?) proneness to develop the same functional disease as the parent.

3. **Perfect Development of the Offspring,** with no appearance of functional disease or lessened power of resistance, (*a*) the offspring of these again being perfectly normal; (*b*) that offspring showing in subsequent generations constitutional weakness (recessive).

4. (?) **Perfect Development of the Offspring,** with increased power of resistance, the immunization of the parent having been accompanied

by the development of an acquired tolerance to the particular toxin on the part of the germinal bioplasm.[1]

Spontaneous Variations: Mutations.—These show a marked tendency to be inherited (p. 161). In man, it is true, it is difficult to assure ourselves that a given departure from the normal has appeared for the first time in the history of any particular stock, so that we are apt to place all such conditions among those already inherited, descending from previous generations. There is no doubt, however, that albinism, Daltonism, hemophilia, and so on, have suddenly shown themselves at a bound in some one individual; no doubt, that is, because our experience with lower forms of life shows that this does happen.

THE INHERITANCE OF ABNORMAL CONDITIONS PASSED DOWN FROM PREVIOUS GENERATIONS.

If certain anomalies and constitutional defects are capable of being transmitted from the individual in whom they first arise to the descendants of the same, *a fortiori*, when a constitutional defect has shown itself in a family for several generations, there is increased likelihood of its being transmitted to further generations. While many doubt the inheritance of constitutional defects of any order that are acquired, the volume of facts at our disposal is too great, and the facts themselves too convincing, for any to deny that those already inherited—anomalies of certain orders, specific and general constitutional disturbances, or, more correctly, diatheses (predisposition to the same)—are frequently transmitted; it is to these that our attention as pathologists is most often called.

Inherited Anomalies (Anatomical).—While it must be kept in mind that by no means all anomalies are heritable—many due to intrauterine disturbances are certainly not—nevertheless, there is a large and important class, that is, a class so large that only some of the best marked of those affecting man will here be noted, and that without description. Of these, we may mention polydactylism among anomalies of excess, hypospadias among anomalies of defect.

Certain conditions it is difficult to classify. There must, for example, be an anatomical basis for color blindness (Daltonism), though that is beyond our present means to determine, and other conditions stand doubtfully between this class and the next, that of diatheses. Is hemophilia, for example, merely a predisposition to bleed, provided the individual be subjected to certain alteration in environment, or is there

[1] We introduce this doubtfully, but because it is remotely possible. Certainly, at the present day the bulk of the evidence is against the inheritance of acquired immunity. It is, however, proved that influences of a chemical nature acting upon the parental organism may coincidently modify the germ plasm in a retrogressive direction; on general principles, therefore, we should be prepared to admit that other substances exist capable of setting up progressive modifications. See footnote regarding Conradi's experiments on page 172.

underlying this a definite anomaly and weakness of the vessel walls? We suspect the latter, but what the exact anomaly is has not as yet been convincingly demonstrated. So, also, as regards many inherited nervous conditions; some undoubtedly are associated with an *agenesia* or *aplasia* (lack of development or imperfect development, respectively) of particular nerve centres, others are due to what Gowers would term an *abiotrophy*, or premature exhaustion and degeneration, of particular groups of nerve cells. Others, again, to no particular weakness of any particular set of nerve cells so much as to a general weakness and instability of the whole of the higher centres; it is not so much specific anatomical defects as strain, brought to bear upon particular centres in a weakened system, that originates the particular form of nervous breakdown.

Diatheses.—From these borderline cases we pass to the diatheses proper. Some of these we have already discussed, notably those associated with sundry of the infectious diseases.

1. We have shown how vague and unsettled is our knowledge regarding acquirement of the specific lack of resisting power to particular infections. There is, on the contrary, a very definite conviction, based upon experience, regarding the existence of "racial diatheses," or, as it may be expressed, failure on the part of certain races of men to have developed resistance against particular infections—of the white races of mankind against yellow fever, the Polynesians against measles, the red Indians, and, to a little less extent, the negroes, against tuberculosis, etc.—and an equally clear recognition of the existence of familial diathesis toward such diseases as tuberculosis, scarlet fever, measles, and acute rheumatism. How far these diatheses express themselves as bodily configurations is still a matter of some doubt; this, however, is generally admitted, that, as regards tuberculosis, a fine skin and fine hair (of any color, not necessarily light), light bones, long chest with narrow sternal angle and expansion below the normal indicate a predisposition to the disease, although it may attack, and attack acutely, those exhibiting none of these traits.

2. Other diatheses are of the metabolic type, exhibiting themselves as a predisposition to metabolic disturbances. Foremost among these is the gouty, or, as some would term it, and, unfortunately, the uric acid diathesis; others are the obese and the diabetic diatheses. With these, also, there is a certain racial liability, although to a large extent this would seem to be a matter of habits of life. Gout is frequent among the English, rare among the Scotch; diabetes common in Jewish communities, as also, among the females, is obesity; the Dutch are liable to greater corpulency than can be wholly ascribed to inaction; the Kaffir women to such overdevelopment of the subcutaneous fatty tissue of the lower part of the trunk as to lead to the formation of the so-called "aprons." Here again diathesis verges upon inherited anatomical variations.

3. Others, again, are the nervous, and these form a very important group. Some of these we have already indicated in discussing whether

here we have to deal with the transmission of anatomical defects. We would only repeat that in some cases clearly the recognition of anatomical changes is beyond our power to determine. Defects there must be, either in the relationship, or, more probably, in the functional capacity of the individual nerve cells or groups of the same. Hysteria, for instance, is notably diathetic, and, with the somewhat allied migraine, is noticeably transmissible, and these are typical examples of what, failing anatomical evidence of disturbance, we regard as functional conditions. Epilepsy also is without a definite anatomical basis, and is again transmissible. Virchow, indeed, would distinguish between a general and a systemic reversion. If the distinction is valid, then the nervous and infectious diatheses are examples of the latter. It is worthy of note that in the development of the nervous system and of resistance to specific infections, we have the latest group of acquirements by the human species, *qua* species; that, as a general law, conditions last acquired are those liable first to be lost. Thus, these two diatheses must be associated with failure to attain complete normal development. We would regard them not as special reversions so much as the first and slightest stages of general reversion.

Homeomorphous and Heteromorphous Inheritance.—While we observe that inheritance of liability to disease may in certain instances exhibit itself by the offspring succumbing to the identical influence as did the parent, and exhibiting the same symptomatology (homeomorphous inheritance), in other cases it manifests unlike disorders, although these may be along special lines. There are, as it were, families of diseases, the members of which may follow in direct descent, or, on the other hand, be interchangeable in inheritance (heteromorphous inheritance).

The best example of this grouping of diseases into families is to be seen in connection with the gouty diathesis. It is notorious that the gouty father tends to have the gouty son: but does not always. The majority of observations place the proportion of cases in which there is a history of gouty inheritance at 44 per cent. (Sir W. Gairdner places it as high as 90 per cent.), and in the conditions affecting the male (most often) transmission is mainly through the father. But gout is far from being the only condition affecting the gouty family more than the non-gouty. Bouchard[1] found the following percentages of incidence of disease in the ascendants and collateral members of the families of 33 gouty individuals:

	Per cent.
Gout	44.0
Obesity	44.0
"Rheumatism"	25.0
Asthma	19.0
Diabetes	12.5
Gravel	12.5
Eczema	12.0
Biliary lithiasis, hemorrhoids, and neuralgia	6.0

[1] Quoted by Le Gendre in Bouchard's Pathologie Générale, 1:1896: 348.

In only 12 per cent. of the cases studied was no heredity, either homeomorphous or heteromorphous, to be made out; or, in other words, in only 12 per cent. of the cases was the gouty condition acquired without antecedent diathesis. Similarly, data were obtained in studying a series of cases of obesity, and rheumatism (both chronic and acute). Everything nowadays points to acute articular rheumatism being an infective disorder; nevertheless, he found a history of heredity in 32 per cent. of the cases; or, in other words, certain constitutions are hereditarily prone to be affected. In migraine, biliary lithiasis, and diabetes one finds the same tendency for members of this same family of morbid conditions to preponderate in the personal and family histories.

It is clear that what we have to deal with here is not so much a special diathesis rendering the individual liable to succumb to one given disease, as a peculiar disturbance of nutrition rendering the individual liable to be affected by one or other large group of diseases. There is, undoubtedly, the tendency in the one direction, *e. g.*, if 44 per cent. of gouty persons give a history of gout in the family, it cannot be denied that there is a special liability toward this one disease; but in another 44 per cent., according to Bouchard, in whom there is not the family history of gout, there is a history of one or more of these other conditions. It is very possible that environment may explain this interchange of disease; that members of a family exposed to the same influences and living in like surroundings will manifest the one special disease, whereas variations in environment lead to the manifestation of the disturbances characteristic of some other member of the group. This, however, does not detract from the remarkable fact that such a group or family of diseases exists and that there is inherited diathesis.

For further discussion of the subject of the inheritance of disease the reader is referred to the introductory chapters (p. 141 et seq.), where also will be found reference to the subjects of atavism and reversionary inheritance, and the development of the so-called *degenerates*. Here, before closing, it is fitting that a little should be said upon the cognate and frequently discussed question of—

The Marriage of Consanguines.—Expressed in the terms of our theory, when the biophores of both parents possess particular side-chains, or groups of side-chains, of like composition, there is a much greater likelihood of those side-chains being potent in the offspring, and for that offspring to possess the traits brought about by the presence of those side-chains, than when, on the contrary, the corresponding side-chains in the two parents vary. If, again, certain side-chains characteristic of the fullest development of the species are wanting in the parental biophores, those side-chains cannot possibly be present in the offspring. In other words, we should expect the marriage of consanguines to reproduce with greater sureness family characteristics, whether progressive or regressive, than will marriage of an individual with the member of another family not possessing those characteristics.

And, as a matter of experience, this is what we find is the case, and not only that, but this principle of inbreeding is that depended upon

by breeders to preserve, intensify, and indeed to fix and render constant variations which are regarded as favorable or advantageous.

The union of those belonging to the same family, when of nearly related degrees of consanguinity, is likely to have good or ill effects, according to the absence or presence of constitutional defects peculiar to the family. When such constitutional defects are present they tend to be intensified in the offspring of consanguineous union. Where they are wanting, the offspring is likely to be of good constitution. And, further, where the family is in any one respect above the normal, *i. e.*, when it presents a favorable variation, placing it at an advantage over ordinary mortals, the marriage of those nearly related is of actual advantage, by impressing and rendering more stable the favorable variation.

In stating this the existence of latent or recessive properties in the germ plasm must be kept in mind. Not all the progeny of a consanguineous marriage will necessarily exhibit the family weakness or the family beneficial property; atavistic, recessive characters may exhibit themselves here and there, but this, undoubtedly, is the tendency.

The vast body of facts accumulated upon the subject of intermarriage of relations and its results can only be classified along the lines here laid down. It is by "in-and-in" breeding that, for example, the Hanover breed of pure white (albino) horses was established more than a century ago, the breed tracing back to a single albino horse, apparently a spontaneous variation. The Ancona breed of silk-haired sheep trace back similarly to a single animal.

A notable example of the effects of intermarriage is intensifying the inheritance of malformations in man is given by Poulton. The village of Iseaux, in Isère (France), being remote from other villages, the inhabitants constantly intermarried. At the end of the last century the majority of these, male and female, presented an accessory finger and accessory toes on hands and feet; forty years ago the monstrosity was still very common, but now, with the improved means of communication and the introduction of new blood by marriage outside the village, it is tending to disappear.

Other village histories can only be explained by this law. Thus, to quote examples given by Le Gendre.[1] At Orthez (Basses Pyrenées), the Protestant families, being a class apart, were compelled to marry among themselves. The members of these were, in general, according to Réclus, poorly built and weakly, and among these were very numerous epileptics, so that each Protestant house possessed a special room reserved for the epileptic members. Since the advent of improved communication and increased facility for travel outside the previous narrow limits the state of affairs has disappeared.

The village (bourg) of Batz, studied by A. Voisin, shows the opposite condition of improvement by intermarriage. There intermarriage is the rule, and all are descendants of half a score of families—have names not found in the neighboring communes. Out of 2733 persons, Dally

[1] Le Gendre. Article on Inheritance, in Bouchard's Pathologie Générale, 1: 1896

found that 870 had the same surname. But here the inhabitants are well built and of good physique; indeed, there is a smaller proportion of exemptions from military service than in the rest of the Department. Lavery cites a similar example in the commune Fort-Mardyck, near Dunkerque. Four families from Picardy were established there in the time of Louis XIV. At the time of Lavery's observations there were 1800 descendants, robust, without sign of any inherited defect, and their birth rate was higher and death rate lower than that of any of the neighboring communes. These had kept to themselves and intermarried among themselves.

The deduction here is obvious: marriage between consanguines may be recommended where the family is of sound physique, possessing no noticeable defect; is powerfully contra-indicated when such defect exists. Inquiry must especially be made as to the existence of neuroses and constitutional predisposition to infectious disease.

CHAPTER III.

THE CAUSATION OF MORBID CONDITIONS OF INTRA-UTERINE AND PARTURIENT ACQUIREMENT.

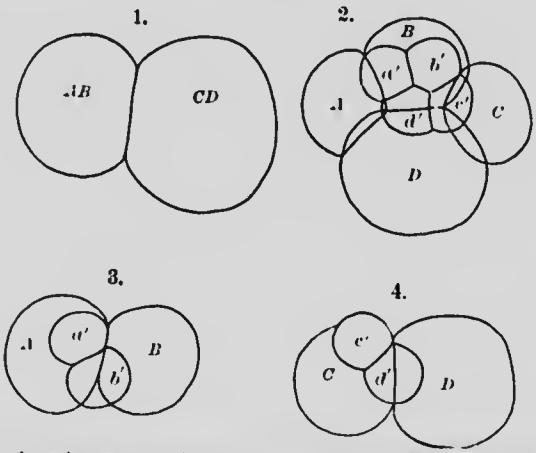
THE subject of antenatal pathology is but yet in what may be termed a fœtal state; much has been accomplished during the last twenty-five years to establish the framework of the subject, but much greater development is before it. Certain matters stand out clearly; they have been established with fair detail. Regarding others, only scattered observations exist among many theories. Were we to deal with the matter at all fully, this detail and the discussion of individual opinions would enter largely. Add to this, that dealing here with the causation of disease, it has to be confessed that, in general, we know more about the processes and conditions which appear to be due to intra-uterine disturbances than about the precise cause or causes of the individual conditions. This is not the place to enumerate those conditions in detail; we can but call attention to the more important. The most striking group—namely, the monstrosities and anomalies—will be treated in the following chapters (IV and V), and there it will be most satisfactory to note, at the same time, what we know concerning their causation. This chapter, therefore, will be relatively brief and will deal in generalities.

Briefly, under the action of various causes acting during intra-uterine existence, there may result:

1. **Death** with—
   - (*a*) Absorption of the embryo: "blighted ovum," the embryo failing to develop and disappearing, the placenta and membrane still exhibiting growth for a time.
   - (*b*) Abortion, the imperfect fœtus being born dead or dying immediately after birth.
   - (*c*) Premature labor.
2. **Monstrosities.**
3. **Malformations** (not so extreme as those causing monstrous births). These may be—
   - (*a*) Of defect.
   - (*b*) Of excess.
4. **Impaired Vitality**, with imperfect development, without gross anatomical change:
   - (*a*) General: infantilism, etc.
   - (*b*) Systemic: more particularly of the nervous system.
5. **Cachexia.**
6. **Infection.**
7. **Traumatism** (this distinct from the traumatism of parturition).

The causes of disturbances are, it will be noted, clearly, though not wholly, identical with those produced as a result of inheritance. As a matter of fact, we must admit, with Woodruff,[1] that causes acting on the ovum soon after fertilization—causes capable of affecting all the cells of the egg alike—must have results somewhat of the same order as are produced by those same causes acting on the bioplasm before fertilization; and, as experimental research is showing more and more definitely that the more pronounced anomalies and monstrosities, when set up by influences acting on the individual, date back to the earliest stages of development, we must not be surprised to find that an important group of disturbances may originate equally from influences acting before and after fertilization, and that no sharp line exists between

FIG. 37



Early stages of marine gasteropod *Ilyanassa*. 1, the first two blastomeres; 2, the usual development of the eight-cell stage; 3 and 4, the first two blastomeres having been shaken apart each proceeds to redivide independently, with the production of dwarf larvæ.

variations (due to the former set of conditions) and *modifications* (due to the latter). There are, however, many conditions which are only of intra-uterine origin.

Basing ourselves very largely upon the results of more recent studies upon the experimental pathology of the embryo, we may group the causes of these intra-uterine disturbances as follows:

1. Physical and mechanical, including injuries of various orders.
2. Malnutrition.
3. Intoxication.
4. Infection.

1. **Mechanical and Physical Causes.**—To purely mechanical and physical causes acting upon the earliest stages it appears evident that

[1] American Med., 10: 1905: 551 and 706.

some of the most remarkable monstrous growths are due. Experimentally, the eggs of lower forms of life, when in the two-, four-, and eight-cell stage, may be violently shaken, so that the cells fall apart, when each has been found capable of developing a separate individual, or, if they remain partially attached, double and other multiple monsters. That violent shaking is the cause of double monsters and of an order of twins in man is most doubtful. Here Jacques Loeb's observations upon altering the tonicity of the surrounding medium affords a more probable cause. He found that placing echinus eggs in the early stage of division in diluted sea-water was followed by such osmotic swelling of the eggs that the membrane broke, and that part of the egg which protruded underwent independent development The same has been noted by Bataillon[1] in the case of teleostean (fish) eggs; by strong movements, the first blastomeres may be forced apart and separated by serous fluid to a greater or less extent, and undergo this independent growth.[2]

FIG. 38

Amniotic threads on hand of seventh to eighth month fœtus; loss of last phalanx of second finger; index finger constricted by band and terminal phalanges form a process adherent to the band from the second finger. (Marchand.)

We believe, then, that mechanical and physical means are active in producing some of the most extreme forms of monstrosities. So also do they best account for one group of anomalies—those brought about by pressure effects, owing either (Dareste) to incomplete formation of the amnion with escape of fluid, or to deficient formation of the amniotic fluid; such may lead to adhesions between the amnion and fœtus, the formation of amniotic bands, and consequent local retardation of growth, or produce effects of like nature without adhesions. Certain orders of anencephalic monsters, spina bifida, talipes equino-varus and yet severer forms of arrest of growth of the limbs, have been ascribed to this cause. Here also may be mentioned the occasional amputation of limbs, and, rarer, arrest of growth of other areas, brought about by loops of the umbilical cord—the fœtus in its movements tying itself in a knot. It must not be thought that all cases of imperfect limb development are due to this cause; in fact, the majority cannot be accounted for, but some undoubtedly must be so explained.

Cases occasionally occur of fœtal fractures, and this usually unaccompanied by any history of maternal traumatism. Labor may have been

[1] Arch. f. Entwickelungs. Mech., 11: 1901.

[2] For a fuller description of the subject of double growths see Chapter IV.

easy, and yet at birth, as in Linck's[1] and in Chaussier's[2] cases, and in Klotz's case about to be published from our laboratory, as many as thirty to one hundred separate fractures of long bones, ribs, sternum, etc., may be counted; obviously, the only satisfactory explanation in those extreme cases is an abnormal fragility, due to imperfect ostcogenesis. In other instances, many bones are found presenting a sharp angle, with cicatrix above, strongly suggesting old compound fracture. Sparling[3] regards those not as necessarily indicating fracture, but as produced by amniotic bands, which have deformed a part and subsequently have been torn away. To such tearing away of bands Ballantyne attributes the occasional existence of wounds and skin defects in the newborn.

2. **Malnutrition.**—Simple malnutrition of the mother, lack of sufficient food, is a well-known cause of puny development and of weakly condition of the offspring. There is little evidence that in itself it leads to any definite anatomical defects. Where these are present there is little doubt that more than mere impaired nutrition is at fault, and that we have to deal with the third cause—namely, intoxication from placental absorption.

Malnutrition of the fœtus may, however, be brought about in another way—namely, by placental disturbance. More particularly in heart disease, and again in the subjects of syphilis, there may be grave alterations of the placenta; so that, either from the fœtal side the placental circulation is greatly lessened, or, on the maternal side, intra-uterine hemorrhages, etc., so reduce the interchange between the fœtal and the maternal blood that premature death is brought about. Yet another, and in this case extraordinarily advanced effect of placental circulating disturbance is seen occasionally in monochorial twin pregnancies, where the twins, developing from a common ovum, have a common chorion and fused placenta. Here, where one twin is the more vigorous, it usurps more and more of the placental circulation, until, through anastomosis, it drives its blood (venous in quality, but arterial as regards the vessel carrying it) into the umbilical artery of the other twin. In such cases the heart of the second twin fails to develop, and with it one or more territories—umbilical and hepatic, anterior or posterior; what does develop being extremely œdematous, owing to imperfect circulation of the feebler twin. In this way is developed a fetus acardiacus, or chorio-angiopagus (p. 208).

3. **Intoxication.**—If, as above stated, simple malnutrition of the mother mainly results in constitutional weakness of the child, without grave anatomical defects, maternal malnutrition, associated with constitutional disorders, has much more serious results—resulting, according to the nature of the disorder, in the whole gamut of disturbances mentioned in the opening paragraph of this chapter. Thus, at the one

[1] Arch. f. Gynäk, 30: 1887: 264.
[2] Bull. Fac. de Méd. de Paris, 3: 1814: 301.
[3] Arch. f. Geburtsh. u. Gyn., 24: 1892: 225

PLATE VI

Osteogenesis Imperfecta, with Multiple Antenatal Fractures of Ribs, Long Bones, etc.

The fractures show themselves as nodosities with abnormal curvatures of the bones.

end of the scale obstructive cardiac disease, by the slowing of the uterine circulation and placental hemorrhages and infarcts, leads to death of the fœtus and stillbirth; at the other, infectious disorders may induce the gravest anomalies and definite monstrosities. More particularly it may be laid down that metabolic disturbances in the mother, when they do not induce actual sterility, as, for example, when they develop during the course of pregnancy, tell severely on the offspring; for example, kidney disease. Among these, obstructive liver diseases, with jaundice and renal incompetence, call for special mention, and may exert specific effects, although here more exact observation is requisite. In this connection the observation of Charrin[1] deserves remark. Taking gravid goats, he injected into them emulsions of liver tissue, and thereby developed in these animals a cytolytic action, *i. e.*, the blood of the goats gained the specific power of destroying foreign liver cells. The kids born to these goats were apparently normal, save that their livers showed grave degenerations. The conclusion to be drawn is that the cytolytic substances developed in the maternal organism, and, present in the blood, had diffused through the placenta or been taken up by the fœtal tissue and had exerted their specific action upon the (foreign) liver cells of the fœtus. Charrin is so experienced an observer that what is stated by him as a fact must be freely accepted. Such observations appear to throw light upon the so-called inheritance of thyroid and other glandular disturbances.

With reference to infectious diseases, we have noted that toxins may tell upon the germ cells. Their influence upon the developing embryo and fœtus is very noticeable. Very often acute infectious diseases—smallpox, scarlet fever, typhoid, etc.—lead to the expulsion of the dead child, and this without any indication that the child itself is infected; indeed, as a rule (although not constantly), with those acute infections in which the specific microbe is known, cultures from such fœtuses yield negative results. Intoxication, the effects of absorption of toxins from the maternal blood, is the simplest explanation of such. Where milder infections, la grippe, for example, occur in the early stages of pregnancy, if abortion is not brought about, the condition of blighted ovum may be encountered, or the development of anomalies.

This influence of the mother upon the fœtus is well shown, more particularly in connection with lead and mercury poisoning. Here Lizé's[2] figures with regard to the family histories of those exposed to the fumes of nitrate of mercury may be cited. (We have tabulated the results.)

[1] Semaine Méd., December 17, 1902.

[2] Union Méd, 2 S., 13: 1862: 106.

	Number of cases.	Number of pregnancies.	Abortions, premature labor, and stillbirths.	Surviving infants.	Remarks.
Mothers alone exposed .	3	7	4	3	
Father and mother exposed	2	14	5	9	Of these, only 3 survived fifth year.
Father alone exposed .	?	12	4	8	Of these, 3 died before fourth year. One alone vigorous.

Constantin Paul's[1] figures for lead poisoning are even more marked. His 81 cases we have tabulated as follows:

	Number of cases.	Number of pregnancies.	Abortions, premature labor, and stillbirths.	Infants born living.	Remarks.
1. Mother showing symptoms of plumbism . .	4	15	13	2	1 infant died within twenty-four hours.
2. Mother working in type foundry, all of whose previous pregnancies had been normal	5	36	29	7	4 of these died in first year.
3. Mother who during period of work in type foundry had 5 pregnancies	1	5	5	0	After ceasing to work had healthy child.
4. Mother working intermittently in type foundry; while working there	3	3	3	0	When away from work for some length of time gave birth to healthy children
5. Mother in whom blue line on gum the only sign of lead poisoning .	6	29	21	8	
6. Husband alone exposed to lead . . .	?	32	12	20	Of these, 8 died in first year, 4 in second, 5 in third

From this table it will be seen that the mothers who suffered from lead poisoning during pregnancy showed by far the most pronounced effects, though, as already noted, paternal poisoning had a very definite influence.

Nor is premature death the only result; as Roque has pointed out,

[1] Arch. gén. de Méd., 1: 1860; 513.

and has been noted by other observers, in the children of workers in lead, there is a painful frequency of idiocy, imbecility, and epilepsy.

We would here recall the other figures given by us elsewhere. There can be no question that intoxication of the pregnant mother tends to exert a most deleterious effect upon the offspring; several observers, indeed, have proved experimentally that poisons, such as lead, mercury, arsenic, carbon monoxide, morphine, alcohol,[1] pass through the placenta, and may be detected in the fœtal tissues.

As regards alcohol, Sullivan's[2] figures are especially striking. He investigated the histories of female chronic drunkards, choosing cases in which other degenerative features were wanting. In sober mothers the rate of stillbirths, abortions, and deaths of children before the third year he established as 23.9 per cent.; in these it was 55.8; squalor may account in part for this high figure, but a more careful study showed that the death rate increased progressively as the mother became longer and longer a victim to alcohol, and when the history of the successive births was determined, thus:

	Cases.	Per cent. born dead.	Per cent. dying before 3.	Total.
First births	80	6.2	27.5	33.7
Second "	80	11.2	40.8	50.0
Third "	80	7.6	45.0	52.6
Fourth to fifth births	111	10.8	54.9	65.7
Sixth to tenth "	93	17.2	54.8	72.0

The infantile mortality, it will be seen, shows the same tendency to increase as do the stillbirths; if the fœtus is impaired, so also is the vitality of the offspring.

4. **Infection.**—Normally, it is scarce necessary to say, there is no communication between the fœtal and maternal circulation, the cells of the fœtal villi acting as a barrier; and thus, as a rule, bacteria circulating in the maternal blood do not find their way into the fœtus. Direct infection of the fœtus from the mother is distinctly the exception and not the rule. Nevertheless, it does occur, and occasional cases have been reported in a considerable number of diseases, cases in which either the specific lesions of the infection, or the causative bacteria have been detected in the fœtus at birth or so soon after birth that infection during parturition is wholly ruled out. Thus there are records of syphilis (the mother alone being infected), tuberculosis, variola (the child being born with the eruption fully pronounced), varicella (but not vaccinia, although there are several cases of at least temporary immunity conferred on the offspring when the mother has been vaccinated in the last three months of pregnancy), measles (some 20 cases), scarlatina (likewise), erysipelas, and septic disorders, acute rheumatism, typhoid, anthrax (in the lower animals), cholera, epidemic cerebrospinal menin-

[1] This has been absolutely proved by Nicloux, L'Obstétrique, 1900: 97

[2] Jour. Ment. Sci., 45: 1899: 489.

gitis, influenza, mumps, relapsing fever, malaria, and yellow fever.[1] The list is a long one, but the number of cases on record is small.

The simplest explanation of such cases is that the specific organism, coming to rest in one of the maternal blood sinuses, or being taken up by the cells of the fœtal villi which have made their way into the sinuses, multiply there, lead to local tissue destruction, which, extending into the walls of the villi, eventually leads to the microbes being carried by the fœtal blood into the fœtal tissues.

PLACENTAL DISEASE AND ITS INFLUENCE UPON THE FŒTUS.

The placenta, while strictly a part of the fœtus, may, nevertheless, undergo primary disturbances, and, as upon it the fœtus depends wholly for its nutrition and supply of oxygen, any extensive disturbance has a most serious effect. What we may term the active part of the placenta is essentially fœtal; our conception of this organ is simplified if we regard it as a series of finger-like processes of the chorion, or outer coat of the fœtus (*i.e.*, fœtal sac), which, containing vascular loops and covered by epithelium, make their way into the wall of the uterus until they penetrate and lie within the large blood sinuses of the uterus. This epithelium has extraordinary phagocytic powers: it absorbs the tissues before it until it gains entrance into the maternal vessels.

The extent of this process varies, or otherwise there is considerable variation in the dimensions of the placenta, and so of the nutrition of the fœtus; the greater the number of the chorionic villi entering into its formation and the more active their phagocytic power, the greater the nutrition of the fœtus and the more active its growth.

It follows, however, from this method of development that the invasion of the maternal sinuses is a precarious matter; the very act of invasion of the walls leads to weakening of the same; in fact, under wholly normal conditions hemorrhages occur on the maternal side, resulting in the formation of what we may regard as accessory sinuses, into which other villi make their way. The adaptation of the parasitic growth to the maternal vessels is such that with increased blood pressure (coupled, it may be, with impoverished state of the maternal blood and impaired nutrition of the villi) there may be very extensive and widespread hemorrhages. When this is the case—and this happens not infrequently in obstructive heart disease—the fœtus is liable to become asphyxiated, the effused blood being stagnant, affording little nutrition and less oxygen to the fœtus, and in itself obstructing the

[1] The literature on this subject, as upon all branches of antenatal pathology, will be found indicated in Ballantyne's Antenatal Pathology, Edinburgh, Green & Sons, 1902. This is, to our knowledge, the only work in any language that attempts to deal with the whole subject of intra-uterine disorders, and is a mine of information. Another useful article upon placental transmission is that by Lynch. Johns Hopkins Hospital Bull., 10: 1902: 283.

normal circulation. Such placental hemorrhages form one cause of premature labor and stillbirth.

Localized hemorrhages, again, may be followed by thrombosis and organization, and where the resulting fibroid areas are extensive, these also greatly reduce the area of nutrition of the fœtus, with resulting impoverished growth and impaired vitality. Fibroid areas of this nature in the placenta are far from uncommon and may be abundant in obstructive circulatory disturbances, as, again, in maternal syphilis; though here, as we shall point out, other factors are concerned in their production.

From causes that are little known—at times, it would seem, from inherent vices of development, at other times, as a consequence of impaired nutrition from the maternal blood (in maternal nephritis and cachexia, for example)—the fœtal villi are liable to be diseased; to be œdematous or even cystic, or to undergo fibroid change, with consequent contraction and obliteration of the contained vessels. According to the extent of those disturbances so is there a greater or less amount of malnutrition of the fœtus and of asphyxia, leading toward premature death.

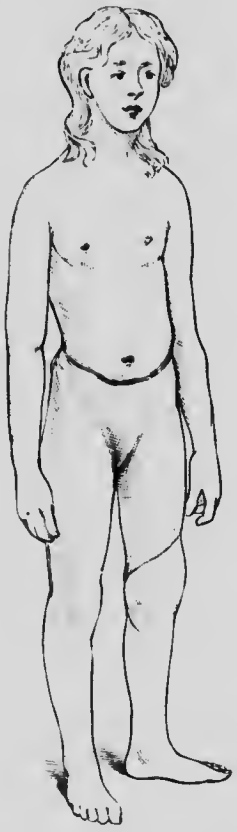
So also there may be placental infection. The effects of this on the organ we see best in the more chronic infectious diseases, and here more particularly in syphilis. In tuberculosis the presence of actual tubercles has been recorded, but is rare, nor have the anatomical changes been so fully studied. In syphilis here, as in other organs, the disease may show itself both by the production of actual gummata or by widespread vascular changes. This, at least, is the usual teaching. The more recent work of Bondi,[1] and more particularly of Thomsen, affords a very different picture of placental syphilis. The latter observer examined the placentas of 100 syphilitic women. He found, in the first place, that proliferation of the vascular intima in the fœtal placenta is far from being a marked feature. What is more characteristic is the cellular overgrowth of certain villous processes, coupled with the extensive œdema of others, both of them contributing to the greater size of the placenta, which is a pronounced characteristic of the condition. Whereas the weight of the normal placenta relative to that of the child is as 1 to 5 or 6, that of the syphilitic is usually given as 1 to 3 or 4. Thomsen[2] found that it might be as high as 1 to 1.5. What is particularly characteristic is the co-existence of these changes in the villous processes with multiple small abscesses, for such are present rather than typical gummata. It is to be noted that in other conditions—in tuberculosis, for example—the abscesses may be present, or, again, proliferation; only in syphilis do both exist to a marked extent. Yet another feature is the extensive leukocytic (polynuclear) infiltration of the umbilical cord. Only in 5 cases out of 30 did he find these cord changes in cases not regarded as syphilitic, and of these 5, three of the infants were subsequently brought to the hospital with syphilitic lesions.

[1] Arch. f. Gyn., 69: 1903.

[2] Ziegler's Beitr., 38: 1905: 524.

As a result of these changes the placenta shows general enlargement, coupled with anemia; is pale, with yellowish whitish regions, indicating the more fibroid areas. It will be readily understood that there is obstruction to the circulation and malnutrition, and that the altered relation of placental weight to that of the child is due in part to the imperfect growth of the latter.

Fig. 39



Girl, aged ten years, showing cicatricial grooves due to constriction of umbilical cord. At birth, according to the mother, the grooves in the abdominal wall and left thigh were occupied by the cord. (Hawthorne.)

It has been laid down by some observers that a distinction can be made out between the fœtal syphilis (the mother being unaffected) and primary maternal syphilis, by the villi being more affected in the former, the sinuses in the latter. No such general rule can be laid down.

The fœtal disturbance most frequently associated with the syphilitic disease of the placenta is *hydramnios*, excessive formation and accumulation of the amniotic fluid, associated frequently with small size of the fœtus. It has to be noted, however, that this association is not constant; on the one hand, the reverse condition of *hypamnios* has been recorded in syphilitic cases; on the other, hydramnios may occur in the absence of syphilis; thus cardiac defects in the fœtus may be a cause.

Other disorders of the fœtal adnexa may here be briefly noted. The *cord* may be abnormally long, and thus liable to be knotted, with more or less vascular obstruction; or, looped round the fœtus, it may be, causing compression, atrophy, and grooving of the body or limbs; it may be excessively short, arresting the movements of the fœtus and seriously interfering with labor. The *amnion* may be imperfectly developed and have undergone fusion with the fœtus, causing the development of bands, and by pressure arresting the development of one or other area, or, contrariwise, as indicated by Klaussner,[1] by setting up a certain grade of obstruction to the venules and lymphatic return, may induce localized giant growth; the *chorion* may exhibit abnormal vascularity.

[1] Ueber Missbildungen der menschlichen Gliedmassen, Wiesbaden, Bergmann, 1905.

DISEASES PECULIAR TO THE FŒTUS.

There remain several disorders of the fœtus, which Ballantyne would class together as "idiopathic," although, seeing that, in connection with almost all of the group, it is to be noted that instances occur of several members of the same family being affected and of the condition being transmitted indifferently along either parental line, the term is, perhaps, unfortunate. Such states, in which there is this strong hereditary tendency, as, for example, elephantiasis congenita, ichthyosis, tylosis, hypertrichosis, achondroplasia (fœtal rickets, osteopsathyrosis), congenital goitre, etc., we shall deal with best under the heading of Abnormalities of Development of Individual Tissues. At the same time, we freely admit the difficulty of exact classification of such disorders. Just as immunity may be inherited in some, acquired in others, so it is with these states; achondroplasia and micromelic (or short-limbed) dwarfism may crop out through a long series of generations; this is a definite inherited diathesis; it may, as indicated by Charrin and Gley's[1] results upon poisoning the male rabbit with the toxins of diphtheria and tuberculosis, or blue pus bacilli, be due to acquired modification of the parental germ plasm, and we are prepared to find that intrauterine (maternal) influences may produce like effects.

Of yet other conditions appearing sporadically, such as general fœtal dropsy, ascites, hypertrophic stenosis of the pylorus, fœtal endocarditis and peritonitis, fœtal nephritis, congenital obliteration of the bile ducts, we know too little regarding the causation or causations to speak with any authority.

THE CAUSES OF MORBID CONDITIONS ACQUIRED DURING PARTURITION.

These may be briefly noted. They are either mechanical, traumatic or infectious. The mechanical causes are more particularly strangulation by short or shortened cord, abnormal shortness of cord obstructing descent, and undue narrowness of pelvic channel leading to the death of the child from exhaustion. Prominent among the traumatic disturbances are laceration and amputation from manual and instrumental aids to delivery; *cephalhematoma*, from rupture of vessels of the scalp through the intense compression of the head and the congestion produced by prolonged arrest of the partly delivered head at the external ring; distortions and partial fractures and dislocation of the skeletal parts; birth palsies, and hydrocephalus induced more particularly by instrumental injury. Among the infectious causes are the presence of pathogenic organisms in the vagina, notably the gonococcus (leading to gonorrheal ophthalmia) and the microörganisms of suppuration. Here, also, must be included improper treatment of the cord at the time of section, leading to local suppuration, infective icterus, and general pyemia.

[1] Compt. rend. de la Soc. de Biol., 10 S., 2: 1895: 705, and 3: 1896: 22 and 1031.

CHAPTER IV.

MONSTROSITIES AND ABNORMALITIES.

HERE rather than elsewhere would seem most fitting to pass in review the subject of monstrosities and abnormal developments in general.

Definition.—The study of monstrosities and abnormalities, their structure, relationships, and mode of causation, is one that lies on the borderland between anatomy, embryology, and pathology. The pathologist is concerned, inasmuch as the conditions clearly represent departures from the normal, and certain of the minor grades of aberration lead to very definite disturbances in postnatal existence, as, for example, the long series of cardiac anomalies, and the *morbus coeruleus* (the "blue disease"), to which they give origin. But many again which are compatible with continued existence have no disturbing effect upon the health of the individual—as, for example, supernumerary digits; and many again, the greatest aberrations of all, are wholly incompatible with postnatal life. The subject is in itself fascinating; the departures from the normal are many of them so extraordinary that one seeks to know the cause; the more examples we encounter the more evident does it become that they arrange themselves into well-defined groups, the members of the groups showing orderly gradations, so that these monsters can be placed in classes and species as regularly as can the various forms of animals and plants. With this regularity it is obvious that underlying their development there must be a law, or laws. And the student is led onward to make himself familiar with the laws of normal development and the facts of human and comparative embryology in order to arrive at a satisfactory grasp of the meaning of these remarkable developments.

It has, however, to be confessed that this is but a side path in the study of general pathology, and, this being so, instead of entering fully into the subject, we must here content ourselves with calling attention to the main varieties and orders of both monstrosities and abnormalities, and a deduction of the main principles that appear to underlie their causation. Those that are of immediate interest as setting up morbid states will be referred to in greater fulness in the sections dealing with the individual organs and tissues.

The terms monstrosity and abnormality are employed to denote grave anatomical departures from the normal, whether general or local (affecting but one section or part of the organism). There is no clear demarcation between the two. All monstrosities are anomalies, or, better, abnormalities (for, as we have already insisted, they are subject to νομος, law); not all abnormalities are usually regarded as

monstrosities; or, otherwise, the slighter aberrations are classed as abnormalities, the more pronounced as monstrosities. To the student who approaches the subject for the first time the number of forms seems as perplexing as the terminology is bewildering. But, as stated, each form finds its place in a general scheme. Two great divisions are to be made out: abnormalities of excess and those of defect, and each of these may be of one or other order—increase or decrease in *size* or in *number*. There are one or two other classes to which we shall refer briefly that do not come into this scheme, viz., those of *transposition* of parts and *hermaphroditism;* the vast majority are included in these two great divisions.

There is lacking a comprehensive and modern work on the whole subject in the English language. Hirst and Piersol's *Monstrosities* is valuable so far as it goes, and Ballantyne's pioneer work upon *Antenatal Pathology* is invaluable for the light it throws upon many conditions. The most masterly *résumé* of the subject is the article by Marchand in the last edition of Eulenburg's *Real Encyclopedie*. There is at the present time in the process of publication what promises to be the leading work upon the subject, judging from the two sections that have thus far appeared, viz., Schwalbe's *Morphologie der Missbildungen* (Jena, Fischer, 1906 and 1907). Taruffi's *Storia di Teratologia*, while most complete, has the disadvantage of introducing a complete new terminology, based upon a theory or theories of causation and relations that have already been found incorrect in several respects.

ABNORMITIES OF EXCESS.

1. **General Excess.**—This may be (*a*) universal, as in true giantism; or (*b*) lateral, one-half of the body exhibiting greater development than the other (as though the first two blastomeres of the ovum had been disproportionate in their potentiality; or (*c*) local, one member or one organ being developed out of all proportion to the rest. These later conditions will be referred to under Hypertrophy.

As to the causation of giantism we know little that is assured. While there exist families of which, through several generations, the members have been noted for their height, heredity is nevertheless infrequently observed in pronounced cases of giantism.

The minimum for true giantism is generally accepted as 6 feet 6 inches, or about 200 cm. Thoma places it at 188 cm. (or 6 feet 3 inches), but in Anglo-Saxon countries this is scarce considered giantism.

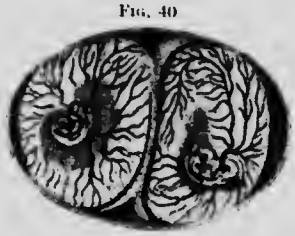
The giant exceeding 7 feet in height comes, as a rule, of a family whose members have been of medium height. In such giants, the excessive height is generally due largely to disproportionate length of the lower limbs. There is some question nowadays as to where the line is to be drawn—if it really exists—between such true giants and morbid giantism, a type of acromegaly. The more recent autopsies on giants have, in general, revealed enlarged pituitary bodies.

Regarding localized giantism, a distinction must be made between those cases that are apparently of inherent nature and those due to disturbed nutrition, even if these be often of congenital origin. In congenital elephantiasis and macroglossia, we have to deal with lymphatic obstruction, accompanied by secondary overgrowth of the connective tissues. Allied alterations in the relative vascular supply best explain, it may be, some conditions of the nature of *macrodactyly*. But where, as in some cases of gigantic hands, there is observable a tendency to duplication of fingers, the indications point strongly to a redundancy of vegetative matter in the *anlage* or growing point of the part. The same is clearly to be invoked in cases of premature and excessive development of the different components of the generative organs. Abnormal inheritance, associated with modifications, it would seem, of metabolism, best explains infantile goitre, hypertrichosis (or hairiness), and lipomatosis, or generalized obesity.

2. **Numerical Excess.**—A wide and varied range of conditions is to be included under this heading—from triplets on the one hand, to partial dedupliction of a terminal phalanx on the other.

Twins (Gemini Æquales).—If individual twins in themselves cannot be regarded as monstrosities, their appearance in a well-regulated human family is usually regarded as anomalous, and certainly the line of demarcation between twins of a certain order and some of the most *bizarre* of monsters is very slight.

Fig. 40



Heteroophal hen's egg with two embryos (of sixth day), each with separate yolk. (Panum.)

We recognize two orders of twins: the *dichorial*, or heteroophal, and the *monochorial*, or monoophal. In the former, each child is born with a separate "caul;" the sex may or may not be identical, and the features, configuration, and characters, while at times approximating, at others present wide differences. Such dichorial twins, obviously, originate from two separate ova, fertilized at the same menstrual period, each of which, in its development, forms its own set of membranes, cord, and placenta, though ultimately the two placentas may fuse.

In the rare conditions of *superfetation* the ova are, it would seem, discharged and fertilized at different menstrual periods.

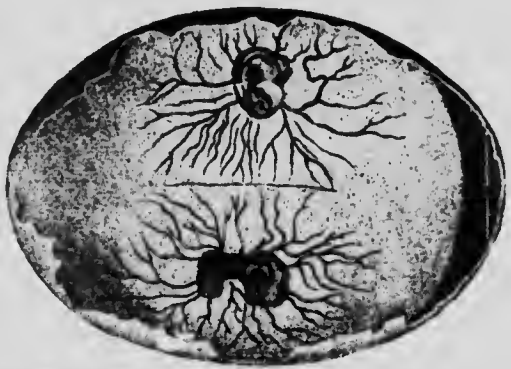
The rule is that each Graafian follicle contains a single ovum, but even in the young child, and in a large number of different species of animals, two, and sometimes three, ova have been observed in a single follicle. In those cases in which heteroophal twins are of the same sex and exhibit great similarity, the possibility must be borne in mind that they have been derived from a single follicle; nay, more, that they are due to early complete division of a single ovum into two independent ova after fertilization, but before implantation in the uterus.

Monochorial twins are the less frequent. Ahlfeld's statistics are,

that of 506 twin births, 444 were dichorial, 62 monochorial. They emerge from a single caul or chorionic sac, have a single placenta, are always of the same sex,[1] and, when equal in development, are remarkably alike. The condition is not hereditary, whereas in certain families there is a distinct tendency toward double, dichorial births.

The chorion, it will be remembered, is the outer wall of the ovum, and a single chorionic membrane enclosing two embryos can only mean that a single ovum has given rise to two individuals. Not infrequently the twins show identical abnormalities; right-sided hydrocele (Ahlfeld's case), spina bifida (d'Outrepont), hypospadias (Lehmann), etc. In cases of dichorial twins, there is never any indication of the separate chorions fusing into one (unless the rare cases above noted of monochorial twins of different sex are to gain this explanation). The non-

FIG. 41



Monosphal duck's egg with two embryos (of seventh day) upon a single yolk. (Panum.)

existence of haphazard fusion of the two halves of the double monster is against the idea of chorionic fusion, for did this occur we should expect to meet with occasional fusion of the embryos in various positions, the back of one to the side of the other, etc.

These cases, therefore, prove that *a single ovum is capable of giving rise to two individuals*, a conclusion wholly borne out by observations on the eggs of lower animals and by experimental diplogenesis.

Among the lower animals, multinucleated ova have been observed by several (Francque, Stockel, H. Rabe[2]); on the other hand, numerous zoologists (Roux, Endres, Morgan, in the frog; Herlitzka, in the newt; Driesch, in sea urchins; Zoja, in the jelly fish[3]) have proved that division of the ovum into its separate blastomeres at the two-, four-, eight-, and in the medusa even in the sixteen-cell stage, may give rise to

[1] One or two exceptions to this rule are recorded, but these, if we mistake not, in the older literature only.

[2] For literature, see Schwartz, Anat. Anz., 18; 1900.

[3] For literature, see E. W. Wilson, The Cell in Development and Inheritance, New York, Macmillan, 1897.

separate, though dwarfed, individuals from the separated blastomeres. In the newt, even as late as the gastrula stage, Spemann[1] was able to gain two complete embryos by experimental division.

It is possible, therefore, that monochorial twins originate (1) from the separate fertilization of the two nuclei of one ovum, or (2) from the fertilization of an ovum with one nucleus, with subsequently (*a*) separation of the primitive blastomeres, or (*b*) cleavage, not of the ovum itself, but of the germinal area developing later upon that ovum; or, in other words, the formation of two primitive streaks upon a single germinal area. Without going into details, we may here say that the study of double monsters indicates that the period of origin is more likely to be late than early, as does also the existence of a single chorion. There is more likelihood for identity where only one spermatozoon is concerned than where two.

FIG. 42

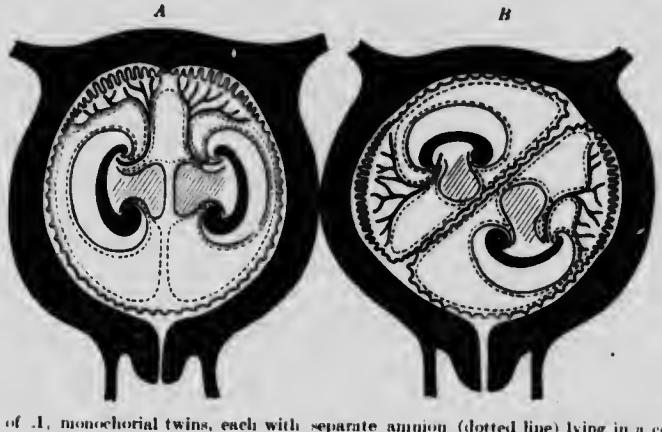


Diagram of *A*, monochorial twins, each with separate amnion (dotted line) lying in a common chorionic sac; *B*, dichorial twins, each with its own chorionic sac.

Regarding these monochorial twins, it is to be noted that the amnions may be separated or fused, that the placenta, almost without exception, is common, that the umbilical cords may be well separated or inserted close together, or have for a varying distance a common amniotic sheath.

Unequal Monochorial Twins (Gemini Inæquales).—Fœtus Acardiacus.—Occasionally we encounter a curious abnormality. Instead of equal twins being born, there comes forth a single, well-formed individual, accompanied by, it may be, an amorphous lump of flesh, contained in the same sac and only recognizable as a product of conception by possessing a distinctive small umbilical cord. Such is a *fœtus amorphus*. Most often more complete organization can be made out in the mass; in general, the lower half of the body, with its limbs, is fairly developed (*Acardiacus acephalus*), or the head end, it may be

[1] Sitzungsber. d. Phys. med. Gesellsch., Würzburg, 1900.

PLATE VII

FIG. 1

Skiagraph of a Fœtus Amorphus. (Charlton.)

Showing presence of vertebral column and ribs, but absence of head and limbs.

FIG. 2

Two Similar Examples of Fœtus Amorphus.

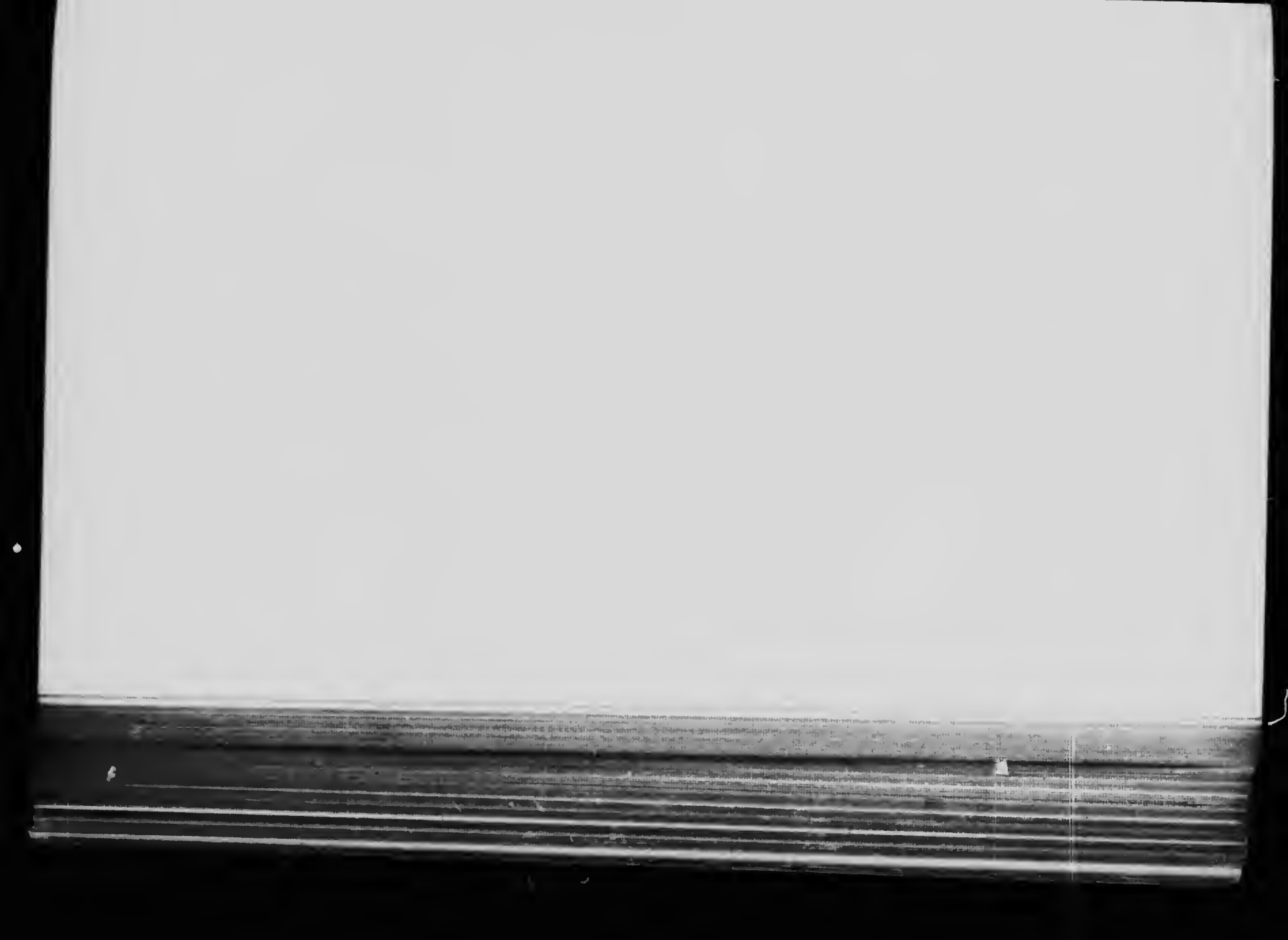


PLATE VIII

FIG. 1

FIG. 2

FIG. 3

Photograph and Skiagraph of a Fœtus Acardiacus Acephalus. (Schwalbe.)

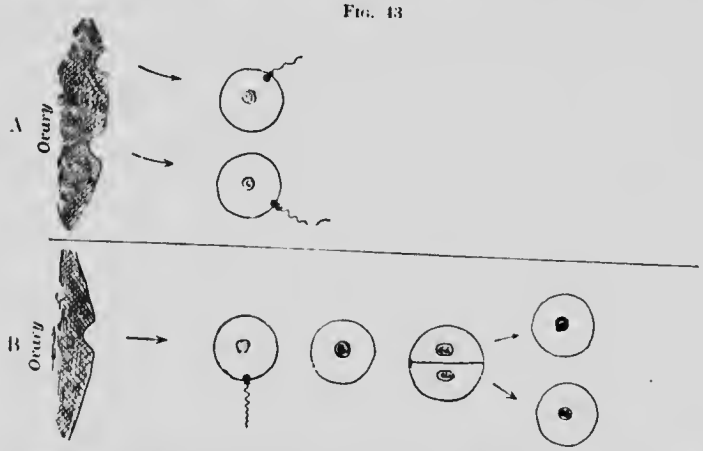
Fœtus Acardiacus Acormus, showing Vascular Relationship to the Umbilical Cord of the Healthy Fœtus. (Barkow.)

little more than the cherub-like head itself (*Acardiacus acormus*), or, lastly, there may be a fœtus fairly complete as regards its skeletal parts, and, unlike the other forms, this may possess a partly developed heart; but this and the other internal organs are imperfectly developed and the tissues are extremely œdematous (*A. anceps*).

A sub-group is to be recognized, including the cases of A. acormus, in which the fœtus is implanted directly upon the placenta without the intervention of an umbilical cord. It is still a matter of debate whether the mode of origin in these cases is the same as that of the others; all, it may be added, have separate amnions.

The causation of this type of monstrosity has been worked out by Meckel, Claudius, and Ahlfeld. In the first place, *the course of the circulation is reversed*. This explains the arrested development of the heart; the acardiac fœtus is nourished by the blood of its more developed

FIG. 43

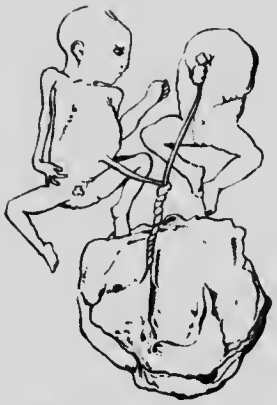


A, schema of production of dichorial twins, two ova dehisced simultaneously, undergoing fertilization by separate spermatozoa; *B*, of production of monochorial twins, a single ovum, fertilized by a single spermatozoon undergoing later cleavage.

and stronger brother. There is fusion and anastomosis of the allantoic and, later, placental vessels, so that the arterial blood[1] of the stronger fœtus (*A*), driven into the branches of the umbilical arteries of *A*, enters the branches of the umbilical artery of *B*, and, being under greater pressure, forces itself into *B's* aorta; passes into its branches and nourishes the various tissues of *B*; arrests the action, and leads to the atrophy of *B's* heart; may be but sufficient in quantity, in quality, and in distribution to nourish portions only of *B's* economy, whereby the other portions undergo aplasia and atrophy. The greater frequency of maldevelopment of the cephalic half of the body is apparently due to the fact that for a period the heart of *B*, repelling *A's* blood, continues

[1] It must be remembered that this blood while in the umbilical artery of *A* is in quality venous, returning from the fœtus to the placenta.

Fig. 44



Developed twin and acephalic monster and their relationship to a common placenta. (Ahlfeld.)

the circulation of the upper half of the body with its own imperfectly aërated blood.

The above theory, worked out by Ahlfeld, whose diagram is here given, is that which has received wide acceptance; but, as pointed out by Marchand and Schwalbe, there are difficulties in accepting it in its entirety. In the first place, the human embryo would not seem to possess the free allantois assumed by Ahlfeld; the teratogenic period must, then, be placed at a later date; in the second, if all hemi- and holo-acardiaci originated at the same early period, it is difficult to understand the singularly wide range of extent of development or retrogres-

Fig. 45

Fig. 46

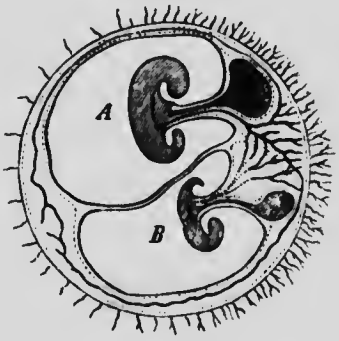
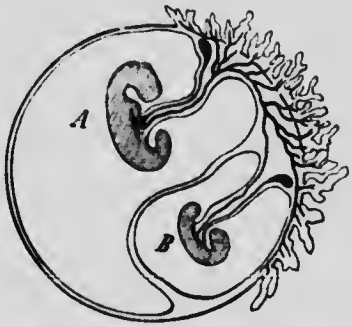


Fig. 47



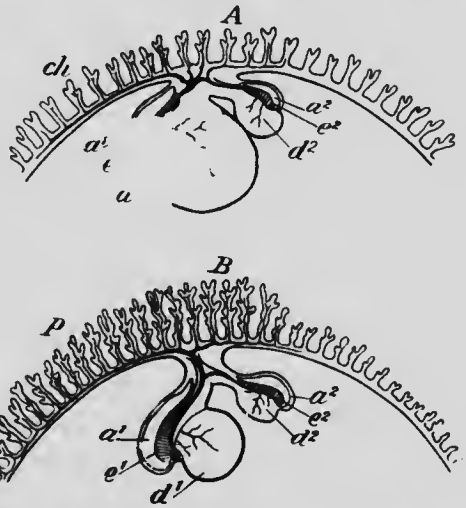
Schema of mode of development of Acardiac monsters. (Ahlfeld.)

sion. With Marchand, we must for many cases accept Dareste's view, that in a large proportion of cases (in the chick), where two primitive streaks develop upon one ovum, one of the two tends to be imperfect, and may presuppose that the imperfection extends to the heart and vascular system. The theory of Schatz[1] is gaining adherents: It appears to me to be too elaborate and involved to be correct, though it may well be that my difficulty in following the lengthy exposition of the same is at fault. The outcome of the arrest of the individual circulation of the weaker fetus may lead to its death long prior to full term. In this case, pressure, autolysis, and absorption may lead it to assume the form of a flattened mass within the membranes of the developing twin, and may result in a *fœtus papyraceus*.

Fig. 48

Development of two embryos of the chick on a common germinal area, the lower of the two imperfect from the first (paracephalus). (Dareste.)

Fig. 49



Marchand's schema of mode of development of Acardiac monsters. *A*, the chorion *ch* is already developed; the yolk sac *d* has divided into two unequal halves, d^1 and d^2, in consequence of which the one embryo a^1 receives through the yolk vessels more abundant nourishment than does the other embryo a^2. As a result its allantoic circulation develops more actively, and the later developing allantoic artery of the smaller embryo anastomoses with it. *B*, later stage: the allantoic vessels of a^1 usurp the whole of the chorion, the smaller embryo gaining its blood entirely through the anastomosis of its allantoic artery with that of a^1, and this, therefore, in the reverse direction to the normal current.

[1] Archiv f. Gynäk., 1901.

Triplets and Other Multiplex Births.—These may be mono- or polychorial, or a combination of mono- and dichorial.

Wilder[1] gives careful notes of a case investigated by him of triplet sisters, evidently monochorial, so remarkable in their identity that not even the mother (contrary to her conviction) could surely identify them; for on one occasion two of the sisters, in answer to inquiry, stated that they had not received their baths that morning, while the third gleefully announced that she had had three!

The largest number of simultaneous human births recorded by a reliable authority is seven; some few cases of quintuplets are on record, whether monochorial or not we have no adequate evidence. In the cat, the monochorial development of five kittens has been ascertained.

DOUBLE MONSTERS.

It will, we feel assured, materially facilitate a comprehension of the many and different forms of double monsters if, instead of first describing the more important forms, we first establish an adequate theory of causation and mode of development, and, laying this down, then proceed to classify them in terms of that theory. For close upon two centuries the explanation of diplogenesis has interested zoologists and physicians alike, and each step forward in our knowledge of embryology has led to the propagation of new theories, which in general have, upon investigation, been found to be inadequate. Nevertheless, with increasing knowledge those theories have come to satisfy and embrace a larger and larger number of conditions, and, especially during the last quarter of a century, we have approached a rational classification.

The names that especially stand out in the study are those of Geoffroy St. Hilaire (1836), whose classification is still quoted; Forster (1861), who collected and classified what at the time was the fullest series of cases; Dareste (1877–1891), the pioneer in the study of experimental diplogenesis; Fol, whose observations on polyspermy were, nevertheless, in a wrong direction; and, among the more immediate moderns, Morgan, of Bryn Mawr; Roux, of Breslau; E. W. Wilson, Jacques Loeb, etc., upon the artificial separation of blastomeres; Ranber, on the "radiation theory;" Marchand, with his theory of fertilization of polar bodies; and Fischel, with his "head and rump centres" theory. Many other names deserve quoting, but these are, perhaps, the foremost.

The difficulty thus far in propounding any adequate theory has lain in the fact that the more cases are studied the more surely it is seen that double monsters belong to two main categories. This has been a matter of contention since 1724. There have been those who would explain all examples as cases of *fusion* of two separate embryos lying in approximation; others equally convinced that *cleavage*, or dichotomy,

[1] Amer. Jour. of Anat., 3: 1904.

of an originally single individual, is the essential cause. It is in the attempt to embrace both classes that, one after another, the various theories propounded have shown their weakness. While we realize that it is only just to the student, as to the older workers in this subject, to afford an account and criticism of previous theories, to set these forth adequately would take great space. For that reason, and because, in addition, we believe that it is less confusing for the student, we venture to put forward a single theory, which we may term the "growing point" theory;[1] it differs from those which hitherto have gained the fullest acceptance, viz., those of Rauber and Fischel—theories which likewise are based essentially upon a comparative study of embryology and teratology and experimental diplogenesis—in that it takes into consideration the mode of cell multiplication.

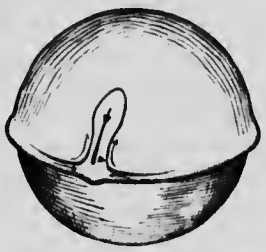
In the lower animals, as already noted, it is possible by various means to loosen and shake apart the earliest blastomeres of the fertilized ovum. Each then becomes, and develops as, a separate individual. Were this to happen in man, each separate blastomere would develop its own chorion and sac, whereby the contained embryos would be prevented from fusion. At most, as already suggested, such early separation would lead to identical dichorial twins. We have, therefore, to look to a later period; and, instead of attempting to ascertain what is the earliest, must strive to establish what is the latest period at which double monsters can develop. To do this, it is best to consider the mode of development of the embryo of the higher vertebrates. This mode is not identical in the oviparous and viviparous forms, or, more accurately, in the lower vertebrates and the amniota (mammalia), respectively, but a common principle includes all. We may thus first study a simple type, such as the fish. Here the whole ovum does not give rise to the embryo. Certain cells only at one pole form the germinal area; the rest, filled with yolk, afford food to the eventual embryo. Nor does the whole germinal area give rise to the embryo. This, as it grows, spreads over the yolk, and at one point, as pointed out first by His, that spreading growth becomes arrested, the edge elsewhere continuing to advance (Fig. 50). Hertwig has laid down that the sinus thus formed represents the cavity of the gastrula of holoblastic forms. It is the cells along the edge of this depression that give origin to the embryo, the primitive streak arising along the line of the same.

Rauber (1877) based the whole theory of diplogenesis upon this mode of development. He presumed the simultaneous appearance of two invaginations which, in the process of development underwent fusion, giving rise to a double monster. The accompanying figures from Kopsch gives the idea of the mode of development of superior dedoplication (anadidymus) (Figs. 53, 54, 55). Fischel, starting from the same basis, points out that Rauber's conception is false in so far as the embryo is

[1] These earlier theories are given fully by Schwalbe, Die Missbildungen, Jena, B. Fischer, Pt. 2, 1907, and are carefully criticised by Fischel, Verh. d. Deutsch. Path. Gesell., Karlsbad, 5: 1903: 272.

not formed by a continuous infolding of the edge of the blastoderm behind the head end; on the contrary, at a relatively early period the cells of the two sides of the groove join to form the tail, or, more broadly, the rump centre, and that these two centres, head and rump, between them constitute the whole embryo at this period, and between them form the whole eventual individual. Starting from this, Fischel also ascribes the vast majority of double monsters to fusion, as indicated by the accompanying diagrams. He recognizes, however, that certain katadidymous forms, double below but single above, may be due to want of primary junction of the two halves of the rump centre. This is not cleavage, but lack of union. As regards the slighter cases of anterior duplication—double-headed snakes, for example, and in cases in which merely the pituitary body is divided—he is at an *impasse;* he denies Gerlach's statement that the head centre grows forward, and yet he has to admit that in order to produce these there must be a cleavage of the head centre, by mechanical or other means. He thus is forced to the conclusion that the head centre gives origin to the head alone, the rump centre being the great formative organ.

Fig. 50



Diagrammatic representation of growth of germinal area of the fish egg as a cap spreading over the yolk with arrest at one point, and infolding to form the *primitive streak*.

Fig. 51

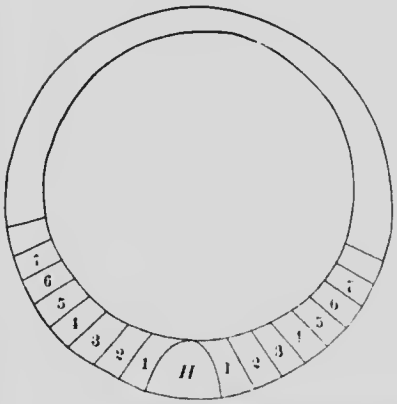
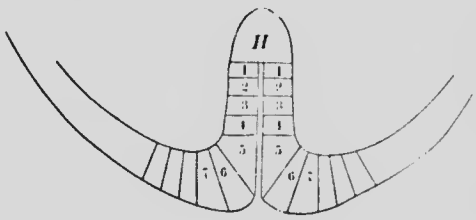


Fig. 52



Mode of origin of *primitive streak* and anlage of eventual embryo according to His.

I am inclined to hold that had Fischel grasped the nature of growth he would have escaped this difficulty and have afforded the adequate theory. What I mean is best illustrated by what we know concerning the mode of growth of the plant. Briefly, this exhibits two primary

growing points, the superior giving origin to the stalk and its appendages, the inferior giving origin to the root, and it is from the cells of

Fig. 53

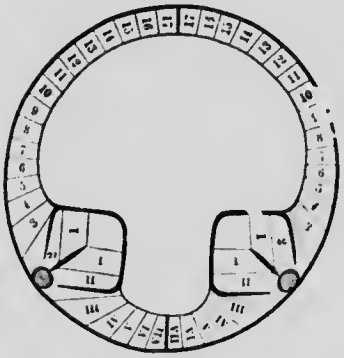


Fig. 54

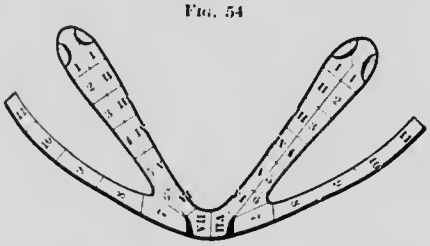
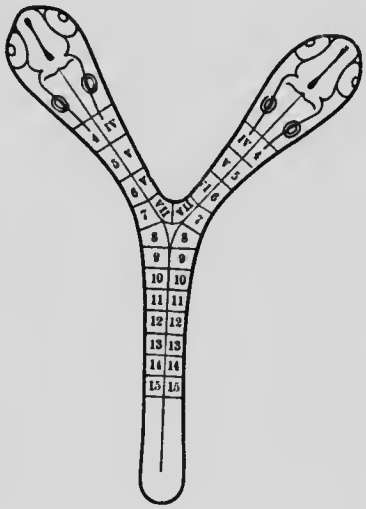
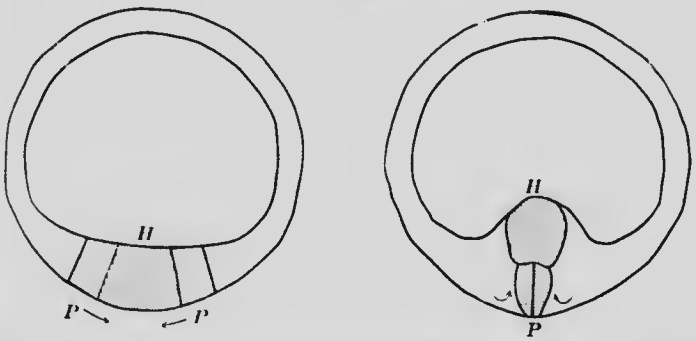


Fig. 55



Diagrammatic representation of Rauber's radiation theory. (Kopsch)

Fig. 56

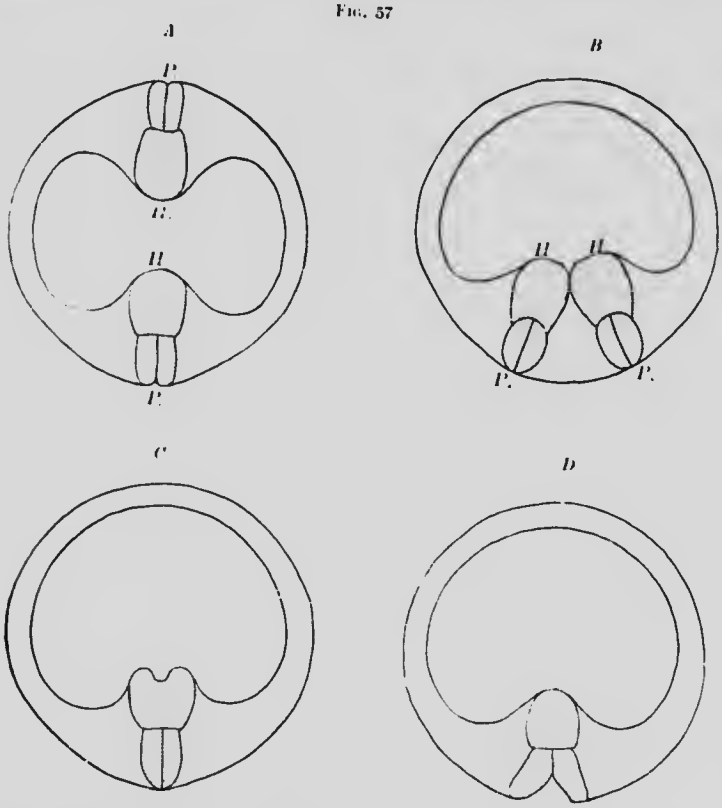


Diagrammatic representation of Fischel's theory, the head centre *H*, formed by the cells that first become invaginated, the rump centre *P*, formed by the fusion of the cells that undergo later invagination.

these growing points that eventually all the component cells and component parts of the plant are derived. In the plant the cells of these

growing points persist and are active throughout life, and their position is, in one sense, fixed; that is, the giant trees of California have attained their height, not by growth forward of, but by growth backward from, their growing points. The primary growing point forms the apex of the plant; its cells are vegetative; they undergo repeated division in such a way that, dividing, the outer daughter cell remains vegetative, retaining the position of the mother cell, the inner or its descendants becoming

FIG. 57



Mode of origin of different orders of double monster according to Fischel's theory. *A*, monochorial twins without fusion; *B*, according to exact area of fusion (the head centre giving origin to the greater part of the body), various grades of craniopagus (head fusion), sternopagus and xiphopagus (body fusion), passing on to conditions of anterior dedupication; *C*, the slighter cases of anterior dedupication by late dichotomy of the head centre; *D*, posterior dedupication by *lack* of fusion of the lateral components of the rump centre.

converted into the eventual specialized tissue cells. In this way there persists a layer of vegetative cells ("cambium"), the cells given off from which become, in series, the primitive cells of successive regions or segments of the trunk. The growing point does not grow forward; it is *projected* forward by the intercalation of cells derived from its daughter

cells, and it continues to occupy a fixed point in relationship to the rest of the economy.

Now, in plants, as all will have noted, we meet with cases in which the growing points have undergone cleavage at either superior or inferior pole; the monaxial trunk of a fir tree may, high up, divide into two or three equal trunks; the radish may fork, and so on. In many species it is natural for the growing point to divide early into several secondary growing points, with the production of many stems or numerous equal rootlets. The plant, it must be remembered, has not bilateral, but radial, symmetry; this notwithstanding, there is a tendency toward

FIG. 58

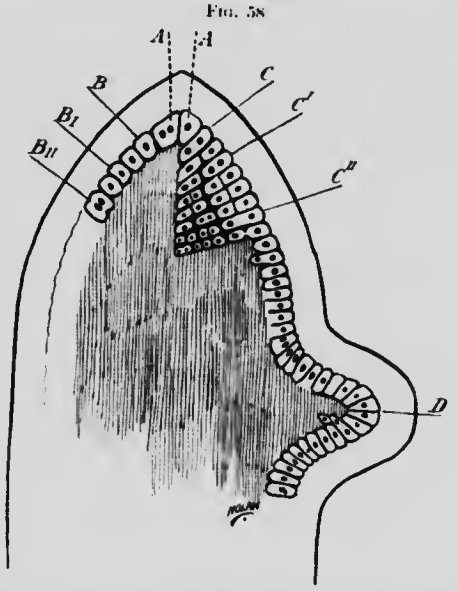


Diagram of section of the growing point of a plant. *A A*, the apical cells which continually divide, giving off backward a series of cells; *B, C, D*, which cells divide as in B^{I}, B^{II}, to form the cells of the vegetative or cambial layer, these cells again, as in C', C^{I}, and C^{II}, divide at right angles to the former plane to give origin eventually to the functional cells of the stem (or root); *D*, development of a secondary growing point.

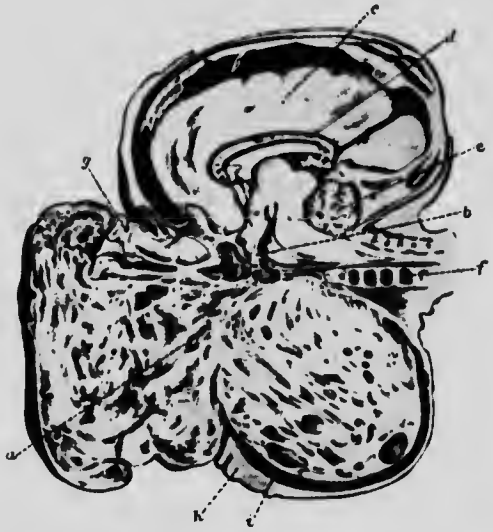
(bilateral) dichotomy, due, we would suggest, to the fact that cell division is binary; if there were a single apical growing point cell, each of the two products of division might assume equal properties and become the progenitor of independent growing points.

So, in animals, what Fischel terms the head and rump centres are *the superior and inferior growing points*. These, once formed, do not grow, but are projected apart; it is the successive daughter cells given off from these that give origin to the different segments of the body and their contained tissues, sundry of those daughter cells becoming secondary growing points for the lateral organs. We have no evidence that the "head centre" gives rise only to the head. There is, however,

this difference between the animal and the plant, that *whereas in the latter the primary growing points may be active through the whole of existence, in the former they cease to function as such so soon as the anlage or matrix of the main axis is laid down.* So soon as this occurs, further increase in length is only by intercalation.

Polar Hyperplasia and Serial Deduplication.—For, suppose this were not the case; that the medullary groove became laid down and the expansions of the neural canal had formed themselves, which are destined to give origin to the brain. Then any further production of daughter cells by the superior growing point could only give origin to a mass of tissue to which no eventual function could be assigned by

FIG. 30



Sagittal section through head of individual with attached epignathus: *a*, epignathus; *b*, region of attachment at hypophysis; *c*, cerebrum of autosite; *d*, corpus callosum; *e*, cerebellum; *f*, vertebral column; *g*, upper and *h*, under lip of autosite; *i*, tongue. (Schwalbe.)

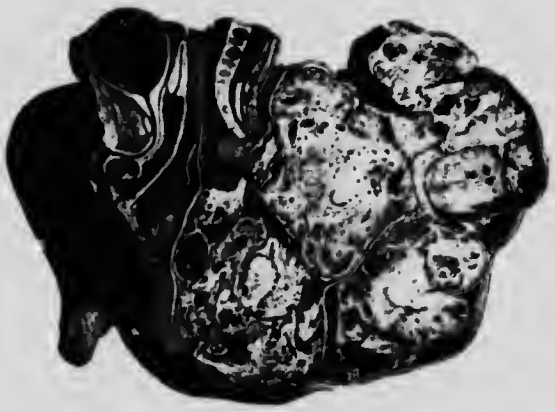
the economy. We know, that is, that the site of the superior growing point in the developed organism is in the region of the sella turcica. The interesting point is that this "absurdity," in the Euclidean sense, does occasionally happen; or, at least, this conception best explains a very remarkable series of monstrosities. There are cases in which, adherent to the region of the sella turcica and projecting through the mouth of the newborn child, there is a large tumor. In the most advanced cases these masses contain bone, and may even show limbs, and are found to contain, when studied, representatives of organs derived from epi-, meso-, and hypoblast. Such cases are known as *Epignathus.* The simplest conception of the origin is that they are due to redundant growth of the superior growing point after the anlagen

of the tissues of the individual have been laid down, and that the "teratogenic termination period" of the production of this form coincides with the development of the "neurula" stage of the embryo; the earlier the period and the more active the proliferative powers of the growing point, the more complete the series of tissues contained in the epignathus.

Similarly, springing from the site of the inferior growing point in the perineal region behind the rectum, we encounter another remarkable form of tumor, having the same general characters—the so-called *congenital sacral teratoma*. To this a like origin must be attributed.

These forms have commonly been regarded as examples of fœtal inclusion, *i. e.*, of the inclusion of one embryo within the tissues of another. But no valid reason has been adduced why this inclusion should occur in these particular regions. Schwalbe concludes that

Fig. 60



Section through a congenital sacral teratoma. (Nakayama.)

there must be "Versprengung," or splitting off of early formative cells, a view which approaches that here given, but, again, does not explain why this should be particularly apt to occur in these particular regions. I regard these forms as homologous with the cases among plants; in the garden rose, for example, where an imperfect flower stalk and head develop from the centre of another flower.

Polar Dichotomy.—Granting that up to the beginning of the neurula stage (when the medullary groove shows itself) the vertebrate embryo presents polar growing points, we now gain the teratogenic termination period for another group of monsters. It has, indeed, been shown experimentally by Spemann, in connection with the newt's egg, that up to this period it is possible to produce both the complete embryos and double monsters; later, this is not possible.

Spemann produced the latter by tying a fine hair round the developing ovum in the plane of the future long axis. He thus obtained various grades of dedoplication. In other words, *up to the well-*

developed gastrula stage it is possible that from a single embryo there may be produced dichotomy, or bifurcation, so that we may by this process gain:

1. Superior dichotomy, affecting the superior but not the inferior growing point, so that the upper end of the body is to a greater or less extent doubled—*anadidymus*, or superior dechiplication (Fig. 62, II and III).

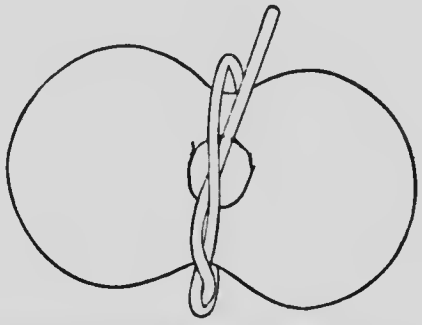
2. Inferior dichotomy, affecting the inferior pole alone—*katadidymus*.

3. Both superior and inferior dichotomy, portions of the trunk region alone possessing a single axis—*anakatadidymus* (Fig. 62, VI).

4. Mesial dechiplication, the superior and inferior growing points remaining single, but their cells projected backward from them on either side, failing to unite, or becoming by mechanical means split asunder—*mesodidymus* (Fig. 62, VIII).

5. Complete cleavage along the whole plane, giving rise thus to two embryos lying parallel, each provided with its individual longitudinal axis (Fig. 62, VII).

Fig. 61



Spemann's method of producing various grades of double monster from the newt's egg by tying a fine hair in the line of the longitudinal axis of the germinal area

Regarding these figures, a few words are necessary with regard to the distinction marked between early and late dichotomy. By early dichotomy, I mean that the cleavage occurs so early that, with separation between the growing point cells at one apex, all the cells which so far have been given off from one or other side of the growing point undergo cleavage, which, indeed, must be held to extend into the area of cell proliferation from the growing point of the other pole, so that as growth continues two axes of symmetrical cell development diverge from this other pole—from which it results that when the anlagen of the primitive streak and structures are laid down they are doubled, and as the anlagen are doubled so from this time onward, the tissues derived from those anlagen are doubled. The result, it is true, is apparent fusion, but there are distinctions to be noted.

In what is referred to as late dichotomy, there, I hold, we have to deal

with the origin of cleavage at a period when the proliferation behind either growing point has been so extensive and so long continued that

FIG. 62

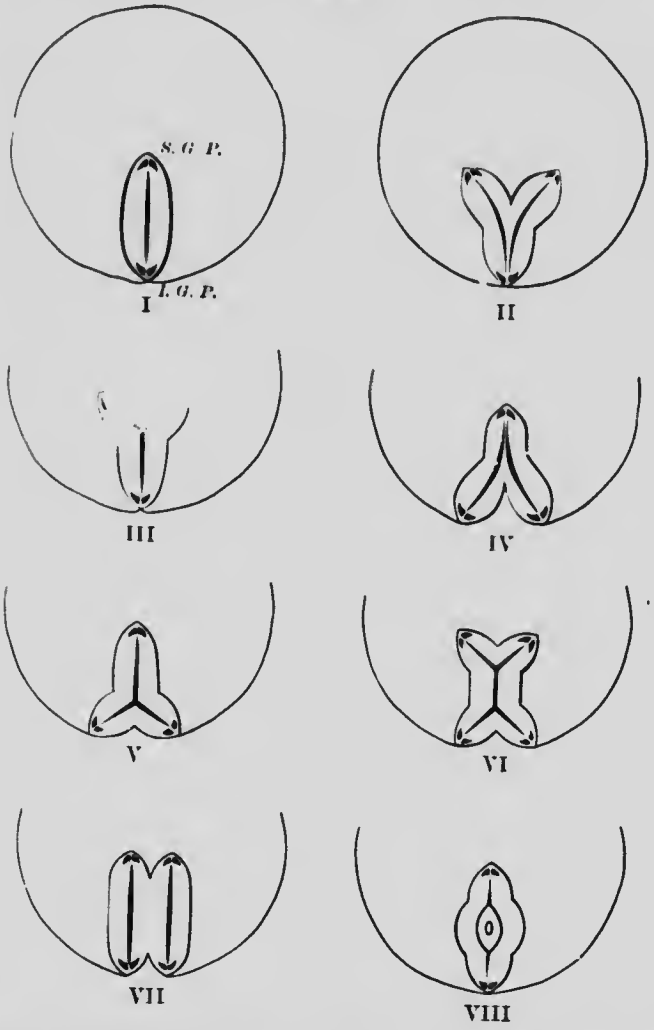


Diagram of various forms of dichotomy or cleavage: I, normal early primitive streak in germinal area with *S. G. P.*, superior, and *I. G. P.*, inferior growing point; II, result of early dichotomy of superior growing point, the separation affecting also the lateral rows of cells given off from the inferior growing point; III, late dichotomy of superior growing point, only the cells given off more recently from the two superior growing points affected; IV and V, similar results from early and late dichotomy of the inferior growing point; VI, relatively late dichotomy of both superior and inferior growing points—anakatadidymus; VII, early (complete) dichotomy involving both growing points—fused double monsters, lateral fusion; VIII, mesodidymus, the growing points remaining single, but the series of cells derived from them on either side undergoing separation.

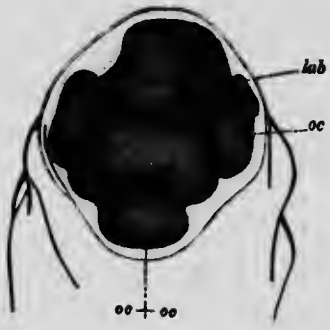
between the two growing points a well-developed primitive streak has been laid down. According to our conception, already recorded, the cells first derived from the growing points—the oldest—will become those farthest removed, while those immediately behind the growing points will be of most recent development. If this cleavage is brought about at a later stage it will affect these more labile and less fixed cells alone.

It follows, thus, that I regard as probable examples of polar duplication an important series which Rauber, Marchand and Fischel, and other modern observers class among examples of fusion. Even granting what must be granted freely, that cases of anadidymus and katadidymus show, upon study, a much more extensive doubling of their axes than external appearance suggests, and that in the former instances more particularly the chorda is often

Fig. 64

Early superior dichotomy in larval newt. (See Spemann.)

Fig. 63



Late dichotomy of superior growing point. Doubling of optic vesicles and forward part of head only of newt embryo in one of Spemann's experiments. (See Fig. 61.)

double as far as it can be traced inferiorly, even this does not prove the fusion of two primarily separate individuals. For the inferior growing plant is not situated at the end of the tail region, but in front of that in the region of the anus (in man). Only where we have evidence throughout the length, of the existence of two longitudinal axes, are we absolutely assured that there have been two complete individuals which have fused. In some fish monsters of this type we have, I think, evidence of this, but they are in the minority, and those conform in the lateral deviation of the fins, etc., to the principles we see in action in those cases in which there can be no question regarding fusion (Janus forms, etc., see p. 228).

In this class, therefore, I include *all cases of double monstrosity in which, at any part of its course, even if it be only at the extreme end, there exists a single median axis.*

PLATE IX

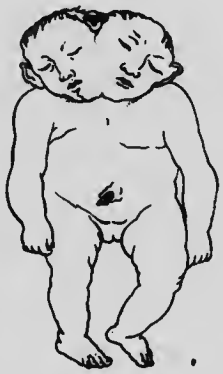
Skiagraph of a Dicephalus Dibrachius. (Schwalbe.)

Of **superior deduplication** we possess a greater series of forms from mere bifurcation of the hypophysis cerebri through those showing more or less imperfect deduplication of the head (Figs. 65 and 66), complete double head (Fig. 67), dicephalus tribrachius (Fig. 69), to dicephalus tetrabrachius (Fig. 68).

FIG. 65

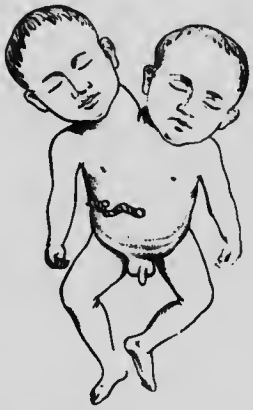
Diprosopus. (Perls.)

FIG. 66



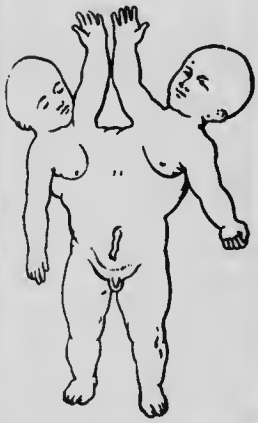
Furtber grade of Diprosopus. (Ahlfeld.)

FIG. 67



Dicephalus dibrachius. (Ahlfeld.)

FIG. 68



Dicephalus tetrabrachius. (Ahlfeld's Atlas.)

FIG. 69

Skiagraph of a Dicephalus tribrachius. Museum, McGill University. (Dr. Girdwood.)

FIG 70

Tricephalic monster. (Ahlfeld's Atlas.)

Of **inferior deduplication** the slightest cases are (not those of double coccyx, but) of deduplication of the external organs of generation. Ballantyne and Skirving[1] have brought together some 20 cases of double

[1] Teratologia, 2: 1895: 92, 184 and 295.

penis. Next to this, we pass through more and more perfect examples of katadidymus tripus up to katadidymus tetrapus.

In both these series of cases there is a single umbilical cord, indicating a common yolk-sac, *i. e.*, development from a single ovum.

Cases of anakatadidymus (Fig. 73) and mesodidymus are distinctly rare.

Fig. 71

Inferior dichotomy. Case of double external organs of generation. (Lange.)

Fig. 72

Katadidymus tripus. (Ahlfeld's Atlas.)

Fusional Deduplication. — In this order are to be included all those cases in which, whether the two elements are equal or unequal, each has its individual main axis, not combining with that of the other, even if, in some cases, the two closely approximate. Keeping in mind the distinction between equality and symmetry, the latter term referring to the position relative to a common plane, we can make the redivision into (1) symmetrical diaxial double monsters, equal and unequal, and (2) non-symmetrical biaxial double monsters, these being always unequal. Of these, the first form a very well-defined class.

Biaxial Symmetrical Double Monsters.—There are certain very striking features regarding these, which include the majority of double monsters: (1) First and foremost, their symmetry: like part is applied to like. We never, for example, encounter monsters applied side to side in opposite directions, or head to tail (the nearest approach to such

is in the cases of epignathus and congenital sacral teratoma already discussed. (2) We may find them chest to chest (ventral fusion), head to head, rump to rump, side to side, but never wholly back to back with bony fusion.

These facts in themselves prove that they are derived from a single ovum and possess like polarity; had we to deal with two distinct ova that had fused, however early, such symmetry would be a chance occurrence, not a law.

We know that the ordinary egg has polarity. Take, for example, a hen's egg that has been incubated twenty-four or forty-eight hours, hold it with the blunt end to the left, the sharper end to the right; the developing chick is always found with the longitudinal axis at right angles to the main axis of the egg, and the head away from the observer.

In all the higher animals the embryo develops, if not on the surface of the ovum (fishes, birds), at least in a very definite relationship to that surface (mammals); its ventral surface is always toward the yolk, its dorsal surface toward the surface of the ovum. Did two *ova* fuse, the commonest form of fusion should be one or other grade of back-to-back union. This is the rarest, and when it does occur, it is partial and easily explained. All symmetrical biaxial double monsters have had their ventral aspects directed toward a common yolk. This conclusion again gives us an indication regarding the period of teratogenesis. *They have originated from a common germinal area.* At what period it is difficult to state with precision, save that the termination of the period must coincide with that of "complete dichotomy," already noted, viz., the separation of germ matter to form two individuals cannot be later than the end of the gastrula stage; the probability is that it is frequently much earlier. The *fusion* of the two, resulting in monster formation, may, as we shall show, occur at a definitely later period. This conception, it will be seen, gives a common

FIG. 73

Anakatadidymus of sheep. (d'Alton.)

Fig. 74

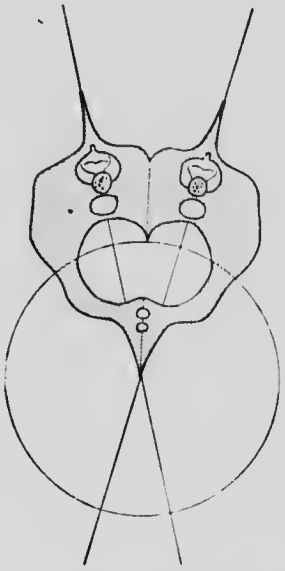


Diagram to demonstrate that two embryos developing upon a common ovum will, if they fuse, show a greater extent of fusion ventrally than dorsally.

origin for all types of double monster—and thus harmonizes the two opposing theories. We have the three stages:

1. Partial dichotomy, giving origin to cleavage deduplication.

2. Complete dichotomy of germinal area, followed by subsequent fusion, giving origin to fusional deduplication.

3. Complete dichotomy of germinal area and yolk, giving rise to monochorial twins.

Granting these postulates, it will be seen that there may be the following main varieties of fusion of two embryos developing on the surface of a sphere. As a matter of fact, we encounter all these, and can thus classify them into the following species:

1. *Ventral Fusion.*—This is relatively common, although frequently it is combined with a certain grade of—

2. *Lateral Fusion.*—The two individuals not being absolutely apposed, they may be regarded as not having accurately faced each other on the sphere, the radii joining the centre of

Fig. 75

Ventral fusion: Thoracopagus disymmetros. Heidelberg Pathological Institute. (Schwalbe.)

Fig. 76

Ventral fusion. Skeleton of a thoracopagus double monster. (After Heller.)

FIG. 77

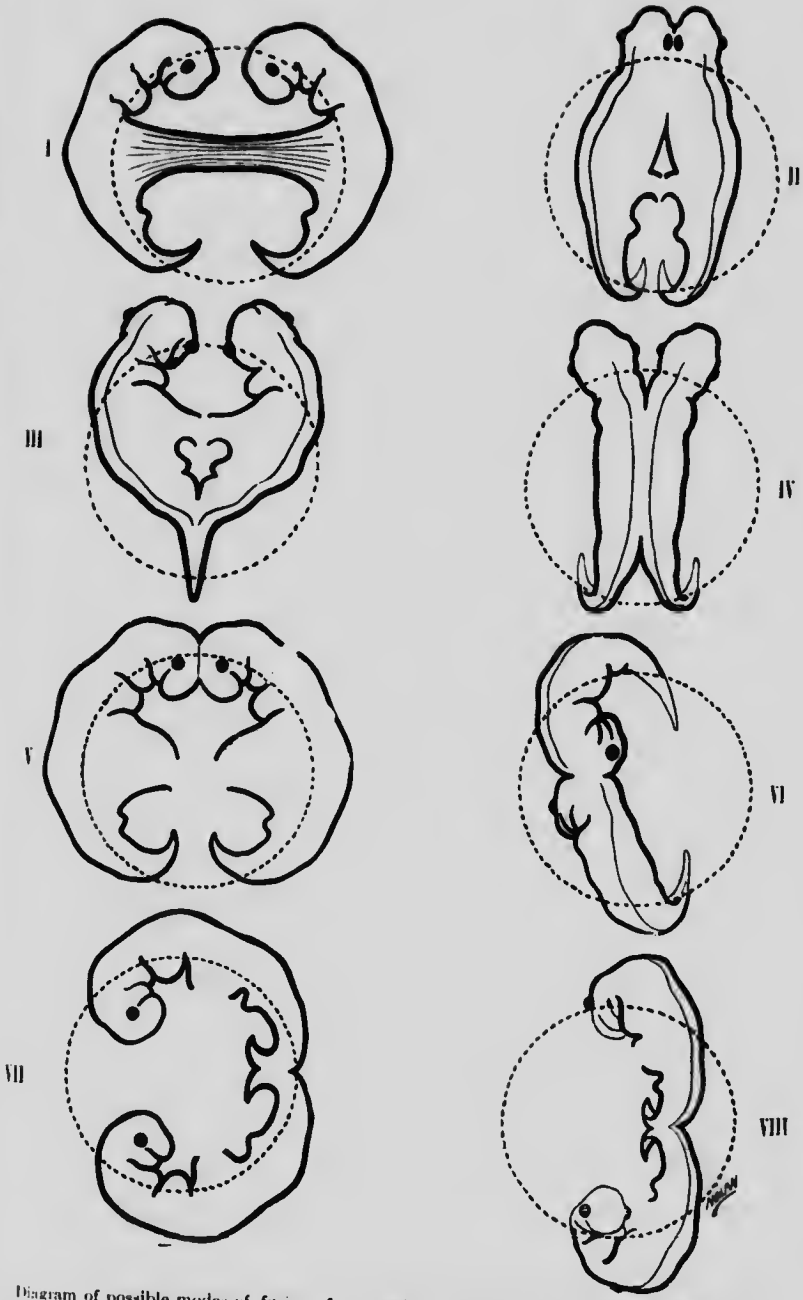


Diagram of possible modes of fusion of two embryos developing on surface of a single sphere (ovum): *I*, by common yolk sac, that is, xiphopagus; *II*, anterolateral; *III*, posterolateral; *IV*, median lateral; *V* and *VI*, cephalic fusion, symmetrical and asymmetrical (see text); *VII* and *VIII*, caudal or inferior fusion.

the ovum to their middorsal surfaces, forming an angle less than 180 degrees.

The greater size and development of the upper half of the body make it that where ventral fusion occurs, the fusion is above the region of the future umbilicus; this is so even in the very slightest cases, *i. e.*, such as xiphopagus, in which fusion is by the xiphoid region alone (the Siamese twins).

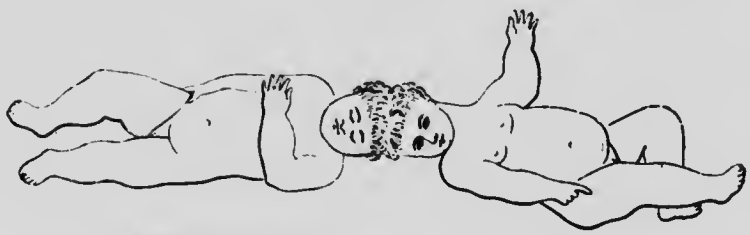
As regards lateral fusion, this is always more pronounced ventrally than dorsally; the conception of growth on the surface of a sphere explains why this must be so (Fig. 74).

3. *Superior Polar Fusion.*—Of this, two distinct subspecies are to be recognized:

(*a*) *Superior Dorsipolar Fusion* (*Craniopagus*).—Here the two individuals are joined by their cranial regions.

We have here a partial exception to the rule of symmetry, and one that throws light upon the period of origin of the monstrosity. The two heads are rarely in absolute conformity; they may be with their sagittal

FIG. 78



Superior dorsipolar fusion: Craniopagus. (Ahlfeld's Atlas.)

planes at angles of 90 degrees, or even more. Now the frontal, and still more the parietal, region is dorsal to the main axis of the body, and juncture by these regions can only mean that fusion has taken place *after the head fold or curvature of the embryo has been developed.* It is an interesting point that in all vertebrates the head of the embryo is not in the direct line of the main axis, but inclines to one or other side. This lateral curvature is well marked in the chick. Consequently, if two such heads fuse, the regions of fusion do not exactly correspond.

(*b*) *Superior Apicopolar Fusion* (*Janiceps or Syncephalus*).—The picture afforded by the Janiceps monsters is very different, and is best indicated by the illustrations (Figs. 79 to 82). Where the axes are in the same line there are two fully formed faces looking in opposite directions. Where they meet at an angle of less than 180 degrees the one face is imperfect; the more acute the angle, the greater the imperfection, until it may be represented only by a single median ear.

It is evident that here we deal with fusion that has occurred at an early period, *before the ventral curve of the head has been developed,* so that the growing points approximate. The accompanying diagrams

Fig. 79

Fig. 80

Apicopolar fusion disymmetrical Janiceps (Cephalothoracopagus disymmetros (Schwalbe's case). The two secondary front or facial aspects are absolutely similar.

Fig. 81

Fig. 82

Apicopolar fusion at an angle less (or greater) than 180 degrees. Monosymmetrical Janiceps (Cephalothoracopagus monosymmetros) (Vrolik's case), Fig. 81, the perfect secondary front view; Fig. 82, the defective secondary front view, with synotia.

(Figs. 83 and 84) indicate what has happened. In the first is represented the perfect Janus type. It will be seen (as universally admitted) that each face (represented by the lateral conical projection) is formed, as regards one-half, from the one individual, *A*, as regards the other, from the other, *B*.

FIG. 83

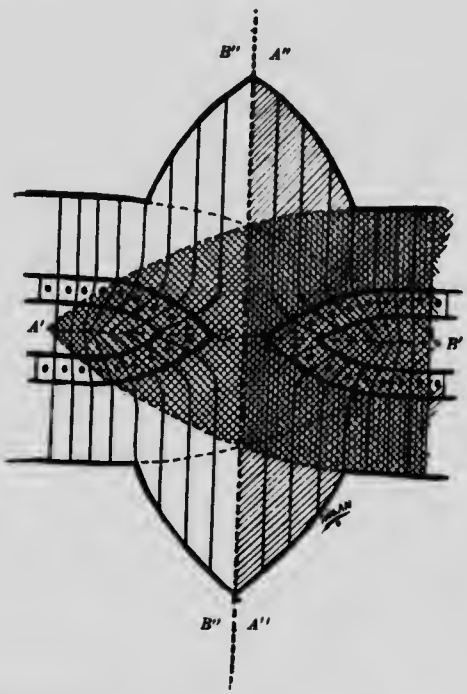


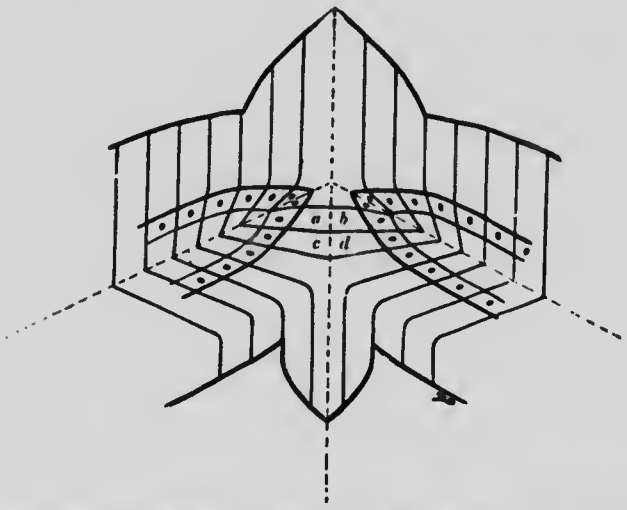
Diagram of mode of development of a disymmetrical Janiceps monster. The longitudinal axes of the component embryos are in the same line. Fusion has taken place early in front of the growing points *A* and *B* respectively; as a result, instead of the cells of the head region derived from *A* growing for each *A'*, they are diverted by the opposing pressure of the cells derived from *B*; each face on either side is thus made up one-half from *A* (*A''*) the other from *B* (*B''*).

We know that the site of what had been the superior growing point is in the immediate neighborhood of the infundibulum; in other words, that the cells derived from the growing point and those immediately behind it give rise by outward growth to the facial structures. If, then, cells in the immediate neighborhood of the two growing points become adherent, the only possibility on the part of their derivative cells is to develop in the line of least resistance. The growing points, as such, do not bifurcate, but their descendants grow out laterally on either side.

When the main axes of the two embryos are not in a straight line, then on the side in which the angle of juncture is less than 180 degrees

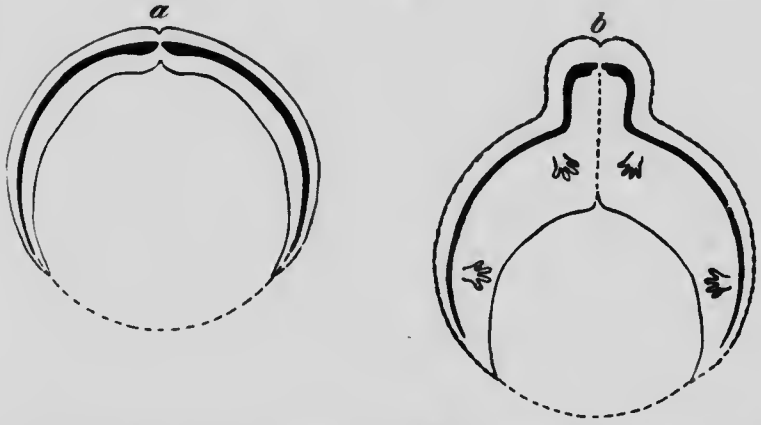
a certain number of cells of the same embryo destined to develop parts of the face by growth in a laterosuperior direction (*a*) will, in their

Fig. 84



Apicopolar fusion at an angle les (or greater) than 180 degrees, with resultant failure to develop parts of the se dary face on the side of the lesser angle.

Fig. 85

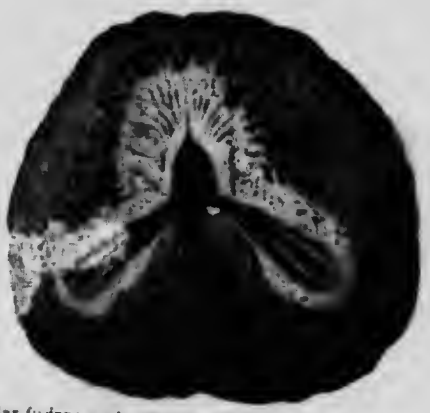


Superior apicopolar fusion: *a*, approximation and fusion of the two embryos before the head curve has manifested itself; *b*, result of growth and development of head curve producing state of cephalothoracopagus.

growth forward, find themselves opposed and arrested by the equal force with which the corresponding cells of the other embryo are tending to grow in an exactly opposite direction. Where fo. es, equal and

opposite, meet each other, as at *a*, *b*, *c*, *d*, in the diagram, the result is that they neutralize each other; in other words, portions of the facial parts do not develop.

Fig. 86



Superior apicopolar fusion: early stage of development of a Cephalothoracopagus monosymmetros in the chick. (Kaestner.)

Fig. 87

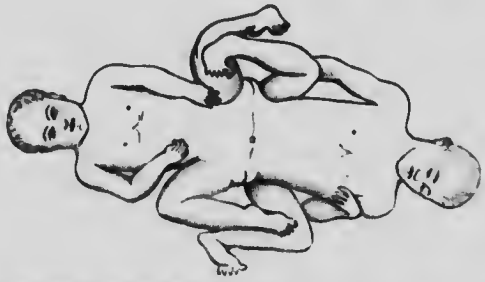
Inferior dorsipolar fusion: Pygopagus monosymmetros. (Marchand.)

Fig. 88

Inferior dorsipolar fusion: Pygopagus monosymmetros. (As with superior dorsipolar fusion the fusion in these cases is rarely absolutely symmetrical.) (Ahlfeld's Atlas.)

A constant feature of these Janiceps cases is that they exhibit also a well-marked grade of ventral thoracic fusion. Why this is so is illustrated in the diagram (Fig. 85). *After* fusion, each head, for its proper

FIG. 89



Inferior apicopolar fusion: Ischiopagus disymmetros. (Ahlfeld's Atlas.)

development, must form its ventral curve; this inevitably brings the bodies together ventrally.

Inferior Fusion.—It is noteworthy that we have identical subspecies at the inferior pole.

FIG. 90

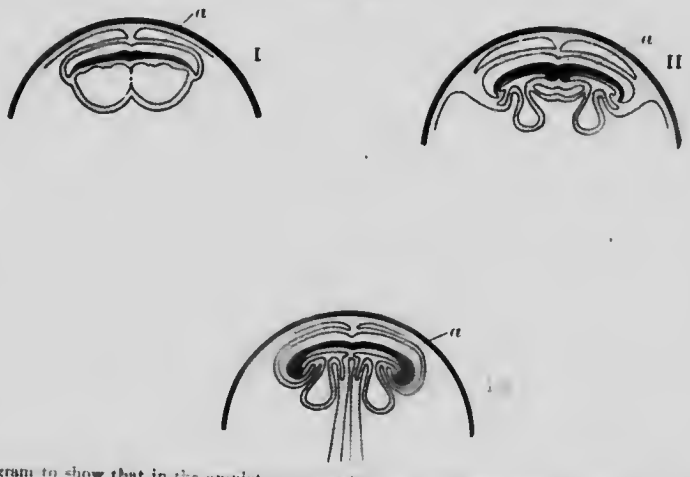


Diagram to show that in the amniota (mammalia), in which the embryo is formed not on the surface but within the ovum and within the amniotic cavity, the same principles apply as in the case of fish embryos developed on the surface of the ovum, the embryo developing parallel to the surface: *I*, superior apicopolar fusion; *II*, superior dorsipolar fusion; *III*, inferior apicopolar fusion; *a*, fused amniotic cavities.

(*a*) *Inferior Dorsipolar Fusion* (*Pygopagus*).—Where the fusion takes place over the ventral curvature of the tail end, it is parts that are dorsal to the main axis that become united.

In rare cases, as the bones form and become rigid, the result of the

sacral fusion is that the two individuals go through life not merely back to back, but with backs so close that the skin fuses; it is found, however, that the intimate bony union in them is only in the sacral reigon.

(*b*) *Inferior Apicopolar Fusion* (*Ischiopagus*).—This corresponds in every respect to the Janiceps fusions at the superior pole, only here it is the lower extremities and not the face that become forced laterally, and this in such a way that one of each lateral pair of legs is contributed by each individual. There may be the same union at an angle, so that there is a pair of legs on the one side, a single, compound leg on the other. There is the same, though slighter, tendency toward ventral fusion as in Janiceps,[1] and similarly the development of a common umbilical cord.

Fig. 91

Thoracic parasite. (Wirtensohn.)

Unequal or Parasitic Symmetrical Double Monsters.—Just as with monochorial twins, in which the fusion is in the placenta and one is the more vigorous, so with these double monsters, in which fusion is in the body: if there be unequal vigor the smaller comes to be nourished directly from the anastomosing bloodvessels of its stronger fellow, becomes acardiac and imperfect, and appears as a parasitic outgrowth. But the adaptation becomes more perfect in this latter case; the circulation is stronger, the parasite is not œdematous, although there is, coincidently, a preliminary stage in which distant parts are apt to have their circulation arrested, and, as a consequence, exhibit aplasia and lack of growth. We thus encounter parasitic thoracopagi, craniopagi, ischiopagi, and pygopagi. With Schwalbe, we may regard these as a further grade of the acardiac monsters, in which the vascular anastomosis has taken place, not in the placental region, nor in the umbilical, but into the body region of the stronger embryo.

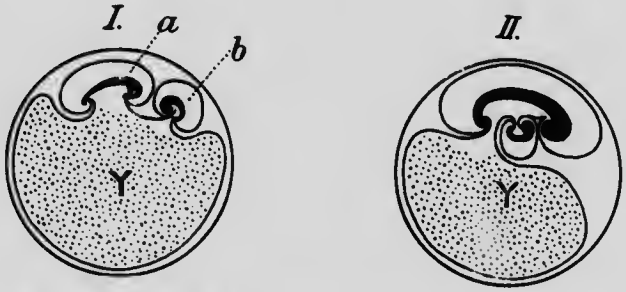
Asymmetrical Double Monsters by Inclusion.—We occasionally encounter aberrant masses of tissue, sometimes (1) projecting; at others (2) definitely included within one or other body cavity. In the first series a weaker embryo has become adherent to the outer surface of the fully formed individual, and, it may be, becoming thus adherent, has become partially included as a result of the infolding and closing in of the body fissures. In the second, there are several possibilities, the simplest of which is that this same process has resulted in complete inclusion and development of the state of "fœtus in fœtu." The accompanying diagram (Fig. 92) indicates the mode of development of these forms.

[1] For in the mammalian embryo the caudal curvature is not so pronounced as is the cranial.

Time and again in examining a series of hen's eggs incubated for twenty-four hours, eggs are met with having two primitive streaks, one of them generally small or otherwise imperfect, not arranged symmetrically and with regard to a common polarity. What is the cause of this want of polarity we do not know; it is possible that two unequal germinal disks have made their appearance in one ovum and undergone fusion. It is cases such as this that represent the early stage of these asymmetrical monsters (Fig. 48).

But fœtal inclusions of this second order can only develop in relationship to the main fissures of the body, in relationship to the mid-line, along the line of the thoracic or abdominal, or, it may be, of the neural cleft at either extremity. Such cases are met with, and however rudimentary and chaotic the collection of tissues found, provided that representations of all three germ layers be present, the simplest explanation for them is this of fœtal inclusion.

FIG. 92



Diagrammatic representations of development of fœtal inclusions. With the more active development of *a*, the larger of two embryos lying in a common germinal area, as the yolk sac becomes exhausted, the smaller embryo (*b*) becomes drawn into the infolding body cavity of the former.

Teratomas.—There are, however, other cases which it is not so easy to explain by this inclusion theory, in which the position of the mass containing elements derived from all three germ-layers is not in relationship to the primitive fissures. These demand another explanation, and a long series of theories has been adduced to explain them, from that of aberrant snaring off of cells, or cell collections, during embryonic or fœtal life, which cells eventually take on independent growth, forming an independent republic, or "free city," within the empire; through theories of aberrant blastomeres—single cells from the period of earliest division of the ovum becoming displaced and eventually taking up independent growth—down to the theory of parthenogenesis pure and simple, developed ova of the individual, or, it may be, spermatozoa, taking on spontaneous growth without the due stimulus of fertilization. This last, for those cases, alone, in which masses of this order develop in the ovary or testis.

We shall discuss these remarkable tumors in association with tumors

in general. For many reasons they might be considered at this point; by mutual relationship it will be seen that they come very close to the double monsters; they are, in fact, one constituent of a double growth. It will, however, be more helpful to a grasp of the more important subject of tumor growth to consider them in the other connection. One group, indeed, we have already discussed—the cases of polar or serial deduplication, the epignathi, etc.—and have shown that we regard them as due to the independent proliferation of aberrant growing point cells—cells of a later stage than the blastomeric, but still *totipotential*, capable of originating tissues of all three layers.

FIG. 93

Ovarian teratoma (ovarian dermoid), to show development of hair, *c*, and teeth, *d*; *a*, sac of dermoid.

Here, as indicating what we believe to be their relationship, we would sum up by classifying the different forms of double growth in accordance with the conclusions arrived at in this discussion.

We may, in the first place, establish four main groups:

1. *Twins.*—Gemini.
2. *Double Monsters Proper.*— Terata.
3. *Teratoid Growths.*—Differing from the latter in that the weaker member of the partnership becomes subservient to and parasitic upon the other, still, however, exhibiting the development of certain recognizable organs, limbs, etc. This is an intermediate and often poorly defined group, grading into the preceding and the following.
4. *Teratomas.*—The results of the independent growth within the tissues of one individual of a cell capable of giving rise to tissues representing all three germ layers, but incapable from its surroundings of developing completed organs and parts.

1. **Twins.—Gemini.**
   (*a*) Heterochorial or dichorial, from separate ova.
   (*b*) Monochorial, from a single ovum (by complete cleavage).
      (1) Equal.
      (2) Unequal. Acardiaci, or chorio-angiopagi.
         Hemiacardiaci; possessing imperfect heart.
         Holoacardiaci, without heart.
2. **Symmetrical Double Monsters; Double Terata.**
   (*a*) By cleavage: *Dichotomous Deduplication.*
      (1) Superior polar: Anadidymus.
      (2) Inferior polar: Katadidymus.
      (3) Superior and inferior polar: Anakatadidymus.
      (4) Mesial: Mesodidymus.
   (*b*) By fusion (following primary complete cleavage, as in 1 (*b*)): *Fusional Deduplication.*
      (1) Ventral: Thoracopagus, various grades down to xiphopagus.
      (2) Lateroventral: Sternopagus, various grades.
      (3) Superior apicopolar: Syncephalus or Janiceps.
      (4) Superior dorsipolar: Craniopagus.
      (5) Inferior apicopolar: Ischiopagus.
      (6) Inferior dorsipolar: Pygopagus.

   All these may be (1) equal or (2) unequal.
3. **Asymmetrical Double Monsters.**—Parasitic fœtus, teratoid.
4. **Teratomas.**
   (*a*) Twin teratomas, due to inclusion and imperfect development of a second embryo developing from the same ovum (and thus equally to be regarded as a second division of Class 3).
   (*b*) Filial teratomas, the products of an aberrant totipotential cell of the host individual. (See Section III, Chapter XV.)

Multiplex births and triple monsters follow the same classification.

REDUPLICATION OF ORGANS; MERISTIC EXCESS.

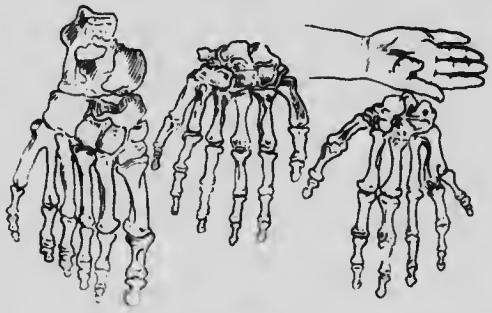
The same principles which we have found at work in the growth of the individual as a whole are in action in connection with the development of the separate organs or parts. Just as in the plant subsidiary growth centres show themselves for the lateral branches, leaves, etc., so we may regard the different limbs and organs of the vertebrate as developed from, or through, the agency of growing centres, which may show aberrations in their growth just as do the primary growing points. Having made this statement, we may proceed rapidly.

With Bateson, we may divide the abnormalities of excess of individual parts into increase in the number of parts arising in (1) longitudinal series and (2) in lateral series. Of the former, the most marked examples occur in connection with the longitudinal axis, the vertebræ and their connections; we may have accessory vertebræ, intercalated,

as it were, in one or other region. There is the formation of an increased number of vertebral centres. Associated with this we may have a corresponding increase in the number of ribs. The two, however, do not necessarily correspond; the number of ribs may be increased without increase in the number of vertebræ (*e. g.*, cervical ribs). The ribs, indeed, arise from lateral-growing points, and may show tendency to dedupliçation of the lateral order, bifurcation of their sternal cartilages or ventral extremities, etc.

The examples of dedupliçation in lateral series are very numerous; the commonest are: (1) *polydactyly*, with all its various grades, from broadening of a terminal phalanx, through double nail, down to doubling of the whole phalanx and appearance of a complete accessory

FIG. 94



Examples of complete and incomplete polydactyly. (Ahlfeld's Atlas.)

digit; (2) polymastia, and the development of accessory nipples and breasts; (3) elongation and partial or complete doubling of the kidneys; (4) the adrenals, testes, ova, and other organs are less frequently the seat of dedupliçation.

Accessory Organs.—Allied to, but different from, the above conditions are the frequent examples of the presence of small isolated accessory organs. The spleen and adrenal afford the most frequent examples, the liver and pancreas less frequent. What we deal with in these cases is evidently a snaring off, or segregation, of certain cells during the course of development, cells already so far differentiated that they have become unipotential, *i. e.*, capable of producing only one type of tissue. These sometimes may come to lodge in distant parts. Thus the testes and the ovary originally lie in apposition to the developing adrenal; in their migration they may carry down with them some cells from the latter organ. As Marchand has pointed out, accessory adrenal nodules may be found in close connection with the developed testes and ovary.

CHAPTER V.

MONSTROSITIES AND ABNORMALITIES—(CONTINUED).

ABNORMALITIES OF DEFECT.

General Defect.—Dwarfism.—In connection with anomalies of defect, we can proceed along the same lines as those followed in connection with anomalies of excess, and begin with general defect.

As with giantism, we recognize a dwarfism due to influences conveyed through the germ cells.

Thoma lays down that if 169 cm. in the male and 163 cm. in the female be taken as the mode, the mean embraces all those having heights within 3.8 cm. on either side of this figure; in other words, one-half the adult population is included within these figures, the other half lies outside. It is suggested that this number 3.8 be multiplied by 5 and subtracted from 169 and 163, respectively, to determine the heights below which dwarfism is present, *e. g.*, 150 cm. (59 inches) for the male, 144 cm. (56½ inches) for the female. It is found that only one individual in every thousand comes below these figures.

These figures we may regard as applying to the true dwarfs, those smaller than normal, in accordance with the law of chance. That the relative amount of "bioplasm" entering into the fertilized germ cell plays some part in their development is suggested by the fact that the division of the ovum into two in the two-celled stage has been found by all observers to result in the production of dwarfed individuals. There is another category, however, of those dwarfed in consequence of intra-uterine defect, affecting particularly the limbs, or of inherited diathesis toward osteogenesis imperfecta. With them should probably be included the cretinoid dwarfs (p. 323), in whom imperfect development is associated with deficient thyroid secretion. Undoubtedly, also, extra-uterine influences during childhood have their influence upon the stature of the adult. This has been well brought out recently in England by a study of primary school-children in London and other cities. Thus at Glasgow it was found that there must be something determining the conformity of height and size to the "law of chance," and that something would seem to correspond with graded variation in the amount or quality of what we have termed the biophoric molecules primarily contributed to the individual. By constantly selecting the larger or best grown seed of any crop and sowing this only, the general average of that crop may be greatly improved within a few years; if, after this, the seeding be left to nature, there is progressive deterioration. Ultimately it is environment that tells, as shown by

the above observation upon the stunting effects of town life and the fact, pointed out by Cantlie, that there is no fourth successive generation of dwellers in London.

Yet another cause of dwarfism, rare in the human race, is inbreeding, as all breeders know well. Calkin's observations upon the partheno-

Fig. 95

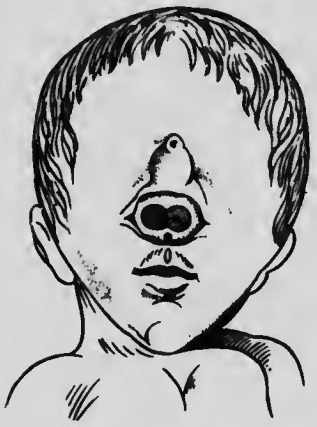


Fig. 96

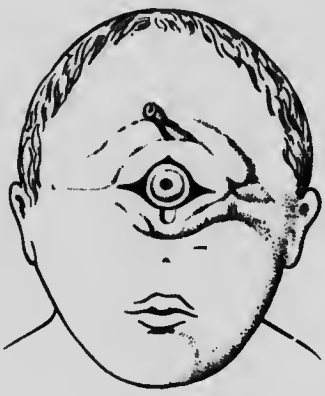


Fig. 97

Various grades of cyclops formation. Fig. 95, arrhincephaly with synotia, the fused orbits still retaining separate pupils; Fig. 96, cyclops proper with median single orbit and pupil; Fig. 97, more extreme grade complete absence of nasal passages, anotia and microstoma. (After Ahlfeld.)

genetic development of the paramœcium, and the eventual dying out or senescence of the stock, may be recalled in this relationship.

Regional and Organic Defective Development.—This is paralled with regional and organic excessive growth, and, like that, may be of more than one form. Thus there may be:

1. **Hypoplasia.**—Congenital or inherited *hypoplasia*, small size of an otherwise perfectly formed organ, due to relative deficiency of matricial matter—of one kidney, of one or both ovaries or testes, of a limb, etc.

2. **Polar Hypogenesis.**—There are certain striking conditions which may best be explained as the converse of polar deduplication and dichotomy. These affect both the superior and inferior poles of the body, as, again, the secondary growing points.

Of such at the superior pole are the various grades of cyclops formation—monsters with the two eyes in a single fused orbit, the nasal passage being deflected upward into a proboscis; with an imperfect double eye in one orbit; with a single median eye; with no eye or medial facial parts. The figures opposite illustrate the cases.

FIG. 98

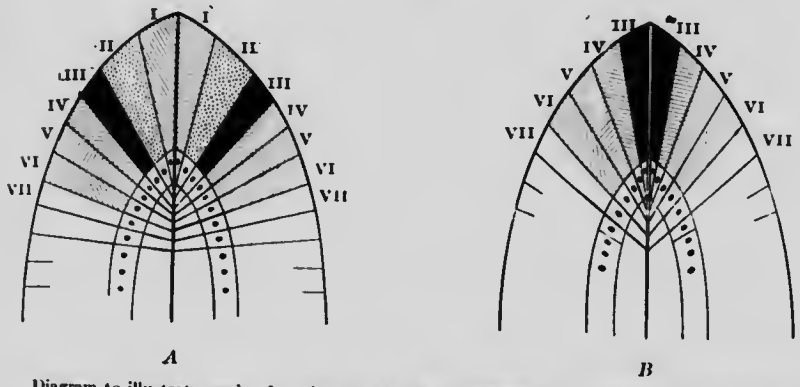


Diagram to illustrate mode of production of polar hypogenesis: *A*, the normal development of the apical portion of the organism, the daughter cells given off by the growing point controlling the development of the apical parts of the body; *B*, premature exhaustion of the growing point cells, those controlling segments *I* and *II* not being developed. As a consequence segments *III* meet in the middle line.

The slightest grade of all is that to which Welker gave the name *trigonocephaly*, showing peculiar smallness of the front of the skull, with approximation of the orbits. The other grades have been termed *arrhinocephalus*, *synotia*, *cyclops proper*. Where, as in the advanced cases, the mouth also disappears, we have *astomia*.

Recalling our conception of the growing point, and how this gives off backward in succession the cells destined to be the mother cells of successive segments, the oldest becoming thus farthest away from the growing point, the most recent in its immediate neighborood, it is obvious that at the superior pole the anlagen for the extreme anterior parts are the last to be laid down. Along these lines cyclops formations are to be regarded as due to *premature exhaustion of the growing point, or arrested growth of the same* at a period when the mother cells for the superior portion of the body and most of the head have been given off.

It is not that the lateral parts undergo secondary fusion in the middle line, having crowded out and arrested the growth of the more median superior regions; those regions have never developed, and the lateral parts have never been other than in apposition.

Siren Formation or Symelia.—At the inferior pole we encounter a corresponding series of anomalies of defect: *Sympus*, or fusion of the two lower extremities into one; *sympus apus*, with still further fusion and a single foot; and *apus*, the fused limbs being represented by a single conical footless stump. These cases lack the external organs of generation, and only rarely, in the slightest grade, is the anus present. The ischia and acetabula are always fused, the pelvis greatly narrowed.

Fig. 99

Sympus. (Ahlfeld's Atlas.)

We would again emphasize that the end of the coccyx does not indicate the site of the inferior growing point, but that lies at a point above and anterior thereto. So that in polar hypogenesis it is not so much the coccyx that is involved as parts originating in front of this. Further, if the homology be correct of the lateral halves of the mammalian penis with the claspers of the ray or skate, and these claspers be the inferior rays or segments of the hind limb, it will be seen that these must be the segments of that limb to be first and most surely affected by premature exhaustion of the inferior growing point. In other words, if there be arrest of formation of the inferior limb rays, with fusion of the representatives of the more cephalad portions of the same, there must be absence of external genitalia.

Hypogenesis of Secondary Growing Points.—Along the same lines are best explained cases of syndactyly and reduction in the number of phalanges, and, as we shall point out later, conditions of the order of agnathia.

3. **Imperfect and Arrested Development of Parts Other than Polar.**—In the course of our discussion of inheritance and in this last chapter there have been adduced more than one factor as effective in producing imperfect and arrested development, viz.: (1) Reversionary degeneration with defective constitution of the biophores, and so of parts of more recent evolution; (2) quantitative defect in the matricial matter set apart for the development of a particular organ; and (3) intra-uterine disturbance (pressure, formation of bands, adhesions, etc.). While certain of the results produced by these agencies are distinctive and recognizable as being due to one order of cause, with many it is difficult, if not impossible, to assign a particular causation; aplasia, or arrested development of a part, however, produced in early embryonic life, leads to the same results, and, as Woodruff

points out, there is no valid reason why one and the same cause, acting on the ovum prior to fertilization, may not exert the same chemical or physical action as it does immediately after fertilization. It is quite possible, therefore, that conditions of a certain order that are acquired may be identical with those due to influences acting on the germ cells prior to fertilization.

Thus, to attempt to analyze and determine in every case of defective growth what is the particular causation, is beyond our power. It becomes necessary from this onward to pass in review the various forms of imperfect development of particular regions and systems. The latter we shall undertake in the special part of this work in which we deal systematically with the different systems. The regional malformations must be noted here; we refer more particularly to defects associated with the closure of the different fissures of the body —of the medullary groove behind, the great anterior thoracico-abdominal fissure and the facial clefts. Following this, we shall conclude this section with a brief consideration of conditions which do not fall under any of the headings thus far noted.

MALFORMATIONS ASSOCIATED WITH DEFECTIVE CLOSURE OF THE DORSAL GROOVE.

This groove, it is scarcely necessary to remind the reader, originates as a longitudinal fold of the epiblast, extending from one end of the embryo to the other, and the epiblast lining it undergoes differentiation at a very early date to form the neuroblast or mother tissue for the whole nervous system, the folding in leading to the formation of the neural canal. In the region of the head this neural canal distends into three bilateral pouches, the neuroblast lining the pouches giving rise to the fore-, mid-, and hind-brains, respectively.

There may be total failure of closure of the groove, or merely local failure, the necessary result in each case being that, instead of there being a neural canal (with expansions to form the ventricles of the brain), there persists exposed nerve matter, which at its edge passes and becomes transformed into the ordinary epiderm. We thus obtain the various grades of *Cranioschisis* and *Rhachischisis*.

Anencephaly, Acrania, or Hemicephaly.—Anencephaly, acrania or hemicephaly is a relatively frequent monstrosity. The frog-like appearance, due to absence of development of the frontals, is very characteristic. Owing to absent closure of the neural groove in the cephalic region, there is lack of development of the vault of the skull and of the hairy scalp. In extreme examples even the orbital plates of the frontal are undeveloped. The freely exposed brain substance becomes extremely congested, so that little is to be made out beyond an amorphous mass of vascular membranes. Nevertheless, the basal portion of the brain has given origin to the optic and auditory vesicles and to the cranial nerves.

As to the direct cause of this condition opinion is still at variance. The view of Dareste still has its adherents, based upon his observation upon the anencephalic chick, that defective development of the amnion is at fault, leading to pressure upon the head at an early period, and, as a consequence, arrested development. Certainly, where there are amniotic adhesions of the fœtal head there are accompanying grave developments of skull and brain; and the lordosis, or curvature of the cervical vertebræ, is difficult to explain on other grounds. But such adhesions are rare, nor is the general development of trunk and limbs of these monsters arrested to an extent corresponding to what

Fig. 100

Anencephaly.

Fig. 101

Iniencephaly. (McGill College Museum.)

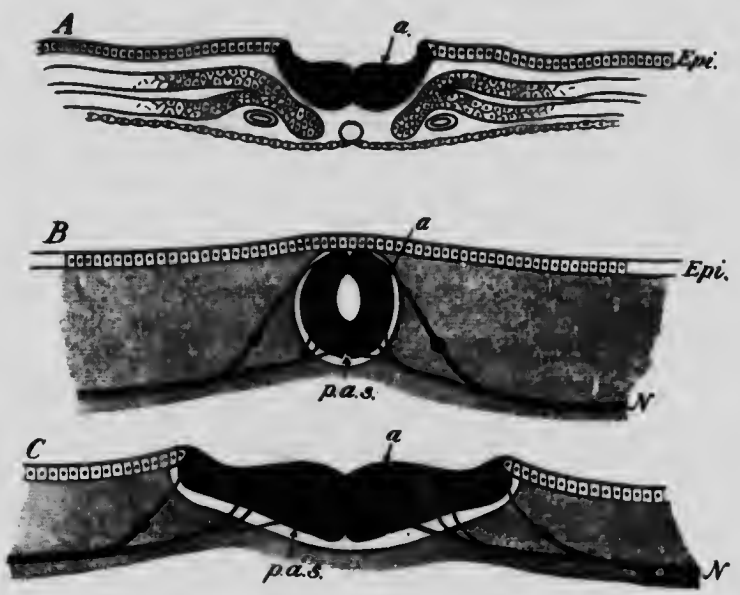
we should expect in defective development of the amnion and escape of amniotic fluid. Another view is that there has been early fœtal hydrocephalus, with distension and rupture of the ventricles and arrested development of the cranial vault. There are, however, no transitional cases to support this hypothesis.

Neither view is adequate to explain the majority of cases. On the other hand, while the body as a whole is found, in general, well developed, there are certain common associated defects, viz., arrested development of the adrenals, while, as Shepherd and others have pointed out, the triangularis sterni muscles are often markedly developed. These facts point to some general vice of development, and so

commonly do we gain a history of parental infection in these cases, that we are inclined to give parental and germinal intoxication as the most frequent underlying cause. There is frequently an associated absence of closure of part or the whole extent of the vertebral canal and condition of *spina bifida*.

Exencephaly.—In these cases the cranial vault is in part developed, more often the frontal region. Where this is the case, the frontal bones are flattened and receding, owing to the escape of brain substances behind. The imperfectly formed brain substance, with its membranes, protrudes behind as a sac overhanging the back.

FIG. 102



A, schema of development of medullary groove; *B*, formation of neural canal by closure of the medullary groove; *C*, complete rhachischisis; the medullary groove remains open; *Epi.* epiderm; *a*, neural tract; *p. a. s.*, pia arachnoid space.

In most of these cases, however, as in meningocele, we deal with deficient formation of the bony vault of the skull rather than lack of closure of the neural canal. These conditions, along with that of hydrocephalus, will be discussed along with the regional malformations of the nervous system. The most extreme condition of this nature is *Inencephaly*, in which, with spina bifida, there is imperfection of the occipital bone, through which part of the brain projects. What is most striking is that there is extreme flexion of the vertebral column, so that the occiput is approximated to the sacrum, the skin passing directly from one to the other.

Rhachischisis, or Spina Bifida.—Strictly speaking every case in which the spine remains "bifid" in consequence of failure of the laminæ of one or more vertebræ to unite is a case of spina bifida, or rhachischisis. What is all important, from a diagnostic and surgical point of view, is the extent to which, and the mode in which, the spinal cord is involved in the defect. We thus distinguish the following series of cases:

1. **Spina Bifida Completa,** in which the primary cause of lack of closure is failure of the medullary groove to close in and form the neural canal. As a consequence the ependyma, or superficial layer of nerve substance, remains in continuity with the skin on either side, the cord forming a flattened superficial plate, as indicated in the diagram (Fig. 102), of this order we may distinguish the following groups,

(*a*) **Spina Bifida Completa Totalis,** in association with anencephaly. The neural matter forms a broad plate extending down the back to the coccyx, and fusing on either side with the skin of the back.

(*b*) **Spina Bifida Completa Partialis,** in association with anencephaly, but affecting the cervical region only, the neural canal becoming formed below this.

(*c*) **Spina Bifida Completa Restricta,** local, affecting a restricted area in either cervical or, more often, lumbar region. Here, whether through abnormal curvature of the embryo, or lack of growth energy, one or other of the last regions of the medullary groove to close remains open—as a flattened, exposed plate of nerve tissue, passing almost imperceptibly into the skin on either side. The cord in these cases, instead of becoming, with progressive growth, relatively short, compared with the vertebral column, remains long, and inevitably its canal opens on to the surface at the upper and lower extremities of the area. Very rarely this has been recorded in the dorsal region. Two results may ensue: (*a*) Either the area remains flattened, there being free discharge of cerebrospinal canal, keeping the surface moist. Such cases, if born alive, inevitably exhibit infection, and, whether from this, or from the free loss of the fluid, die within a few days; or (*b*) owing to the absence of pressure, fluid accumulates in the anterior pia arachnoid space under the defect, causing the flattened cord to project backward, in which process the openings of the neural canal are apt to become occluded by pressure of the cord against the edge of the orifice. In this way originates the true *myelocele*.

In all these cases the neural epithelium covering the defect is apt to undergo extensive degeneration; the cord is represented by a flattened mass of greatly congested vessels, between which isolated nerve cells may be distinguished; the spinal nerves are given off from the anterior aspect and traverse the cyst (if present).

2. **Spina Bifida Incompleta.**—In all the remaining cases there has been due closure of the medullary canal, with junction of the cutaneous epithelium in the median dorsal line; the cord has become surrounded by its meninges, but there has been failure of the laminæ and associated tissues to develop adequately.

(*a*) The cord remains in almost immediate contact with the skin, and, with accumulation of fluid in the anterior arachnoid space, becomes represented by a flattened ribbon of nerve matter, from which pass the spinal nerves traversing the cyst—*meningomyelocele* of the first order. This form is relatively common.

(*b*) Lack of pressure leads to accumulation of fluid in the central canal of the cord in the area of defect—*myelocystocele*, or *syringomyelocele* (hydrorrhachis interna). Here the spinal nerves lie outside the cyst wall.

(*c*) Through some defect in the walls of the vertebral canal there projects a cyst formed of the meninges—*meningocele*. Such defect may be either between the laminæ, the cyst projecting backward, or, rarely, of the nature of a cleft between the bodies of the vertebræ. There are no nerves in association with the cyst.

(*d*) Fluid accumulates in the *posterior* pia arachnoid space, and at the same time a portion of the spinal cord also protrudes through the defect in the bony tube—*myelomeningocele* of the second order (very rare).

(*e*) Localized lack of junction of the laminæ, but no fluid projection, a pad of fatty and muscle tissue filling the space between the skin and the cord—*spina bifida occulta*. This form shows itself in either the cervical or lower lumbar region, and characteristically the area of defect is covered by a clump of long hairs.

DEFECTS OF THE ANTERIOR THORACICO-ABDOMINAL FISSURE.

We need but remind the reader that the embryo, at first a flattened, elongated plate on the surface of the ovum, becomes gradually more cylindrical, the sides curving in to form the body cavity. For a considerable period these sides do not meet, and the developing viscera are exposed ventrally; for some time, indeed, a portion of the bowels actually protrudes, as does the allantois, with its vessels. Eventually this great thoracico-abdominal fissure may fail to unite, and thus we encounter the following conditions:

Fissura Sterni.—Affecting the whole or part of the sternum, above or below. Either the sternal elements proper may fail to develop or the whole wall may be wanting, with resulting exposure and *ectopia* of the thoracic viscera. Where this is complete, the lungs cannot expand and extra-uterine life cannot be. Where incomplete, the heart alone may be exposed *ectopia cordis*, at times with, at times without, development of the pericardial sac.

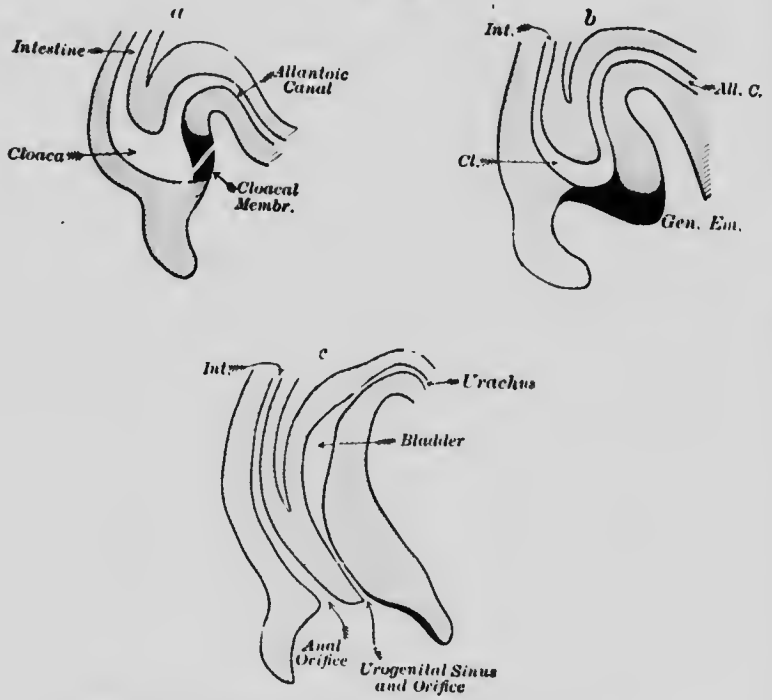
Complete Abdominal Fissure.—Eventration.—This is occasionally encountered, the viscera in general protruding through the median aperture.

Hernia Funiculi Abdominis.—Hernia funiculi abdominis is more common, or incomplete closure of the walls at the point of entry of the umbilical vessels. In this case a portion of the viscera lies within and distends the proximal portions of the umbilical cord.

Very rarely, the *omphalomesenteric duct*, the communication between the primitive small intestine and the yolk sac, may persist and remain patent, extending into the cord.

Fissura Vesicogenitalis.—Or the persistence of the fissure may be limited to the lower end of the abdomen. It will be remembered that the urachus represents the old communication between the bladder and the umbilical cord, that originally from the region of the cloacal

Fig. 103



Schema of development of rectum and urinary passages from cloaca.

membrane and end of the gut the allantois was developed, passing to the region of the navel, and that in the dorsal end of this, at first freely communicating with the abdomen, the bladder develops, its ventral end being continued as the urachus. The bladder thus is, from the first, closely connected with the cloacal membrane. This latter eventually becomes perforated, the hind gut beyond it atrophies, and the rectum thus opens into the anus. Reichel, Enderlen, and the more recent workers on this subject hold that the various grades of *ectopia vesicæ* are to be ascribed to a very early and abnormal division or fissure of the cloacal membrane extending navelward in the region of the bladder and abdominal wall, whereby the two sides of the abdominal wall

do not come together, and the bladder, also being associated in the fissure, is left open in front.[1] Associated with this condition we encounter that of *epispadias*, or patency of the urethral canal, on the upper aspect of the penis. The pubic arch, along with the abdominal wall, fails to gain complete formation; the two sides do not meet, and there is no symphysis; the anterior fissure of the bladder is continued along the urethra. The penis in these cases is short and imperfectly developed.

Another frequently associated condition is the persistence of the cloaca, so that the gut, instead of opening into the anus, is connected with, and discharges into, the bladder, or opens into both.

In the most extreme cases, according to Marchand, the division through the genital eminence may be permanent; so that there is half a penis or half a clitoris on either side.

DEFECTS OF SPECIAL REGIONS.

Defective Development of the Diaphragm.—At this place, while discussing imperfect regional development, it is well to take into consideration the condition of defective closure between abdomen and thorax. This, the so-called *congenital diaphragmatic hernia*, is not uncommon, and certain grades are compatible with continued existence. We have, indeed, encountered it in a man aged fifty-seven years, who died from other causes.[2] As a result, the pleural and peritoneal cavities are in direct communication through an orifice frequently wide enough to allow a large part of the stomach, the spleen, the left lobe of the liver, and several coils of the intestine to lie in the pleural cavity, though sometimes the defect is trivial. It is much more common on the left than the right side, the presence of the liver appearing to favor the orderly development of the right half. When occurring on the right side, part of that organ passes into the pleural cavity.

While the condition is spoken of as diaphragmatic hernia, it must be remembered that, strictly speaking, a hernia is a protrusion of some of the abdominal contents through some abnormal opening, carrying the peritoneum before them, and as here most often the orifice is complete and there is no such covering of parietal peritoneum, most cases are properly those of false diaphragmatic hernia. At times, however, there is a membrane, peritoneal on the one side, pleural on the other, covering the defective area of the ligamentous or muscular portion of the diaphragm; then the viscera protruding into the pleura form a true hernia.

The commonest site of defect is in the ligamentous portion; smaller

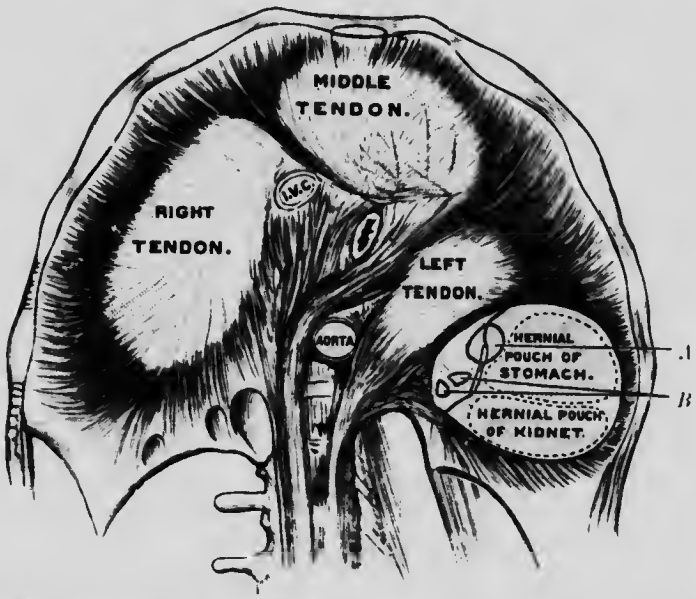
[1] For a full study of this complicated subject and criticism of the literature, reference may be made to Enderlen, Ueber Blasenectopia, Wiesbaden, Bergmann, 1901.

[2] Fry, Montreal Medical Journal, 25: 1897.

defects may occur behind in connection with the œsophageal foramen, or in front, from lack of development of the portio sternalis, when there may be *ectopia cordis abdominalis*. When the defect is large, the lung on that side is unable to develop fully, and, indeed, may remain in an atelectatic condition; in an infant dying at birth we have seen it scarcely recognizable. In the commoner, left-sided condition, the heart usually assumes a median position.

A more severe grade of this same condition of arrest of development is complete, or almost complete, absence of the diaphragm. This is incompatible with continued existence.

FIG. 104



Congenital diaphragmatic hernia in man, aged fifty-seven years, partly false, there being at *A* and *B* direct communications between the peritoneal and pleural cavities, from the edges of which fatty omental folds of tissue passed into the thorax; partly true, the serous membrane forming a covering over the stomach and left kidney as they lay in the pleural cavity. The muscle of the diaphragm is shaded dark.

Defective Closure of the Facial Clefts.—Here, apart from the phenomena of polar reduction already noted, the abnormalities of defect show themselves specially in connection with the bilateral facial cleft extending from the orbit to the mouth. According to causation, Marchand divides them into primary and secondary—primary, due to inhibited local growth and fusion of the parts; secondary, due to amniotic adhesions and other causes of arrested junction; the former regular, or reproducing with fidelity an earlier developmental stage, whether unilateral or bilateral, the latter irregular, with more or less distortion

of such earlier state. The inherent nature of the primary disturbances is indicated by the frequent inheritance of *harelip* in various grades.

In its very slightest grade, *harelip* affects only the upper lip, and that on one side; in severer grades there is associated lack of union between the maxillary process and the intermaxillary bone, so that there is an alveolar cleft; this may extend into and affect the hard and soft palate—*cleft palate*—in which case the nasal cavity communicates with the mouth. In the severest cases of all we encounter either a cleft passing along the side of the nose into the orbit, or, again, though this is very rare, lack of formation of the intermaxillary bone, in which case there is a condition of median cleft of the lip.

To recite rapidly the various orders of defect in this region, they are—following Marchand's classification—as under:

Median cleft of the nose, with one nasal passage or with a simple tube on either side. Allied to this is the rare condition in which one nostril is fully formed, the other a mere conical snout, or proboscis.

Lateral nasal cleft, through lack of closure of the lateral frontal with the median nasal process.

Cheiloschisis. Simple harelip. See above.

Cheilognathoschisis. Cleft of lip and jaw, usually bilateral, with the intermaxillary forming an isolated median process (rare).

Cheilognathouranoschisis. Cleft of lip and jaw and palate.

(*a*) *Median cleft of lip*, with lack of development of intermaxillary bone and broad cleft of lip (seen in arrhinencephaly).

(*b*) *Unilateral cleft of lip and jaw*, due to defective union of the nasal and maxillary processes. Often associated with lateral cleft of the palate, lack of union of the alveolar process with that of the other side, and the vomer. Most frequently left-sided.

(*c*) *Bilateral cleft, with median or bilateral palatal cleft.* Here the intermaxillary forms a snout-like projection connected with the nasal septum and the vomer.

(*d*) *Unilateral or bilateral harelip, with closure of the mouth through fusion of the upper and lower lips.* In the first case only one-half of the mouth cleft is left, forming a common opening with the nose; in the latter the cleft and communication is bilateral.

(*e*) *Primary lateral facial cleft. Cheilognathoprosoposchisis.* Persistence of primary condition, or separation between the maxillary process of one side and the lateral and median frontal, or nasal processes.

Makrostomia. Fissura buccalis. Lack of union of the sides of the mouth cleft, either unilateral or bilateral, the mouth thus reaching to the ear.

Aprosopia. Complete lack of formation of the various processes forming the face, which thus is represented by an irregular cavity.

According to Marchand (who discusses the subject fully), the variation in the number of the teeth which may be present on the intermaxillary is not an indication that the intermaxillary on either side is formed of two halves, and that the lack of union is now on the one side now on the other of the outermost of these two halves, but is to be ascribed to

the fact that the anlagen for the teeth are not directly connected with the anlagen for the intermaxillary and upper jaw, but are developed at a later period and liable to deduplication when, by a cleft or other defect, the row is interrupted.

FIG. 103

Development of the face of the human embryo (His): *A*, embryo of about twenty-nine days. The nasofrontal plate differentiating into processus globulares, toward which the maxillary processes of first visceral arch are extending; *B*, embryo of about thirty-four days: the globular, lateral frontal, and maxillary processes are in apposition; the primitive opening is now better defined; *C*, embryo of about the eighth week: immediate boundaries of mouth are more definite and the nasal orifices are partly formed, external ear appearing; *D*, embryo at end of second month. (Heisler.)

Uranoschisis. Cleft palate. Affects the hinder portion of the hard palate, along with the soft palate at one side. Very rarely does it affect the anterior part of the hard palate only.

Staphyloschisis. Fissure limited to the soft palate, and in the slightest grade to the uvula only (bifid or double uvula).

A series of these cases of harelip and cleft palate is markedly hereditary, but not all. In other cases, as in micrognathia, the arrest is of mechanical origin. In the majority no clear primary cause is to be

made out. As already stated, the irregular forms are obviously secondary to such mechanical disturbance as is produced by amniotic bands.

Other malformations of the face which are regional, affecting more than one organ, are best discussed here.

Malformations of the Lower Jaw.—Agnathia.—Absence or great aplasia of the lower jaw bilaterally. When this is the case the outer ears tend to approximate, and may, indeed, fuse in the median line of the neck below the upper jaw (synotia). There is accompanying microstomia. Winckel[1] ascribes the conditions as due to lack of growth owing to amniotic pressure on the back of the head, the lower jaw area being thus compressed against the neck. This, however, does not satisfactorily explain the synotia, and, with Dareste and L. Blanc,[2] we would ascribe the condition to arrest of development of the third cranial vesicle (or, we would say, of the lateral growing point forming this region), with abnormal fusion of parts before and behind. The region of the third vesicle (fourth ventricle) remains a simple tube; the corresponding parts of the face are not developed. There is lack of development of the first branchial arch, in consequence of which the lower jaw and the basal portions of the superior maxilla are wanting. Certain bony portions of the internal and middle ear are still found, as also the external ears, but they come close together and fuse in the midline.

This *otocephaly* is often accompanied by disturbed development of the region of the first vesicle, producing what Blanc terms *cyclotia*. Whereas in cyclopia the eyes remain in the upper part of the face, here, owing to the lack of development of the superior maxillaries, the eyes pass downward and join, and the new orbit is formed under the anterior portion of the sphenoid.

Microgнathia, or imperfect development, with small size of lower jaw and condition of chinlessness, may possibly be due to the compression suggested by Winckel.

Cleft tongue, median cleft of lower jaw, fistula and cyst of the lower lip are all rare conditions.

(Here, while discussing the malformations of the lower jaw, attention may be called to the opposite conditions of excessive growth, viz.: (1) Dedupliction of the alveolar process with development more or less complete of a double row of teeth; and (2) *dignathia*, dedupliction of the lower jaw, the converse of agnathia.)

Anomalies of the Branchial Clefts.—Incomplete closure of the second and lower branchial clefts leads to the formation of *congenital fistulæ* and certain *congenital cysts* of the neck. These clefts pass from the exterior to what becomes ultimately the pharynx. The fistula may be complete, with a free passage of communication from without inward; may be incomplete internally or externally, resulting in a

[1] Munchener med. Wochenschr., 1896; No. 18.

[2] Jour. de l'Anat. et Physiol., 1895. See also Le Gendre, Bouchard's Pathologie, I. 260.

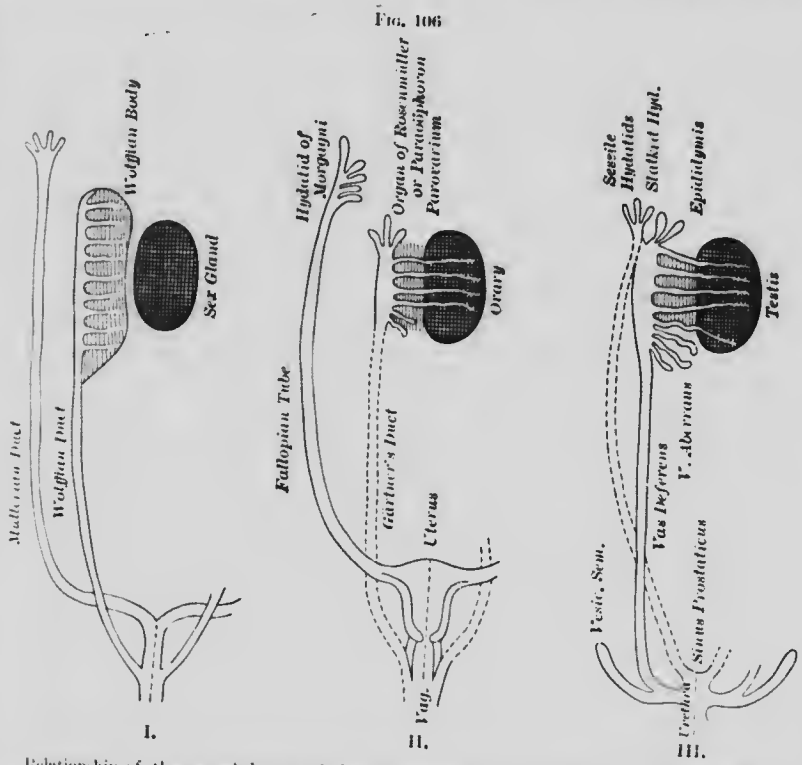
blind fistula; or, finally, the passage may be obliterated at either end, but persistent in its central part, in which case a cyst develops. According as this cyst originates from the more external or the more internal portion of a cleft, so may it be lined with squamous or with ciliated epithelium. Bland Sutton[1] more particularly has studied these conditions; he points out that the outer openings of the fistulæ, according as they are developed from one or other cleft, occur along a slightly curved line, with its concavity forward, extending from the external auditory meatus downward toward the sternoclavicular articulation on either side. Counting the Eustachian tubes which represent the first, there are potentially four pairs. It is the second pair which most commonly persists wholly or partially, as an abnormality.

Cloacal Defects.—It will be remembered that, as at the front end of the body, so at the hinder, there occurs a most complicated series of developments, which, by arrest or imperfection, favor the production of numerous anomalies. To these we have already referred briefly in discussing ectopia vesicæ. To understand the other anomalies, it will be well to review rapidly the main transformations. The gut, in its earliest stage, ends blindly in the coccygeal region. It comes close to the surface at the cloacal membrane and is continued a little beyond this as the "post-anal gut," regarding which all that is necessary to say is that it undergoes atrophy at a comparatively early date, though not without at times leaving rudiments which may be the seat of subsequent change. For the present we may neglect this and regard the original gut as ending beneath the cloacal membrane. From the front of this cloacal region there passes forward to the surface of the embryo the allantois, along what will eventually become the umbilical cord. Thus, at first, into the common terminal cloaca there pass two channels, the intestinal behind, the allantois in front. Next, by the formation of lateral folds, which meet in the middle line, the division between these two channels is carried down to the cloacal membrane, so that now two separate *cul de sacs* exist, the rectum behind, the allantois in front. In the normal course of events nothing occurs in relationship with the posterior channel save the absorption of its share of the cloacal membrane to form the anus. In connection with the anterior passage there are several changes. The proximal portion of the allantoic channel becomes converted into the medianly situated bladder; the passage itself becomes what is termed the urogenital sinus. Into this now opens the Wolffian ducts, passing down from the kidney region. The anterior portion becomes closed off eventually to form the urethra (in the male its proximal part only, the distal part being contributed by the genital eminence, from which is developed the penis in the male, the clitoris in the female). Into the more posterior portion of the sinus open the Müllerian ducts, which undergo fusion at the lower end to form the vagina (in part, the anterior portion of this being contributed by the urogenital sinus) and the uterus, and remain

[1] Tumours, Innocent and Malignant, 1st edit., 1894: 323.

distinct above as the Fallopian tubes. Thus it comes to pass that the Wolffian ducts, passing along the sides of the cervical end of the uterus, open into the vagina. But at the same time these Wolffian ducts split off the ureters, which gain entry into the base of the bladder, while the main duct on either side atrophies in the female, and, at most, at birth is represented by the rudimentary Gärtner's ducts. In the male they become converted into the vesiculæ seminales and the spermatic cords.

Fig. 106



Relationship of the sexual ducts and their rudiments in the two sexes. *I*, the indifferent primary type; *II*, the differentiation in the female; *III*, the differentiation in the male.

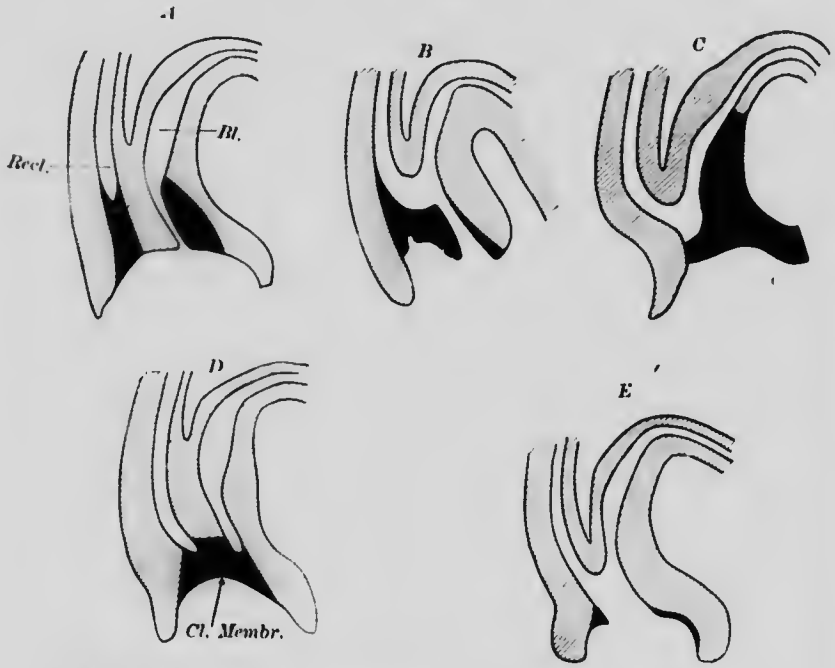
The Müllerian ducts, on the other hand atrophy in the male, and are, at the most, represented in the prostatic portion of the urethra.

Here we shall deal with the rectal conditions only, taking up the genito-urinary defects later.

Atresia Ani.—Of this there are various grades: (1) A simple membranous septum closing off the rectum from the exterior, as the last remains of the cloacal membrane; (2) a thicker layer of tissue in the anal region, so that some little, or it may be considerable, distance intervenes between the anal site and the blind end of the rectum (Fig. 107, *A*); or (3) rarely the end of the rectum lies free in the pelvis. In the

last case there has been primary lack of development of the lower end of the bowel. In cases other than the simplest, where there has been a cloaca formed, the connection of the intestinal tract with the urogenital sinus is apt to persist in the shape of fistulous or wider communication between the rectum and the urogenital organs (Fig. 107, *B*). Thus there may be:

FIG. 107



The various defects due to imperfect development in the cloacal region: *A*, imperforate anus, atresia ani, the rectum closed off from the genito-urinary passage, which is patent; *B*, imperforate anus, the rectum opening into the bladder or urethra; *C*, persistent cloacal membrane, imperforate anus and absence of urethra with persistent cloaca; *D*, the same, but with separation of rectum from the genito-urinary passage; *E*, persistent cloaca, through lack of continuation downward of ridge separating the rectum from the genito-urinary passage.

Atresia ani vulvovaginalis, the rectum communicating with the vulva or the vagina, and meconium being discharged through these passages.

Atresia ani uterina, communicating with the uterus; very rare.

Atresia ani urethralis, with the urethra (pars membranacea).

Atresia ani vesicalis, with the bladder; rare.

Persistent cloaca. Here we have a still more complete arrest of development at an early stage; there is complete closure both of rectum and genito-urinary passages from without, and all open into a common cavity (as in *C*). More rarely a later stage is indicated, the various channels being formed, but all being closed off from the exterior (*D*) or lastly the cloacal condition persists, but the membrane becomes absorbed (as in *E*).

TRANSPOSITION OF VISCERA: SITUS INVERSUS.

There are yet other orders of anomalies, which only come under the heading of anomalies of defect, in so far as they do not represent the normal constitution. Such are transposition of viscera and hermaphroditism. Transposition of viscera naturally only shows itself in connection with viscera that are not paired or do not occupy the median line—the heart and aorta, the stomach and intestines (organs which, originating in the median line, with development become diverted in one or other direction), the spleen and the liver. To this statement there is one slight exception, viz., the lungs, which, while paired, exhibit different lobation on the two sides.

There is also one known functional exception, viz., the speech centres in the island of Reil. Normally, it would seem that the left set of centres is functional, the right latent; this may be reversed.

The transposition may, on the one hand, affect only a single organ or group of organs; or, on the other hand, there may be complete situs inversus. Thus, the heart alone may be transposed, or the transposition may affect only the main arteries, the aorta passing from the right, the pulmonary artery from the left ventricle; or the thoracic organs may be normal, while the liver, spleen, and viscera exhibit transposition. Evidently, these partial cases can only be ascribed to local aberrations in development. With regard to complete situs inversus, it has been put forward that the individual presenting the condition has been one of a monochorial twin pregnancy; that, derived from the longitudinal division of a single ovum, he becomes a complete reflection, as it were, of his brother twin; where no history of twin birth can be obtained, it is suggested that that other brother became a fœtus acardiacus, or papyraceus. Undoubtedly, there are facts telling in favor of this view; for example, in not a few cases of dedupliction by cleavage and superior dichotomy the organs of one-half of the upper portion of the monster are transposed, as compared with those of the other. But, on the other hand, there is lacking evidence that it is a rule for monochorial twins to show this reflection. From what we can learn in the majority of cases, no indication is afforded of the existence of situs inversus in one of the two. A more likely suggestion is that the main current of blood to or from the germinal area becomes diverted at an early stage of existence, and thus purely mechanical influences lead the vessels of one side of the organism to receive more blood, and therefore to grow more vigorously than those of the other. But it has to be confessed that we are still without any confidence regarding these hypotheses.

HERMAPHRODITISM.

Sexual Differentiation.—The existence in the normal male and female of useless rudiments of parts characteristic of the opposite sex must not be taken as an indication that man is descended from an originally hermaphrodite ancestry. Of such in the line of descent there is no

trace. Rather such rudiments are, in Mendelian terminology, recessive features, due to the origin of the fertilized ovum from both male and female germ plasm. There has been a long debate as to whether the sex of the individual is predetermined or is due to intra-uterine nourishment; the fact that in the fifth week the anlagen of the sexual organs are of a common type, and indistinguishable, appearing to favor the latter supposition, and to explain why, when the individual develops in the one direction, rudiments of the organs of the other sex should be present.

At the present time this matter is being actively debated, and it cannot be said that a positive conclusion has been reached. A study of the chromosomes supplied by the male and female parent to the fertilized ovum has shown that in many species, notably of insects, these vary in size and shape, and the different forms are found to pair with remarkable accuracy.[1] The natural inference is that variation in form connotes difference in properties and molecular constitution; that these observations favor the view that there exist, if not determinants, at least biophoric matter of different orders and function contributed by the parents. But as we ascend higher in the scale these differences become less instead of more marked. Now in this study of the chromosomes, Henking, Montgomery, McClung, and others have called attention to the presence in several species of an "accessory chromosome," a chromosome which either (*a*) has no pair or (*b*) is of relatively large size and pairs with a minute companion. McClung[2] was the first to note that the spermatocytes of certain species are to be divided into two approximately equal groups, one-half bearing this accessory chromosome, the other half not possessing it, and to suggest that as sex is the only distinction which separates the fertilized cells into two approximately equal groups herein lies the physical and anatomical basis of sex. This view has gained strong support from Professor E. B. Wilson, but is contested equally strongly by other cytologists, who do not find the accessory chromosome a constant feature throughout the animal world.

The fact remains, however, that in every individual there exist the anlagen for all the primary and secondary sexual characters of both sexes. In every individual hermaphroditism and blended rather than particulate sexual inheritance is potential or possible; the remarkable fact is that it is so remarkably rare. Possibly the existence of this accessory biophoric material, whether of specialized properties or not, turns the scale in one or other direction.

True Hermaphroditism.—True hermaphroditism, in fact—the existence in the one individual of both ovary and testis—is among the very rarest of anomalies, and when it does show itself, one or both of the organs are sexually immature. With Klebs, we can recognize the following forms:

1. *Lateral hermaphroditism*, an ovary being developed on the one side, a testis on the other. This, in man, is the commonest form.

2. *Unilateral hermaphroditism*, there being on the one side both ovary and testis, on the other either ovary or testis or absence of both.

[1] Vide Arnold and Moore, Proc. Roy. Soc., B., 77: 1906: 563.

[2] Biological Bulletin, 3: 1902: 43.

3. *Bilateral hermaphroditism*, there being on both sides both ovary and testis.

The terminology is perhaps confusing, but an consideration is found adequate to express the conditions.

In all these cases the general configuration of the body is of an intermediate type, now tending more to the male, now toward the other sexual type. In general, the external genitalia are of the intermediate type, *i. e.*, hypospadias is present, with small penis, separation of the two scrotal halves (or labia majora, for in general the testicle or testicles are undescended), small external orifice corresponding to the vagina, or vagina not recognizable externally but opening into the urethra. Internally, there is usually a uterus duplex, with tubes and ligaments.

False Hermaphroditism.—As is well demonstrated in eunuchs and those castrated before puberty, the development of the secondary sexual characters, including that of the external genitalia, is largely governed by the development of the essential sexual organs, the ovaries or testes. Thus, it is where there is a congenital imperfection of the latter that we are particularly apt to encounter conditions in which imperfect formation of the external genitalia leads the individual to assume the external configuration of the other sex, or, more accurately, an intermediate type. We in this way distinguish:

1. *Pseudohermaphroditismus masculinus.* The individual being a male, *i. e.*, having testes, but the external genitalia and bodily habit approximating toward the feminine.

2. *Pseudohermaphroditismus femininus.* The individual being a female, with more masculine characteristics.

The first of these conditions is much more common. There is an insignificant, distorted penis, recalling the clitoris, perineal hypospadias (very often), the two scrotal halves without testes, which either are pelvic or in the upper part of the inguinal canal, and are immature. The outer margin of the urethral orifice may simulate labia minora, and its passage resembles a small vagina. Internally, the sacculus prostaticus (uterus masculinus) may be large, projecting behind the prostate proper as a bicornuate uterus of considerable proportions, provided with tubes; and where the testicles are undescended, they may lie in a broad ligament. Vesiculæ seminales and vasa deferentia and a small prostatic body are, however, present, and section of the testicles reveals the nature of the case. In such cases the growth of hair is more that of the female, with little or no development of beard or moustache, while the breasts may enlarge (*gynæcomastia*) and approach the female type. In feminine pseudohermaphroditism, on the contrary, the clitoris tends to assume penile dimensions and the urogenital sinus (urethra and vagina) to be continued as far as the glans, whereby the labia majora become approximated and simulate the scrotum, the simulation being still greater when, as sometimes happens, one or both ovaries pass down the canal of Nuck. The urethra where it joins the vagina may be surrounded by a small prostate, the uterus small, the tubes imperfect, the ovaries also small and imperfectly developed.

CHAPTER VI.

POSTNATAL ACQUIREMENT OF DISEASE.

Following upon what has already been said, namely, that exciting causes of disease after birth must, of necessity, be of external origin, it is evident that these causes of acquired disease are either of the nature of alterations in the environment which tell directly upon one or other tissue, or are due to the entrance into the system from without of substances, either living or dead, which have a deleterious action upon the functions of the tissues. Thus, briefly, we may classify the agents producing disease acquired after birth into:

1. **Mechanical**—inducing "trauma."

2. **Physical**—under which can be included:

(*a*) Alterations in the pressure of the atmosphere, including both diminution and increase.

(*b*) Alterations in temperature, local and general, including both lowered and heightened temperature and freezing.

(*c*) Effects of electricity, both atmospheric and induced.

(*d*) Effects of light and of absence of same.

(*e*) Effects of soil and climate.

(*f*) Sociological effects, habitation, clothing, dwelling, occupation, and other environmental conditions.

3. **Chemical Causes**—under which, besides (*a*) the gross effects of caustic and other agents upon the tissues, we should include (*b*) the main effects of vitiation of the atmosphere by various gases, and (*c*) the main deleterious effects of improper food, as again, to some extent, the deleterious effect of certain occupations.

4. **Parasitic**—under which heading are to be included the deleterious effects of:

(*a*) Minute vegetable parasites—bacteria and fungi.

(*b*) Minute animal parasites—sporozoa, amœbæ, etc.

(*c*) The larger animal parasites, including worms (cestodes, trematodes, nematodes) and arthropods (araehnids and insects).

In the consideration of these as causes of disease, we have ever to keep in mind that vital activity co-exists with and depends upon physical and chemical changes in the living matter, and that "stimulation," with its resultant manifestations of increased vital activity in one or other direction, is to be recognized as primarily the action of physical or chemical agents, either category of which essentially induces alterations in the molecular condition and relationship of cell protoplasm. So long as these molecular arrangements are within certain limits, for so long are they not merely not harmful, but actually beneficial to the

organism. When these limits are overstepped in one or other direction, then it is that the molecular arrangements (or arrest of molecular arrangements) are harmful, that cellular and organic disturbances are set up, and conditions of local or general disease developed. In other words, it is purely a matter of degree whether a given agent, physical or chemical, which is capable of exerting an influence upon protoplasmic matter, acts as a physiological or a pathological agent.

It thus follows that everything capable of acting upon living matter comes under this heading of physical (and chemical) causes of disease. And as the causative agents of disease thus are so abundant, the most that we can do is to classify the causes and then to indicate those which are most frequently in action, and those which, in their action, induce certain special trains of phenomena. Here we shall say but little about most of these causes and, more especially, we shall but glance at those which are generally spoken of as physical causes, because these are fully debated in the ordinary text-books of hygiene, in which a discussion of the effects of alterations in the composition of the atmosphere, effects of food, clothing, soil, habitation, climate, and offensive trades form so important a section.

Acting on the same principle, we shall not here describe in order the various microbic parasites; for nowadays, in every medical course, the subject of bacteriology, or, more accurately, of microbiology, has been elevated to a special subject. The case is somewhat different in connection with the animal parasites; these still are usually described not in any special course, but in connection with the subject of pathology; hence it is necessary that we mention these in rather more detail. But here, again, my treatment will be very brief, and that because in all schools of good standing parasitology is being treated as a special subject, and text-books exist dealing wholly therewith.

While not enumerating and discussing the effects of individual mechanical and chemical noxæ, as also the individual bacteria, and the part they play in the causation of disease, we shall discuss broadly the part played by these as a class in the production of disease. Thus, in the following pages we shall take up in order:

1. Traumatism and mechanical causes of disease.
2. The physical (and chemical) causation of disease, treated broadly.
3. Bacteria as causes of disease.
4. The animal parasites, described in fair detail, and their part of the production of disease.

MECHANICAL CAUSES OF DISEASE.

Although in most mechanical injuries we do not deal with a simple and single mode of action, we can usefully divide mechanical causes of disease and bodily disturbance into the following:

1. Concussion.
2. Puncture, with which may be included the effects of projectiles under high velocity.

3. Section.
4. Contusion, with which may be included lacerations and tearing.
5. Compression.
6. Distension.
7. Atmospheric pressure.

A little thought will show that in every one of the above we are dealing with pressure acting in various ways upon the tissues—how various will be seen if we briefly discuss the various forms.

1. **Concussion.**—Here we are dealing with a brusque and momentary application of pressure to a soft, fluid or semifluid body. We see thus the effect of concussion best marked in the brain and in hollow viscera having gaseous or fluid contents, as, for example, the lungs, the urinary and gall-bladders, and the stomach.

A sudden blow upon the skull, not fracturing the bone, and thus causing no direct laceration of the brain substance, is found to produce hemorrhages and extravasations of blood over the surface of the hemispheres and in the main tissues bordering upon the ventricles. Remembering that the brain is a soft viscus, floating, as it were, in a bath of surrounding fluid, the superficial hemorrhages may, in part, be explained by *contrecoup*. Following upon any such blow the more solid contents of a cavity will partake of the motion imparted to that wall to a greater extent than will the more fluid contents. In this way the more solid brain may be driven violently against the brain case and its delicate vessels ruptured, more particularly on the side of the organ opposite to the region receiving the blow. Under similar conditions the semisolid tissues, bordering upon a cavity possessing fluid or gaseous contents, are apt to undergo rupture and exhibit hemorrhages on the side of the cavity nearest to the blow, and this, because motion is imparted to these tissues by the blow, and in the absence of adequate support or restraint they tend to continue moving into the cavity, *i. e.*, the more superficial tend to separate from the underlying tissues and so to undergo rupture. In this way are to be explained the hemorrhages with rupture affecting the urinary and gall-bladders, the stomach, and more rarely the intestines, following upon concussion, when these viscera are filled with fluid.

In the case of the thorax, it has frequently been observed that sudden violent blows, insufficient to rupture the skin or fracture the ribs, have been followed by rupture of the lung substance with pulmonary hemorrhage and pneumothorax, or escape of air into the pleural cavity. The same explanation holds here, namely, the different rate of movement of the lung tissue and the contained air. Other effects may show themselves as a result of thoracic concussion, namely, profound disturbance of the heart beat and of the respiration. These appear to be in part due to the profound stimulation of the vagi, though, as G. W. Crile[1] has shown, the condition of collapse, and even of death, mainly results from the mechanical irritation of the heart muscle itself.

[1] Philadelphia Medical Journal, March 31, 1900.

2. **Puncture.**—The most familiar example of this form of traumatism is in wounds caused by stabbing. Here we have pressure applied locally by a fine instrument sufficient to cause local solution of continuity of the tissues. The results largely depend upon the region involved, and very largely also upon whether the instrument pierces any higher nerve centre or large bloodvessel or hollow viscus in its passage, as also upon whether the instrument introduces at the same time infective agents. On the one hand, we may have little or nothing beyond merely local disturbance; on the other, sudden death, or we may have profound hemorrhage or general infection, set up either by bacteria passing into the tissues from hollow viscera or by bacteria introduced into the wound from without. Usually projectiles, travelling at a high rate of velocity, produce wounds which can be compared to puncture wounds in general, but according to the velocity and the size of the projectile, so it must be kept in mind that practically every form of traumatism above discussed may be brought about by projectiles, concussion, contusion, laceration, and puncture wounds. Still further, the very force with which projectiles suddenly impinge upon the tissues leads to a more general and immediate disturbance than is seen in the case of ordinary puncture wounds. At certain rates of speed there may be laceration of soft parts, concussion, and multiple fracture of the bones extending over a very large area.

3. **Section.**—This, which, surgically speaking, is the commonest form of trauma, consists in the separation of tissues by a sharp-bladed instrument, whereby there is a minimal disturbance to the tissues which do not come into immediate contact with the instrument. So small are the individual cells and tissues, and such their shape and arrangement, that it is impossible to introduce any instrument, however fine, in such a way as to insinuate it between the cells without injuring them. Consequently, all along the surface of a cut there must inevitably be a layer of injured cells. But in pure section, pressure and tearing effect upon contiguous tissues are reduced to a minimum by the pressure being brought to bear in a shearing manner, namely, the instrument is not merely employed as a wedge, forcing the elements of the tissues apart, but, by the oblique movement of the wedge, a cutting action is brought about and the tissues severed rather than forced asunder.

4. **Contusion.**—In contusion, as distinct from concussion, we have the pressure exerted directly upon the part, and have a pressure exerted such that the elements of the part are torn asunder to a greater or less extent—hemorrhage resulting. The separation of the part may be slight (*contusion*), or, on the other hand, may be such as to produce separation of the constituents visible to the naked eye (*laceration*), or even may be such as to cause complete *separation* of one portion of an organ from another, as where a limb, or the scalp, or portion of the integument is forcibly torn off. It follows that, in the first place, we have hemorrhage from the ruptured vessels of the part, and that, in addition, we have more or less profound alteration of function; while, again, the sudden profound disturbance brought about by laceration or rup-

ture of the nerves may set up general disturbances and *shock*. Later, the solution of continuity and exposure of the parts to the atmosphere may be followed by the results of infection of the wound or wounds.

5. **Compression.**—With regard to compression, little need be said here. Continuous pressure tells especially upon the more fluid portions of a tissue, and so it is that the vessels, both blood and lymphatic, tend to be occluded as a result. We have especially to deal with disturbances of nutrition in the part and with the accumulation of fluid in the vessels and the lymphatic spaces beyond the area of compression. Such compression may be external, and one is familiar with its results where Esmarch or other bandages have been too firmly applied to a limb; or where, again, in consequence of low blood pressure, the capillaries of the back or other portion of the body are emptied by the mere weight of the body, and *bedsores* (decubitus) result. Or it may be internal, as where tumors and collections of fluid developing in one or other part of the economy press upon the neighboring organs. Its results are malnutrition of the affected parts, with atrophy, which may go on to necrosis and disintegration of the parts.

6. **Distension.**—The mode of action of a distending force upon the tissues is similar to that of compression, namely, the pressure tends to act more especially upon the more fluid portions of organs, driving the fluid away, so that here again we tend to have malnutrition of the part subjected to a distension, and subsequent atrophy. We recognize a well-marked example of the effects of such distension in hydronephrosis of the kidneys, in which condition, in consequence of obstruction of the lower urinary passages, and of the continued excretion, we have eventually practically the whole of the kidney tissue proper undergoing atrophy, and the organ may eventually be represented by an enormous thin-walled cyst. The distension may be of intravascular nature, and produce results of like order, as in passive congestion, brought about by heart disease or venous obstruction. Where, as in hemorrhages and the escape of blood into the brain substance, the distending force acts rapidly, we may, by compression of the surrounding vessels and the arrest of nutrition of the cells of the higher nerve centres, have a rapidly supervening death.

7. **Atmospheric Pressure (Gaseous).**—In addition to the chemical changes brought about by the reaction between the contained gases and the tissues, we must realize that there is a purely mechanical interaction between the organism and the atmosphere, dependent upon the pressure exerted by the latter. We may add that in animals living in water the same is true in regard to aqueous pressure. There are, that is to say, certain limits to pressure within which life can continue and beyond which the continued manifestation of vital processes become impossible. In the case of man, this variation in pressure especially influences the system by influencing the partial pressure, as it is termed, of the oxygen circulating in the blood. Blood and other fluids take up larger or smaller quantities of gases according to the pressure in the gaseous medium, hence, if the atmosphere becomes rarefied, although

certain troubles are induced by reduction of pressure on the various surfaces and the consequent dilatation of the vessels of these surfaces, the main disturbance induced is that the amount of oxygen taken up from the air is materially reduced and a condition of partial asphyxia is brought about, or oxygen hunger in the tissues. Where the atmospheric pressure is much increased, the vessels of superficial parts are compressed, and the blood in consequence is driven from them into the deeper organs. It may be added that the main symptoms of "caisson disease" do not show themselves while the individual is subjected to a greatly increased atmospheric pressure, but develop when the transition from the increased to the ordinary atmospheric pressure is too sudden. Partly this may be due to the sudden alteration in the distribution in the fluids of the body which thereby occurs, but it is now generally believed that when under heightened atmospheric pressure the blood absorbs or dissolves increased quantities of oxygen, then upon sudden transition to a lowered pressure it can no longer hold this gas. As a result, the gas presents itself within the vessels in the form of discrete bubbles, these seriously interfering with the circulation in the smaller vessels.

PHYSICAL CAUSES.

Temperature.—Owing to the remarkably sensitive and effective mechanism whereby the heat of the body is controlled, the human mechanism can stand exposure to a wonderfully wide limit of temperature—can, on the one hand, continue to exist when the surrounding medium is as much as 100° F. below the freezing point (Baek); or, on the other hand, as shown long years ago by Blagden and Fordyce, as high above as 260° F., or, roughly, about 50° F. above the boiling point of water; and if the body be not exposed to these temperatures for too long a period, the general effects, save for alteration in the distribution of the blood, are singularly slight, or, more correctly, are within physiological limits. The body as a whole, that is, can be exposed to temperatures far beyond those at which protoplasm is frozen, on the one hand, and undergoes heat coagulation on the other. The explanation is, that through the warming of the air immediately over the surface of the body when that body is subjected to intense cold, there is developed a layer of warmer air in immediate contact with the cells, so that these cells are not subjected to the temperature of the surrounding medium. In the case of extreme heat, a similar protective layer is developed by the abundant giving off of moisture on to the surface, and, in consequence of the rapid evaporation of this moisture, the development of a layer of air immediately above the superficial cells which is much cooler than the surrounding medium and which thus is similarly protective

Where the air is already saturated with moisture, evaporation cannot occur, and the high temperature rapidly becomes dangerous. Whether by prolonged exposure to great cold or to great heat, and by

the exhaustion or imperfect action of the heat-regulating mechanism of the body by direct contact with fluid or with solid bodies, the temperature of which is either below the freezing point of water or about 115° F., or, again, in the case of heat, where the body is exposed to direct radiant heat above a certain intensity, there morbid disturbances may develop. At first these may show themselves only locally in the part affected, but sooner or later general disturbances are produced. It is a striking exemplification of Wilhelm Müller's statement that the most diverse agencies produce identical changes in the tissues, that whether the cause be extreme heat, *i. e.*, burning, or extreme cold, *i. e.*, freezing, the succession of changes both locally and generally in an affected part very closely resemble each other. The first change in either case is a paralysis of the vessels of the affected part, so that the heat-regulating mechanism can no longer, by changes in the amount of blood circulating through the part, maintain the normal temperature of the part or an approach to the same. The consequence is arrested vitality of the cells of the part, which, according to the intensity of the physical agent, may be followed by death of those cells. Following upon this we have to recognize the supervention of general disturbances brought about, in part, by the profound irritation of the nerves in and bordering upon the affected region, in part, by the passage into the circulation of the products liberated from the dead and dying tissue cells.

Here we have to note, as, indeed, we have in connection with all physical agents, that two distinct periods have to be clearly recognized: a period during which the physical agent is active, during which the local and primary disturbances predominate; a second or resulting period, in which the disturbing cause has ceased to act, and during which we are dealing with what are purely secondary effects. In the case of burns and frost-bites, for example, while it is true that, if the burning be extreme or generalized, life may be arrested during the [illegible] either by shock, by suffocation, by heat coagulation of the [illegible] other tissues, or by a combination of two or more of these, [illegible] there may be death under exposure to cold brought about by the [illegible] cooling of the organism and its effect upon the respiratory and [illegible] centres, nevertheless, in the majority of cases with which we have to deal, the phenomena we observe and treat are not the primary, but the secondary.

Herein is the broad distinction between physical and parasitic causes of disease, a distinction not quite universal, it is true, but still general, namely, that in parasitic diseases we are dealing with the continuous development and action of the agents which are toxic to the tissues, while physical agents most often have a temporary action, so that it is the after-results of their action that we have to consider.

Light.—We rarely have to deal with light as a direct cause of disease; nevertheless, we recognize that intense light does very definitely affect the eyes (may even set up acute conjunctivitis), and, by the fatigue and overstimulation of the retina and optic nervous system, may, sec-

ordinarily, set up other nervous disturbances. So, also, it may irritate the skin and produce a series of disturbances there of an inflammatory type. Where very intense, it is difficult to distinguish between the effects of those of the radiant heat which is combined with it; but that light rays alone may cause profound disturbances seem to be indicated by the severe atrophic and other changes which may occur, not only in the superficial parts (skin and hair), but occasionally in the deeper, as, for example, in the bones after exposure to the Röntgen rays. What are the circumstances under which it happens that at times the employment of the *x*-ray apparatus leads to such severe disturbances have not as yet been wholly determined. In sunstroke, although this cannot be stated with absolute precision, we would seem to be dealing primarily with the effects of radiant heat rather than with those of light pure and simple; and with the effects of this heat, acting more especially upon the head and neck, but how this heat acts, whether by direct stimulation of the nervous centres of respiration, etc., or by raising the temperature of the blood therein circulating, and thereby bringing those tissues toward the temperature of coagulation of their proteid constituents—all this is yet a matter of debate.

With regard to absence of light, the most that can be said with regard to man is, that it appears to tell obscurely, especially upon the blood, leading to a more or less anæmic state; although miners, who spend the major portion of their days underground, are able for long years to maintain very fair health. It is those who are not accustomed to the deprivation of light upon whom that deprivation tells most. Certainly, sunlight is not as essential for animal as it is for plant life, and there is a basis of observed fact for Woodruff's[1] contention that prolonged exposure to the intense sunlight of the tropics is actually dele as to those of northern race whose skin is devoid of protective pigment.

Electricity.—With the increasing employment of electricity in every-day life, the subject of electricity has rapidly assumed a more prominent position among the causes of disease and of injury to the organism. But, perhaps as a consequence of insecure knowledge of electrical phenomena possessed by most medical men, singularly little has been written so far upon this branch of our subject. Indeed, the results of the passage of electric currents through the body have been found so varied that it is difficult to make any but the most general statement with regard to the subject.

Like other agents, electricity depends for its effects upon the dose and the mode of administration. According to the method whereby the electrical current acts upon or gains entrance into the tissues, according to the relationship of the body to other substances which are or are not conductors, and according to the intensity and the nature of the current, so do we obtain very diverse results.

To a certain extent we can distinguish two very different series of effects, those induced by the constant, or continuous current and those

[1] Effects of Tropical Light on White Men, New York, 1905.

by the interrupted or alternate current. The body, brought suddenly into a continuous circuit of moderate intensity, shows very little effect, the nerves and muscles remaining unexcited. Where we are dealing with a current of much feebler intensity, which is interrupted, we may obtain violent excitation. Indeed, nervous excitability and muscular action, which we are accustomed to regard as the main evidence of electrical action upon the body, cannot be regarded as directly dependent on the intensity of the current. Nevertheless, even with a constant current, the intensity does undoubtedly very materially tell upon the system; and, if this be very powerful, then, just as a constant current, passed through water and other fluids, causes electrolytic changes, so may such a current, acting on the body, produce decomposition of the tissues in the neighborhood of the negative pole and the diminished excitability in the neighborhood of the positive pole (electrotonus). These results have been long recognized and abundantly studied by physiologists. D'Arsonval suggests that here, probably, we are dealing not with the effects of electricity itself, but with the action of the chemical products of electrolysis upon the surrounding tissues.

With regard to the alternating current, if this be of low frequency and low potential, its passage is not recognized, although it has been found that thereby the metabolism of the tissues is raised. If we are dealing with a current of medium potential, we then obtain violent contraction of the muscles, and, by increasing potential, as is accomplished in commercial electricity, we can obtain currents which, as D'Arsonval puts it, *appear* to cause death. But very often this death is only apparent. What we have to deal with, according to D'Arsonval, is inhibition of respiration. Oliver's experiments very clearly show that, in the majority of cases, it is the heart that is first arrested, and this arrest appears to be associated with a condition of contracture of the arteries throughout the body. That death is apparent is shown by the fact that artificial respiration, if steadily continued, very often restores the respiration and the heart beat. Oliver gives one case in which the heart of a dog had ceased beating for thirteen minutes, and, nevertheless, after continued artificial respiration and the consequent slow discharge of the blood from the overfilled right side of the heart into the lungs, eventually the organ began to beat again.

With currents alternating with extreme rapidity and of high potential, as D'Arsonval was the first to point out, we get the paradoxial condition of absence of any marked disturbance; thus, employing the Hertz apparatus, in which alternations of some billions per second are produced, one can subject the human being without after-disturbance to electricity of such high potential, that, at lower rates, with interruption, apparent or actual death would immediately be produced. One can, indeed, employ currents of such high potential and high frequency that the carbon filament of an ordinary electric lamp held in the hand will glow and give off a bright light without the individual experiencing any sensation of the passage of the current beyond, perhaps, a slight warmth in the hand holding the lamp.

Vibratory Motion.—The effects of rapid vibration upon the organism have not been fully worked out. As Meltzer[1] has indicated, vibration is essential to life. A certain minimum is indispensable, and must be regarded as associated with the molecular activities of living matter. Beyond a certain frequency in extent, vibration is, however, harmful. He and Welch have studied the effect of rapid vibration upon the blood corpuscles and have shown that, over a certain point, the cells become broken up when subjected to rapid vibration.[2] Beyond this, however, little has been accomplished.

CHEMICAL CAUSES.

Under this heading we include all those causes in which there is a direct molecular interaction between the noxa and the constituents of one or other set of cells in the organism. We thus have to consider not only those cases in which there are gross effects leading to immediate death of the cells, as by the action of caustic and other agents, but also those cases in which the cells, while not destroyed, have their functions arrested or disturbed without actual death of those cells being the immediate consequence.

Poisons.[3]—Every substance, solid, liquid, or gaseous, which is capable of entering into combination with the fluids of the body, and in this condition of being absorbed so that it enters into and acts upon the cells of the body, may thus be the cause of morbid phenomena of disease.

Chemical substances having a deleterious action upon the cells of this body may exert that in two ways: either they may immediately destroy or severely irritate the tissues with which they primarily come into contact, or, becoming absorbed, they may become diffused in the circulating fluids of the system, and thus have an action upon cells at a distance from the point of primary contact. The first order we speak of as caustic agents; the second as intoxicants. Both are poisons, if we accept the definition of Kobert, that "poisons are non organized substances, organic or inorganic, existing within the organism or introduced from without, which, from their chemical constitution, are able under certain conditions to be harmful to living beings, by destroying or affecting their health or relative well-being." The series of changes occurring in the organism in general in consequence of the action of such poisons is known as *intoxication*, and may be of many orders.

The somewhat involved nature of the definition we have given becomes justified when we realize that poisons are only such relatively; substances are harmful only when present in sufficient concentration either to set up molecular disturbance and chemical change in the

[1] Zeitschr. .. Biol., 1894. [2] Jour. of Physiol., 5: 1884: 255.

[3] We have incorporated into the ensuing sections portions of a paper read by us at Washington. Trans. Assoc. Amer. Phys., 16: 1901: 38.

protoplasm of the cells or to arrest normal molecular changes in the protoplasm. And, conversely, it follows that all substances capable of solution in the body fluids and absorption into the cells composing the body are also capable of acting as poisons, and this because the effect upon the cells depends upon the extent of their absorption, and above a certain point (the limit varying with each substance) their action is unfavorable to the continuance of the orderly cell processes. Thus, to give the most notorious example, water, which is absolutely essential to existence, and forms 70 per cent. of the body weight, and in some cells as much as 90 per cent.,[1] if introduced into the tissues above a certain amount (60 c.cm. per kilo of body weight), is found to be a poison, and, indeed, fatal. It thus causes the diffusion of both hemoglobin and of the red corpuscles, preventing due oxygenation, and, absorbed by the cells of certain tissues in excessive amounts, it deleteriously affects their activities, among other ways, by inducing undue ionization. It follows, thus, that the number of potential poisons is enormous.

How are we to classify them? The old familiar division into animal, vegetable, mineral, and gaseous is, for pathological purposes, absolutely useless; no particular sets of reactions follow upon the action of animal poisons, for example, as distinct from vegetable; the effects of a mineral may simulate that of a vegetable poison. Nor, for our purposes, useful as it would be, can we classify them according to the symptoms which they originate, and this because, with a given poison, the symptoms caused by one concentration may be widely different from those of another, and in one individual the effects produced may differ widely from those produced on another. It is more to the point to observe the changes in the individual tissues and to attempt to classify the toxic bodies in relationship to various forms of intoxication, *i. e.*, of the changes induced in the organism. This we do to a large extent in our study of the degenerations.

Ehrlich's Two Groups.—Ehrlich has introduced a broad division of pharmacological—and toxic—agents into two main groups, which must here be noted. Like that just suggested, it bears more particularly upon the reaction of the cell to the poison. The assimilation of foodstuffs, as we have pointed out in our chapter upon growth (p. 82), is by him regarded as a linkage of side chains to the nucleus of the living molecule, or, as we would express it, biophore. The members of Ehrlich's first class bear a close resemblance in this respect to the foodstuffs. He regards them as being linked to the living protoplasm. Their effects are not immediate; time is required, as he supposes, that [illegible] may become built into the living molecule, and so they exhibit [illegible]at we may term a long latent period before developing these results. The members of this group are one and all the products of living matter and if not proteins, are of proteid affinities. Such are the bacterial toxins, the venoms of various animals, certain plant poisons, such as abrin, ricin, robin, certain definite poisonous proteins, and Ford would add

[1] The gray matter of the fœtal brain

certain glucosides. With the majority of these the result of union with the living molecule is to give rise to the discharge from the cells of *antibodies*, antitoxins, and the like.

The second group, while diffusing into the cell, and having very definite effects upon the cell activities, is regarded by him as not being built up into the living molecule; there is no latent period, the action is immediate, and there is no production of antibodies. Into this class come all the poisons not included in the first. How these act, Ehrlich finds it difficult to lay down, save that they do not become assimilated with the "biophores." Some, like the anesthetics as a body, can be shown not to enter into chemical combination with the cell substance, since they can be recovered intact by simple processes. It is well within the bounds of possibility that the process affecting these bodies is of the nature of adsorption rather than true chemical combination.[1] Again, it may be that some at least enter into chemical combination with the cytoplasmic constituents and act by blocking the intermediary substance and so arresting the activites of the biophores. The probability, indeed, is that this huge class will become divided into several divisions. Save for its suggestiveness, this classification of Ehrlich's is altogether too broad for our immediate purpose.

Studying the degenerations, we determine that the poisons introduced from without are not the sole intoxicants. We can, indeed, proceed to establish two broad groups, the *exogenous* poisons arising outside the system, the *endogenous* arising within. But we have to be careful about our conception of what is endogenous and exogenous, and laxity in regard to these matters has caused great confusion, and has rendered particularly useless one term—auto-intoxication—capable of being of high value. According to vulgar parlance, the contents of the alimentary canal are a part, and an important part, of the "inside" of the individual; yet, strictly speaking, the food taken is not within the system until it has been absorbed by the cells of the organism. The following crude diagram (Fig. 108) of the simplified individual will make this point clear. It will be seen that only that which is within the shaded portion is really within the body. Intoxication arising from the absorption of substances from any point outside the shaded area must be regarded as exogenous. It was by an unfortunate lack of clearness regarding this—a lack unusual in French writers—that Bouchard, who popularized, if he did not originate, the term auto-intoxication, classed all the toxic results, not only of perversion of cellular and tissue activity, but also of gastro-intestinal fermentation and the absorption of the products of bacterial activity in the digestive tract, under the one indiscriminate heading. It is true that the absorption of the products of bacterial activity, of fermented and altered foodstuffs, may, secondarily, affect the metabolism of the cells of sundry organs, and the products of perverted activity may be the direct cause of the general

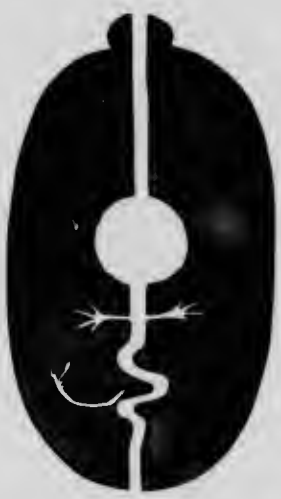
[1] For a useful study of adsorption phenomena, see Bayliss, Biochemical Journal, 1: 1906: 175.

disturbances; indeed, in such cases we have a genuine auto-intoxication; but then the intestinal irritants become only the predisposing cause, not the direct. From this point of view every poison acting through the alimentary canal, from alcohol to mineral acids, is to a greater or less extent an auto-intoxicant, and this is clearly an absurdity.

Intoxication by bacterial products is in no sense auto-intoxication, nor is it permissible to speak of gastro-intestinal auto-intoxication unless thereby is meant (and this the users of the expression rarely mean) that matter excreted into the bowels by the cells undergoes reabsorption. In consequence of this vague and illogical use the term has fallen into disrepute.

These considerations lead us to recognize that, from a pathological standpoint, we have to distinguish two distinct orders: (1) Those

Fig. 108



intoxications set up by substances actually derived from the cells of the organism, which alone are to be regarded as truly endogenous; and (2) all other intoxications set up by substances foreign to the economy: all these are exogenous. Having established this, we can proceed to divide these into their classes:

1. **Exogenous Intoxications.**

1. *Non-parasitic.*—Intoxications due to the actions of poisons not produced in association with the organism, which gain an entrance into the system through the skin, digestive, respiratory, or urinary tracts.

2. *Parasitic.*—(*a*) *Parasitic proper*, due to the introduction into, and growth *within* the tissues of parasites of various orders, animal and vegetable, which, growing, give rise to toxic substances.

(*b*) *Saprophytic*, due to the growth of parasites of various orders on one or other surface communicating with the exterior of the organisms, the products of growth becoming absorbed and diffused into the tissues.

II. **Endogenous Intoxications.**—Of pure type; auto-intoxications proper.

1. *Internal secretory*, intoxications due to altered internal secretions on the part of the body cells affecting (1) the secretory cells and tissues themselves, and (2) the other tissues of the organism, through diffusion of the altered products of cell activity.

2. *Disintegrative*, due to the absorption of the products of disintegration of dead cells (*e. g.*, in burns, internal hemorrhages, etc.).

3. *Metabolic*, the results of impaired metabolism and imperfect excretion.

III. **Intermediate or Mixed.**—Of impure type.

1. *Obstructive*, due to arrested elimination.

2. *Gastro-intestinal*.

One of the classes here formulated calls for remark, namely, that which I have termed the Intermediate. As will be noted more fully in the pages devoted to it, while (1) in certain cases it is quite clear that we deal with the effects of reabsorption of external secretions, pure and simple, these cases are relatively rare. (2) In other cases there are indications that we deal with failure to secrete, with accumulation of metabolites that normally undergo discharge. (3) In yet others, with the deleterious effects of the absorption, not of the excretions themselves, but of toxic derivatives of the same, the products of bacterial disintegration. In such cases the poison itself originates outside the system, and is to that extent exogenous, although derived from a substratum of endogenous origin.

It is in this order that the various orders of intoxications and their relationship to the development of disease will be discussed.

CHAPTER VII.

EXOGENOUS INTOXICATIONS: NON-PARASITIC.

Foreign substances undergoing absorption or gaining entrance at the surface of the body have a twofold action: (1) Local, at the point of application, and (2) general. Only in rare cases is the first action wanting, as, for example, in that of hydrocyanic acid above a certain strength, when the general effects are so swiftly induced that there is no time for the local disturbances to show themselves.

For the local effects we have no special name; according to the nature of the poison, these are either degenerative or necrotic; and, if time be allowed, they are followed by evidences of inflammatory reaction of one or other grade.

Studying the general effects, such toxic agents either:

1. Cause arrested cell activity from the first.

2. Cause increased cell activity, followed by exhaustion and paralysis of function.

3. Cause increased cell activity, followed by disintegration.

Paradoxical as it may seem, the only satisfactory way for us to classify these exotic poisons as causes of disease is by a study of their effects. A given poison produces a particular chain of general disturbances; it is for us, as pathologists, to determine the basal lesion or lesions giving origin to these symptoms. Attempting this, we find that the different toxic agents have selective actions on one or other tissue. Thus it is these selective effects that must form the basis of our study, while secondarily in connection with each, it has to be determined whether the effect is characteristically inhibitive, irritative, or disintegrative.

It is the study of these exotic poisons that forms the basis of toxicology, and, to a considerable extent, of pharmacology. It is in works dealing with these subjects that extended observations upon the mode of action of any particular poison will be found. Nevertheless, we, as pathologists, have to consider these poisons, but approach them from a different standpoint; not from that of the individual drug or poison, but from that of the organism and the disturbances therein induced. It becomes necessary, therefore, that here we should at least call attention to this subject, if only in outline, keeping before us throughout that our endeavor at this point is not to discuss the general effects of poisons—the disturbances set up in the body at large. These constitute the *processes* of intoxication. It is the primary effects leading up to these general disturbances that here concern us. As already laid down, the poisons one and all exhibit a more or less obvious selective

action on the different tissues; we shall, therefore, pass in review the tissues most liable to be affected.

Poisons Acting through the Nervous System.—The system which most commonly appears to be affected in intoxication is the nervous system. This is, after all, what is but to be expected, for of all cells of the body the neurons are the most highly differentiated and most responsive to stimuli. At the same time, it has to be admitted that classification, according to their different effects upon the nervous system, is not easy, and this because the effects of a poison (1) vary very largely according to its concentration in the blood and rate of absorption by the neurons; (2) nor can we with any success apply data obtained from animal experimentation to the case of man. The higher we ascend in the scale of animals the more complex is the development of the nervous system. Thus it may be laid down that man is, in general, more sensitive to cerebral manifestations of intoxication than are the lower animals. A very large number of substances which in man set up extreme cerebral disturbances, acute delirium, and convulsions, have little or no effect on the lower animals, unless given in large quantities.

Admitting this, we may cautiously divide the poisons acting on the nervous system in the first place into:

1. Those causing immediate arrest of activity, *e. g.*, hydrocyanic acid.

2. Those causing immediate diminution of activity, *e. g.*, the hypnotics and sedatives.

3. Those causing primary increased activity, followed by diminution of function, *e. g.*, the intoxicant alcohol and the aldehydes, atropine and other alkaloids.

4. Those causing primary increased activity, followed by exhaustion and, it may be, disintegration—strychnine (also tetanus and rabies toxins).

In the second we can classify according to the part of the nervous system upon which the poison exercises its selective action, thus:

1. Higher cerebral centres: The hypnotics as a group, carbonic acid, santonin (in the frog).

2. The bulb: Picrotoxin (a convulsivant, the convulsions ceasing when the medulla is destroyed). Apomorphine (the centres which determine vomiting appear to be situated in the medulla).

3. Spinal cord: Here the type poison is strychnine, the higher centres and the cranial nerves not being affected by this poison. Brucin, quinine, thebaine, salts of potassium and ammonium to a less extent.

4. Peripheral nerves: Ether, chloroform, CO_2 (according to Waller's observations these induce changes in electromobility). Diphtheria-toxin (which, by Sidney Martin and others, has been shown to cause active local destruction of axis cylinders or axones). Possibly, lead and alcohol act in a similar way.

5. Nerve terminations: Curare (end-plates of motor nerve), cocaine, etc., sensory nerve-endings. Veratrin, nicotin (stimulate nerve-endings).

Meyer and Overton have shown that the hypnotics as a group undergo an almost selective solution in fats and lipoid substances, and the indi-

cations are strong that the abundance of lecithins, cephalins, and allied bodies in nervous tissue explain why these are taken up by it. As Ehrlich and later writers have pointed out, adsorption rather than chemical combination proper is the process mainly involved. Nevertheless, whether by disturbing cell metabolism or by some slight chemical action, undoubtedly there is a direct effect on the nerve cells. As demonstrated by Hamilton Wright, working in my laboratory, where large doses of bromides are given, there is distinct histological alteration in the appearance of the nerve cells.

Of these, the most marked is the disappearance of the lateral gemmules of the cells, and he and other observers would suggest that the retraction and degeneration of these gemmules afford the anatomical explanation of the hypnotic action of the bromides and allied substances. If the communication and passage of stimuli from neighboring cells and processes is through the intermediation of these gemmules, and by their retraction the neuron becomes isolated, we obtain the explanation of the action of not only hypnotics, but of another set of drugs, like alcohol, which produce intoxication in the narrower sense, and may regard the incoördination in the action of these nerve cells, which is the essential characteristic of the condition, as being produced by the varying effects of the drugs upon different cell groups, leading at one period to excessive or irregular extension of the gemmules, at another to paralysis or retraction of the same. It cannot, however, be said that this function of the gemmules has been surely established, while disappearance of the gemmules has been recorded in many toxic conditions. To make it safe to accept this hypothesis, with some reservations, the alcohols and the aldehydes must be regarded as primarily exciting the nerve cells, the narcotics as primarily paralyzing the same. Among other primary excitants must be mentioned a series of alkaloids — atropine, hyoscyanin, caffeine, and, to some extent, nicotine. All these are liable, under certain conditions, to produce delirium, followed by diminished excitability and coma. As pointed out by Langley, nicotine has the almost specific effect of stimulating, and finally paralyzing, the preganglionic nerve-endings of the sympathetic system.

On the Muscular System.—Substances specially affecting striated muscles act first and with most marked effect upon the heart, so that the circulatory overshadow all other effects, and in general very little has been observed in connection with these muscle poisons throwing light upon symptomatology. In the most obvious muscular disturbances, tonic and fibrillary contractions and paralyses are, with rare exceptions, produced by poisons which act primarily on the nerve centres. There are, nevertheless, drugs acting directly on the muscle plates:

1. **Irritative.**—Causing increased contractility: Veratrine (in small doses), quinine, caffeine, hypoxanthin, creatin, B. coli toxins (Roger, leading to prolonged partial contracture).

2. **Inhibitive.** Leading to enfeebled contraction: Metallic salts, of potassium, alkaline earths, copper, etc.

Still less can be said regarding non-striated muscles. There is a

certain amount of evidence that ergot leads to contracture. Conversely, morphine would appear to act directly on the intestinal muscles, and so arrest peristalsis; similarly, atropine has been shown to relax the lower end of the cat's œsophagus (provided with plain muscle), while it has no effect upon the upper half (provided with striated muscle). How far the paralytic action of bacterial toxins is responsible for the intestinal dilatation of peritonitis is not absolutely decided. The direct action of certain drugs in producing vasodilatation and vasoconstriction, respectively, must be due to their influence upon the unstriated muscle of the arterioles. The recent observations of Josué, among others, upon the experimental production of arteriosclerosis, show that one group of substances—adrenalin, barium chloride, nicotine, etc.—acts directly upon the muscular middle coats of arteries.

On the Blood.—There are very many substances which materially modify the condition of the blood, but of these the majority possess little action unless they be directly injected into the vessels. It would seem that in the act of being absorbed from one or other surface these become modified. Further it has to be remembered (as preventing blood changes) that even when deleterious substances gain entrance into the blood there is a constant removal of the same by the liver and the tissues. Granted this, we recognize certain groups of poisons which act upon the blood in one or other way:

1. **Hemolytics (or, better, Hemoclastics).**—Bodies acting upon the erythrocytes and leading to their dissolution, with liberation of the contained hemoglobin. This destruction may be brought about by physical means, as by altering the tonicity of the plasma (intravascular injections of H_2O, etc.) or by freezing and thawing, or by drugs, leading to disintegration of the red corpuscles, *e. g.*, saponin (1 part in 125,000 of this in the blood sets up hemolysis), abrin, and ricin. The liability of certain bacterial products, of animal venoms, etc., to induce hemolysis, will be discussed in the section on immunity. In the slightest cases such hemolysis produces hemoglobinemia (and hemoglobinuria); in more severe, methemoglobinemia, the liberated hemoglobin becoming acted upon. Methemoglobin would seem to be developed both in the presence of certain oxidizing agents (the chlorates, sodium hypochlorite, nitrites, etc.), and of reducing agents (pyrogallic acid, pyrocatechin, tolylenediamin, hydroquinone. Yet another group of bodies combine to form more stable compounds with hemoglobin without of necessity setting up hemolysis—carbon monoxide, sulphuretted, seleniuretted, and telluretted hydrogen, prussic acid, cyanogen, and the sulphocyanates, and, according to Liebreich, acetylene. All these combinations prevent the due inhalation of O and CO_2, and, as a consequence, tend to lead to asphyxia.[1]

2. **Leukolysis.**—Two distinct processes may lead to leukopenia or reduction in the number of leukocytes in the circulating blood, nor is it

[1] The reader will find a useful review of data bearing upon hemolysis and leukolysis in Wells' "Chemical Pathology," p. 191.

always easy to determine which is in action in a given case. These are (*a*) leukolysis proper, or destruction and dissolution of the leukocytes, and (*b*) local accumulation, the white corpuscles either accumulating within the vessels of internal organs, the pulmonary or abdominal capillaries, or undergoing actual migration. Such accumulation is apt to involve more particularly one or other form of leukocyte; thus, as pointed out by Opie, in peritoneal inflammation there is a remarkable accumulation of eosinophile leukocytes in the omental and mesenteric capillaries, with reduction in the number present in the general blood. But the indications are that, pathologically, acute leukolysis frequently occurs. Albertoni finds that pancreatin brings about a rapid and complete destruction of leukocytes; several of the bacterial toxins introduced into the blood appear to have a like effect. Bile salts present in excess possess this property. In many of these cases the leukopenia is followed by a pronounced leukocytosis, the increase in lymphocytes being apt to be especially marked. We deal here not so much with a stimulative multiplication of the leukocytes (though this may show itself later) as with a characteristic attraction of the cells in the lymph glands and bone-marrow out of the tissue spaces into the capillaries.

The Organs of Circulation.—Poisons may affect primarily (1) the heart, (2) the vessels, more particularly the arteries, or (3) the nerve centres controlling the circulation, whereby the heart and vessels are secondarily affected. The effects of one or other of these actions upon the blood pressure and the circulation in general may be identical; thus, great care is necessary in order to come to a sure conclusion regarding the mode of action of any one poison. After the general circulatory effects have been determined, it is necessary to study the effects upon the isolated heart, or, still better, of transfusion through a vessel of the apical region of the left ventricle, after Townsend Porter's method, that region being devoid of nerve cells. Similarly, following the oncometric method of the late Professor Roy, the effects upon the blood flow must be studied through the isolated peripheral organs—kidneys, spleen, etc. In this way, *per exclusionem*, we can find the mechanism primarily influenced.

1. **Acting Directly on the Heart.**—Here we can re-divide the poisons into (*a*) those causing stoppage in systole, and (*b*) those arresting the organ in diastole. To the former group belong the glucosides and allied bodies, digitalin, digitalein, digitoxin, strophanthin, convallamarin, antiarin, etc. Some of the animal venoms, such as that of the skin of the toad, have a like action, as have also the salts of barium. Causing diastolic stoppage are the metallic salts—of copper, arsenic, antimony, potash, etc. Alcohol (Roy and Adami) and chloroform (McWilliam) in sufficiently large doses also act directly on the ventricular muscles, causing weakening and ventricular dilatation. Here we have the explanation of the acute dilatation of the heart seen in heavy drinkers (Steele and others).[1]

[1] As pointed out by Ringer and Ford, in smaller doses nearly all these substances stimulate the heart and strengthen its beat; once again it is a matter of degree.

Other substances, like muscarin, act through the nervous system almost entirely; most of these nervous "diastolic" poisons act by paralyzing the augmentor or accelerator mechanism rather than by exciting the inhibitory vagus centre.

2. **Action on the Vessels.**—Here we gain similar groups of poisons: (*a*) causing contraction, (*b*) causing dilatation, and (*c*) acting secondarily through the nervous system.

1. After much contradictory evidence, it is now generally accepted that ergot acts directly on the vessels, for if dilatation be brought about by vasodilator stimulation, the passage of ergot or ergotin through the vessels of the part leads to constriction. At the same time there is direct action upon the heart. Adrenalin and barium chloride have, of late, been found to have even more profound local constricting effect.

2. Nitrite of amyl and the nitrites in general, chloral hydrates, quinine, and atropine in small doses, lead to increased rapidity of flow through removed organs; hence they directly induce dilatation; the same has been noted with regard to acids as a class (Gaskell).

It is interesting to note that these various drugs do not cause constriction or dilatation, respectively, of the vessels of all organs. They have, to a certain extent, a selective action. Quinine acts more especially upon the spleen, digitalin upon the vessels of the kidneys, amyl nitrite upon the vessels of the face and respiratory tract. Adrenalin, as Herter shows, while it causes intense contraction and blanching of the vessels of most organs, when applied to the surface of the pancreas causes profound vasodilatation.

It may be noted that some, at least, of the bacterial toxins have a direct effect on the circulatory system. Thus Bouchard found tuberculin to act as a vasodilator, Roger that those of the B. septicus putidus had a most powerful action on the heart, with slowing and prolongation of the contraction, and death in diastole. Kemp and Dewey, on the other hand, employing typhoid toxins on the terrapin's heart, gained no slowing, but diminution in the size of the beats, and eventual death in systole.

The Digestive System.—Here again we have to distinguish the action upon the nervous, muscular, and secretory mechanisms of digestion, both direct and reflex. The full study of any individual poison, to determine how it affects the digestive system, demands (1) observations upon the results when introduced into the digestive channel: (*a*) when the nerves to a part (vagi and sympathetics) are intact, and (*b*) when one or other set is divided; and (2) study of the effect when it is introduced into the circulation simultaneously. Apomorphine, for example, has a direct effect upon the central nervous system, causing emesis when injected subcutaneously; ipecacuanha usually has no such effect; it causes vomiting only when introduced into the stomach, then acting reflexly by stimulating the vagus terminations. Cut the vagi, and even large doses are without effect. Magnesium sulphate and saline purgatives, as a class, at most cause increased peristalsis to a slight degree when introduced subcutaneously or into the blood; to produce abundant watery evacuations they must act from within the gut.

With antimony tartrate, the action may be both direct and reflex. And when definite anatomical lesions show themselves along the course of the alimentary canal, we cannot immediately conclude that these are due to the immediate action of the poison upon the tissues from without; even in the stomach they may be due not to absorption but to elimination of the already absorbed poison. Here, again, true conclusions can only be reached by comparing the effects of ingestion and of subcutaneous or intravenous injection. It is not surprising, therefore, that, contrary statements exist regarding the mode of action of many of the digestive poisons.

This being the case, it is best to pass in review the main orders of digestive disturbances in relation to their causes:

Salivation.—Drugs set up salivation and arrest of salivary secretions mainly by reflex nervous mechanism; the poisons must be absorbed before they fall upon the salivary gland. Of such reflex salivation, that set up by emetics affords a good example. To some extent the process may be regarded as eliminative, *e. g.*, in mercurial salivation.

Vomiting.—While, as seen by study of the isolated stomach, several poisons can act directly upon the gastric musculature, setting up irregular peristaltic movements, contraction or relaxation, and paralysis, the process of vomiting is not due to the stomach alone. As Magendie showed, replace the stomach by a simple bladder, and vomiting still may be set up. Obviously, the stomach and alimentary tract in general play a secondary role in the process; to coördinate all the factors involved in the act, the nervous system must dominate, and, as Sir Lauder Brunton has shown, vomiting may be initiated in two ways: (1) reflex, by gastric irritation of the branches of the vagus; (2) direct, by excitation of the nerve centres. We have already afforded examples, in ipecacuanha and apomorphine, of these two modes of action.

Diarrhœa.—The causes of diarrhœa and the modes in which they act are manifold. Broadly speaking, under this heading discharges of two different types are included: (1) the premature removal of the liquid contents of the small intestine without due absorption and modification, and (2) the discharge of excessive secretion from the mucosa of the small and it may be of the large intestine.

Dysentery.—Dysentery, which, it may be recalled, is properly not a specific disease, is that form of diarrhœa characterized by straining and irritation of the lower bowel, accompanied by mucus, and, it may be, blood, derived from the inflamed mucosa of the colon and rectum.

The first process, that of premature removal, is brought about by increased *peristalsis*. This may be due to direct action on the nerve centres or to reflex irritation. Injections of rhubarb or senna will cause purgation when injected into the veins; croton oil only when introduced into the alimentary canal, and then, if the vagi be cut, no diarrhœa results. In other cases the action is even more indirect. Aloes, for example, acts only when injected, and then only when there is a free flow of bile; ligate the common bile duct, and no diarrhœa ensues.

As regards the second process, that of increased secretion, the saline

purgatives, as already noted, mainly act by this means, not causing purgation when injected intravenously.

When there are actual lesions—acute congestion, with or without ulceration—there is undoubtedly increased discharge, accompanied by diminished absorption. Regarding these lesions, it must be remembered that they are of two orders: (1) those produced by direct irritative action of poisons acting upon the exposed surfaces, and (2) those due to elimination of an absorbed poison.

1. The former, naturally, are most apt to be seen in the upper part of the digestive tract. Bodies of the nature of acids or caustics setting up direct necrosis of the mucosa cause the greatest injury. This, however, often tends to be localized rather than generalized; it is regions of narrowing and compression—of arrest of the irritant—that are most liable to exhibit disturbance, as, for example, in the œsophagus, opposite to the larynx, the bifurcation of the trachea, the cardiac end of the œsophagus.

2. The eliminative lesions may occur from the stomach downward. Thus arsenious acid introduced subcutaneously will produce multiple hemorrhages and fatty degeneration of the mucous coats of the stomach, which pass on, as shown by Filehne, to multiple peptic ulcers, provided the gastric contents be acid. Whether the curious duodenal ulcers occasionally met with in extensive burns are eliminative is still an open question. The acute hemorrhagic, necrotic, and ulcerative condition of the colon seen after swallowing corrosive sublimate may be reproduced when the poison is introduced by other paths. We have similar evidence that mercury and antimony are eliminated through the colon. By analogy, the ulcerations of the lower bowel present in uræmic states are of like eliminative origin.

The Liver.—The usual function of the liver is to neutralize or eliminate poisonous substances brought to it in the circulation; thus, on the one hand, its cells can excrete or modify relatively large amounts of toxic matter without being greatly affected; on the other, this very function, coupled with its position at the head of the portal circulation, renders them peculiarly liable to be damaged, and to exhibit either acute or chronic disturbances—cloudy, fatty, and other degenerations, with nuclear changes or even acute necrosis; or, again, atrophic changes coupled with fibrosis.

The rapidity with which many substances are absorbed from the intestinal canal and taken up by the liver cells is remarkable. Laffter, working under Heidenhain, found that rhubarb injected into the duodenum appeared in the bile in less than five minutes. Sulphindigotate of sodium introduced into the circulation began to enter the bile one minute after its injection.

In general, direct, as distinguished from reflex, toxic disturbances of the organ are more prominently in evidence, but the development of jaundice, as the result of strong emotion, in itself indicates the modifying influence of the central nervous system upon the organ.

Certain classes of poisons stand out especially as being excreted or

acted upon by the liver, and as liable to set up disturbances in the process, notably:

1. Among metals and metallic salts, lead, copper, mercury, arsenic, phosphorus. The last more particularly modifies profoundly the cellular actions, leading to nuclear and cytoplasmic disturbances. These metals, upon analysis, are found in greater quantities in this organ than in any other part of the body; they are excreted into the bile, a vicious circle being set up (*i. e.*, they may be reabsorbed again from the intestines).

2. The toxic products of digestion, indol, skatol, toxic albumoses, with which may be included the toxic products of bacterial growth in the intestines. Where these are found in excess, we gain evidence of *hepatic incompetence;* the overloaded cells permit the toxic bodies to pass through the organ into the general circulation, and, more particularly with non-neutralized digestive products, there are induced torpidity, slowness of pulse, dilatation of cutaneous vessels, muscular weakness — conditions which can be reproduced experimentally by injecting certain products of proteid and amylaceous digestion into the systemic circulation (albumoses, lactic acid, indol, etc.).

3. The toxins of pathogenic bacteria. One of the commonest changes in acute infections is a state of cloudy swelling of the liver, passing on in the more acute states to one of fatty degeneration. Certain toxins have an even severer action upon the liver cells, setting up localized areas of cell death (focal necroses). These we see in typhoid, diphtheria, the plague, and a number of other acute infections. There continues to be doubt as to the exact mode of causation of these necroses, but some at least are found to be due to the direct action of toxins.

4. The products of hemolysis. These and their effects will be discussed when we take up the subject of jaundice.

The Pancreas and Spleen, and Ductless Glands in General.—Our knowledge of the direct action of poisons upon these organs is not sufficiently extensive to permit of any general statements.

The Kidneys.—Just as the liver is the great organ for the elimination of toxic substances from the portal circulation, so the kidneys are the most prominent eliminating organs for toxic substances in the systemic circulation, and bear the brunt in cases of systemic intoxications. Thus, the considerations laid down in connection with the former organ apply here very largely, *mutatis mutandis*. There may be nervous or direct irritation of the organs, leading to increased or decreased discharge of urine or of specific constituents of the same, cloudy and fatty degeneration of the tubular epithelium of particular areas, or disintegration and necrosis of the same; or, where the process of elimination is carried on over a long period, the gradual development of fibroid changes. Certain toxic substances, *e. g.*, the metals above mentioned, act both on the hepatic and renal parenchyma; others, like cantharidin, act more particularly on the renal cells.

The Skin and its Constituent Glands.—Physiologically there is an interesting relationship between the sudoriparous and the salivary

glands. Those substances which, like emetics, set up an increased salivary flow, in general lead at the same time to diaphoresis. This is well marked in the case of pilocarpine. Other substances, like atropine, arrest both salivation and diaphoresis. Whether the action of diaphoretics is directly upon the gland cells, or through the terminal nerve filaments, is still a matter of debate.

Numerous disturbances, eliminative, vasomotor, trophic, may be set up in the skin by very numerous poisons; we are still far from understanding the causation of many of these conditions. One of the commonest is extensive localized or general erythema (active congestion of the superficial vessels). Mercury, the bromides, the iodides, iodoform, salicylic acid, etc., are on record as producing the condition. Closely allied to these are the erythemas produced by irregularities in diet or by eating certain foods. To a very large extent these erythemas and urticarias are idiosyncratic—only certain individuals are liable to manifest the lesions. Either some nervous disturbance must be at the bottom of these idiosyncrasies, or, as it is now suggested, some minute variation in the constitution of the cytoplasm of the endothelium of the vessels of a part, rendering it peculiarly susceptible to the actions of the toxins or poisons.

In the case of purpuric eruptions, it would seem that we have clearly to deal with this direct action of the poisons upon the endothelium of the smaller cutaneous vessels, for this often exhibits fatty degeneration. It is the localized weakening and necrosis of these cells that would seem to precede the rupture and hemorrhage, *per rhexin* and *diapedesin*, which set up the purpuric ecchymoses. This, it is true, is not the only cause of purpura, but would seem to be the commonest. We have encountered minute capillary emboli leading to minute hemorrhagic infarcts. In some cases of bacterial origin, as in the rose spots of typhoid, it is now fully demonstrated that there is local growth of bacteria, leading through the toxins to local degeneration and necrosis of the containing vessels, congestion, and, it may be, rupture of the same.

CHAPTER VIII.

EXOGENOUS INTOXICATIONS: PARASITIC CAUSES.

Of greater frequency and greater importance are the parasitic intoxications. Some of these, it is true, are due to absorption from without; there are parasites—using the term broadly—which live in the alimentary canal, for example, and do not themselves penetrate into the tissues; and living there, produce toxins which are absorbed. These are the exception. All that is necessary is to note that such exist, and that their products act after the same manner as those of the main mass of parasitic forms growing in the organism. All fall into one of the three groups: (1) Microparasites of vegetable nature; (2) microparasites of animal nature; (3) the larger animal parasites. In discussing how they act in setting up disease we shall pass them in review in the above order.

BACTERIA AS CAUSES OF DISEASE.

Of all the various pathogenic microorganisms, the bacteria stand out as the largest class, and it has been by a study of their properties that the modern doctrine of infection has been developed. The realization of their existence and growth within the organism has brought about the greatest revolution in medicine and in surgery that our science has experienced. As already noted, we shall not deal with them in detail; that work is accomplished in the many special works upon bacteriology, wherein bacteria are dealt with from the point of view of the medical man, works in which the manner in which the individual pathogenic bacteria cause the different diseases is carefully discussed. We would but recall, and that rapidly, the characters of bacteria as a class, and deal generally with the methods whereby they may cause disease.

Briefly, then, bacteria are, as a class, characterized by their extreme minuteness; some, indeed, like the organism of contagious pleuropneumonia in cattle, are beyond the power of the strongest microscope to render visible—are one ten-thousandth of a millimeter in diameter, or less; they possess no distinct nucleus, do not (so far as we can determine) conjugate, but multiply purely by fusion; are, some of them, motile, by means of flagella, and some, again, but not all, exhibit sporulation, whether by internal development of such spores (endospores) or by conversion of the whole of the minute organism into an encysted resting stage, as occurs in some of the spherical forms, though whether these so-called *arthrospores* are spores proper is gravely doubted. Mor-

phologically, they can be separated into the three broad divisions of cocci, spherical or blunt oval forms, bacilli or rod-like forms, and spirilla, or forms exhibiting either complete spirals or segments of the same; transitional forms occur which it is difficult to range in either one or other division.

The temperature limits between which they grow are very various, as are also the media in which they grow, but of pathogenic bacteria as a class it may be said that they grow best at, or about, the temperature of the body of their hosts, and best also upon media containing organic matter, which, like the blood and tissues of their hosts, have a slightly alkaline reaction to litmus. The majority grow best in the presence of free oxygen (aërobes). A large number can exist in the complete, or almost complete, absence of *free* oxygen (facultative anaërobes); a small number (of pathogenic forms) can only grow when free oxygen is practically absent (obligatory anaërobes), obtaining the oxygen that is essential for existence by the breaking down and reduction of oxygen-containing foodstuffs. Possessing no mouths or organs, they can only live by absorption; in other words, in a fluid medium holding the necessary foodstuffs in solution. That they may act on potential foodstuffs, and bring about their dissociation, converting them into a soluble and nutritive form, they secrete enzymes—just as do the cells of the digestive tract of higher animals. These enzymes in the different species are of different orders—proteolytic, cellulose fermenting, diastatic and glycolytic, dissociating the various sugars, etc.—and, as first pointed out by Lauder Brunton and MacFadyen,[1] forms which, in a protein-containing medium, actively produce a proteolytic ferment, transferred to a starchy medium may now develop more particularly a diastatic ferment. There is a definite adaptability, and, what is more, they may develop a distinct adaptation, forms which at first were wholly inert toward certain sugars, gradually gaining the power to ferment them (see p. 102). Added to this, the pathogenic bacteria produce *toxins*, or substances having a poisonous action upon other living organisms.

With reference to their toxic powers, we may divide bacteria into three groups:

1. The non-toxic.

2. Those incapable of multiplying within the tissues, but grown outside the body, capable of producing toxic substances, which, being absorbed, set up disturbances. To this class belong many of the saprophytic and putrefactive bacteria, among them sundry organisms of so-called wound infection—microbes which will grow in pus of surface wounds, and there, through their products, set up irritation without gaining entry into the tissues. Here, also, are to be included many of the microörganisms of the digestive canal, which, growing in excess, set up local and general indications of intoxication. Many of these, it would seem, can under conditions become converted into members of the next group.

[1] Proc. Roy. Soc., 46 : 1889 : 542.

3. Bacteria capable of growing within the tissues and there setting up *infection.*

It is thus by their products of growth that bacteria cause disease, the difference between a bacterial intoxication pure and simple and an infection being that in the former case the products alone are absorbed; in the latter, the bacteria themselves gain entry and grow.

Toxins.—The term "toxin" is now so generally and so vaguely used to embrace all the deleterious products of bacterial growth, that, doubtless, substances of very different orders are included under the term, including the direct excreta of the bacteria and the secondary products of the action of these discharges upon the medium of growth. That we have to deal, at least, with these two groups of bodies is, it seems to us, conclusively indicated by Sidney Martin's studies upon diphtheria. Martin has shown that from the spleen and other organs of those affected by this disease it is possible to isolate a highly toxic albumose, whereas from the false membrane in the throat (in which alone the bacilli have undergone multiplication, and are present in abundance) but little of this albumose is to be obtained. Nevertheless, an extract (sterile) of the false membrane has singularly toxic properties. From a study of the effects of this extract he concluded, with Roux and Yersin, that the primary product discharged by the diphtheria bacillus is an enzyme, that this diffusing, with some difficulty, it may be, and in very minute quantities from the region of growth of the bacilli, does not itself poison the tissues, but, acting upon certain proteid substances of the organism, converts them into highly toxic albumoses—and these it is that set up the symptoms of disease.

And there is much to be said in favor of this view of the nature of at least an important group of the primary products of bacterial growth. Like enzymes, extraordinarily small quantities suffice to produce eventually maximal disturbances; action is not immediate and is cumulative, herein differing from anything of the nature of a direct chemical process. They are brought down by the same substances which precipitate enzymes, are characteristically thermolabile, rendered inert by temperatures of 56° to 60° C. (the exceptions being no more marked than in the case of enzymes), and they diffuse either not at all or very slowly).

Not all pathogenic bacteria produce noticeable amounts of toxins discharged in the process of active metabolism. Some, like the typhoid bacillus and the bacillus coli, afford culture fluids of very low toxic powers, but if they be frozen and triturated, as by Rowland's method, or subjected to great pressure, the body juices are found to be intensely toxic. The observations here are exactly parallel to the well-known experiment of Buchner. The fluid in which the yeast plant is grown contains a ferment which will invert sugar, but will not convert that into alcohol. Express the active yeast cells under an hydraulic press, and the body juices, acting on the inverted sugar (glucose), produces alcohol. Here we have to deal with the existence of intracellular enzymes, bound up with the living cell substance, and the stimulus exerted by Buchner's

observation has led to the discovery of abundant intracellular enzymes in the tissue cells. These "intracellular toxins" seem, obviously, to be bodies of the same order.

The views here put forth of the existence of primary and secondary toxins—the primary of the nature of enzymes, the secondary the active toxic substances—are not as yet universally accepted, although they are gradually gaining wider recognition.

In this connection reference must be made to the remarkable studies of Vaughan,[1] of Ann Arbor, and his pupils, upon the composition of the bacterial body in relationship to its pathogenicity.

THE NORMAL DEFENCES OF THE ORGANISM.

Recognizing, then, that we have these two ways in which bacteria can cause disturbances within the organism, namely, by the absorption of their products of growth and the substances produced thereby (simple intoxication), and by growth and production of toxins within the system (infection), it must next be asked, How do the bacteria gain entry into the tissues and thus cause the latter state?

The human body and, for the matter of that, the bodies of all multicellular organisms are to be regarded as closed corporations, in which corporations one of the special functions of the outer layer of cellular units is, for the benefit of the whole system, to hinder the entrance of individual organisms of other natures. And here it must be kept in mind that, contrary to first conceptions, these outer layers are not the external layers only, in the usual acceptation of the term, but are all layers bounding surfaces and channels which, however indirectly, communicate with the exterior. The mucous membrane of the stomach and intestines is thus strictly external, as will be grasped from the diagram given on p. 272.

There is in the higher animals only one direct channel of communication between the interior of the body and the exterior, and that only in the female, namely, the Fallopian tube, which has so fine a channel, and so protected, that to all intents and purposes it is closed; only under very exceptional circumstances—we have encountered one such case—can acute peritonitis be brought about by suction of infective material from the uterus through the tube. The case in question was that of a thoroughly healthy girl who, in the last days of her menstrual period, took part in a gymnastic competition, dying within eighteen hours. The viscera were found absolutely free from anything that could suggest a primary focus; the peritoneal exudate contained a pure culture of streptococcus, and similar streptococci were present in the uterine cavity. It must be recalled that, save at the menstrual period and after parturition, the mucus of the cervical canal acts as an efficient plug against suction of vaginal or uterine contents through the Fallopian

[1] Trans. Assoc. Amer. Phys., 20: 1905: 265.

tubes. There are on record other cases of apparently primary peritonitis in which, *per exclusionem*, this mode of infection must be invoked.

Living outside this close corporation are countless other individual organisms. On the very surface of the human body, for instance, we know that there exist millions of microbes, mainly bacteria, many of them potentially pathogenic—pyococci, streptococci, B. pyocyaneus, B. coli, etc. The mouth contains them in abundance—pyococci, streptococci,[1] pneumococci. There may be countless millions in the intestinal canal, but these are outside the body, and, while they find nourishment in the cast-off dead cellular debris, in certain discharges from the surfaces and in the food material ingested, they are not taken into the tissues, or, as we shall point out, if they gain entrance, there are many mechanisms for arresting their growth and destroying them.

Of those mechanisms we recognize the following:

1. Surface discharges. Certain discharges or excretions either simply wash off the microbes, which, left at rest, might multiply, or, in addition, have definite bactericidal properties. But for the flow of the saliva, the mouth would be an admirable incubator. That flow carries them, with swallowing, to the stomach, where, if not already destroyed by other means, the acid gastric juice kills off the greater number. The mucus poured out from the various glands of the mouth and respiratory and other tracts, while it favors the arrest of bacteria, forms a layer through which microbes grow with difficulty to come into direct contact with the surface cells, and, in general, before this contact can be accomplished, either by the action of the cilia of those cells (respiratory tract, etc.), or by peristaltic or other movement, the mucus is liable to be carried away. Certain observers hold that mucus has, in addition, definite bactericidal properties.

The gastric juice is particularly active in destroying bacteria. The number taken in at each meal with the food must be great. Milk, for instance, that has been kept—as most milk is kept—for twenty-four hours and more, may, on warm days, contain, it may be, 2,000,000 or more bacteria per cubic centimeter (15 minims). Nevertheless, a few hours after food the duodenum may be found quite sterile, and in general, as indicated by the slower development of the peritonitis following perforation of the stomach or upper portion of the intestine, as compared with that succeeding rupture of the lower portion of the small intestine, the bacteria which persist in the stomach are both reduced in number and, at least temporarily, inhibited in their activity. When there is gastritis, with arrest of secretion, or diminution of the hydrochloric acid, the same is no longer true. Then not only are the bacteria not destroyed, but, escaping into the small intestines, they find alkaline contents of the same or favorable medium of growth, and, proliferating, may by their products induce extensive irritation. Following Pettenkofer, Hankin found, for instance, that in normal health

[1] During our bacteriological course in 1905 the students, making cultures from each other's mouths, gained streptococci in 80 per cent. of the cultures.

he could with impunity swallow billions of living virulent cholera spirilla without ill effects. Happening to repeat the experiment when he was suffering from transient gastric catarrh, there developed an acute diarrhœa, with abundant spirilla in the stools. It is interesting to note that what we may term are the commonest normal inhabitants of the intestines, namely, the B. coli and Bact. acidi lactici groups, are forms relatively tolerant of acids.

Even the excreta—the urine, milk, and, to a slight extent, the bile[1]—have been demonstrated to exert a certain inhibiting and, in some cases, mild bactericidal action.

There are yet other protective external mechanisms. If a current of impure air, bearing dust, spores, etc., be caused to impinge upon a moistened surface, as it impinges it leaves behind its solid particles. The back of the pharynx, and, as an important auxiliary, the turbinated bones of the nose, act as such moistened plates, arresting the bacteria taken in with the inspired air. So effective is the mechanism that (in nose breathers) few bacteria gain entrance into the trachea. The further action of the moistened surfaces of the trachea and bronchi results in this, that the expired air of a healthy man is found absolutely sterile. As Arthur Ransome has shown, the same is true during quiet breathing, even where there is active tuberculous lung disease (although, as Flügge has demonstrated, the fine particles or globules of moisture discharged from the mouth of such a patient in speaking, coughing, sneezing, may contain the bacilli, and be infective). These globules, it is scarce necessary to say, are formed of saliva.

On such a surface as the back of the pharynx the mere presence of a frequently renovated layer of moisture would not seem to be a sufficient guard against lodgement of microbes and subsequent proliferation of the same. Ruffer[2] has called attention to the existence of a further mechanism. Even low down in the animal kingdom, as pointed out by Gaskell and Miss Allcock, Hardy, and others, we find that the surface discharges and mucinous coverings are not sufficient to arrest the growth of bacteria, and that certain leukocytes, passing out on to the surface, act as scavengers, and these, whether by actually taking up the microbes and digesting them, or, by their "explosion" and discharge of bactericidal contents, succeed in cleansing the surface and removing bacteria and low forms of life, which, growing in too large quantities, might poison the outer cells, and so break down the line of defence.

If we examine a scraping or swab from the surface of the pharynx or nose, we find that this contains fairly abundant leukocytes. In other words, leukocytes are constantly passing out between the epithelial cells to gain the surface. Many of these, properly stained, show within them bacteria and their remains. They are acting as scavengers and

[1] We have found that the bile, while not actively bactericidal, has a distinct inhibitory effect upon the growth of forms like the B. coli.

[2] British Medical Journal, 1890: ii: 491.

cleansers. It seems probable that the majority, having performed their functions, undergo dissolution or are swept away by currents of saliva. But some, at least, find their way between the lining cells into the subjacent tissues. This can be well determined if one takes, as did Ruffer, the rabbit's tonsil, kill the animal, remove and immediately harden and prepare the tonsil—staining sections for microörganisms. The tonsils are essentially lymph nodules, lying immediately beneath the surface epithelium. Such sections show, besides the lymphocytes forming the lymph nodes, two other orders of cells, the one polymuclear[1] —some of which contain bacteria— the other, larger cells of endothelial type and origin (Metchnikoff's *macrophages*), of which some contain polymuclear leukocytes and their remains. Such leukocytes, in short, as have wandered back from the surface find their way into the lymph channels, and so to the lymph nodes, and reaching there, are liable, if weakened, to be taken up by the larger hyaline endothelial cells lining the channels.

It is wrong, therefore, to imagine, as it is too often taught, that the hindrance to the entrance of bacteria into the tissues is, under all circumstances, complete in the healthy individual. *A certain number of microbes is always gaining admission* — nay, [illegible] being actively introduced by the cells of the organism. But *under such circumstances they do not cause infection. In health they tend to be destroyed very soon after their reception.* The evidence that this is the case is now overwhelming. It is true of the lower respiratory tract. Careful study of the peribronchial glands shows the same presence of intracellular bacteria, although not so abundantly as in the tonsils.

It is true also of the intestines. Here it can best be followed in the lower portion of the small intestines, the region in which the proliferation of bacteria attains its maximum. It is in this region that one notes that the lymph-glandular tissue of the submucosa is the most extensive (Peyer's patches and solitary follicles). Bizzozero[2] and Ruffer have shown that (in the rabbit) the lymphoid tissue presents appearances identical with those seen in the tonsil. Repeating the work in our laboratory, Dr. A. G. Nicholls[3] has shown that the amount of taking up of bacteria by these nodules in various animals is very considerable, though the rabbit, with its large cecum, and arrest there of fermenting food, usually affords the most convincing demonstration.

Take a healthy, well-fed rabbit, kill it, open the abdomen, pull out the lower coils of the small intestine so as to stretch the mesentery; harden the mesentery with formalin in the stretched condition; with a sterile swab clean off the endothelial covering on either side; cut it out

[1] Polymorphonuclear is the more correct term, but we admit that it is too sesquipedalian for daily service. We employ polymuclear, with the reservation that it must be understood that by this we do not mean that the cells are multinuclear only that they possess nuclei of many shapes.

[2] Centralbl. f. d. med. Wissensch., 23: 491; see also Ribbert, Deutsch. med. Woch. 1885: 197.

[3] Jour. of Medical Research, N. S., 6: 1904: 485.

without opening the intestine. Now, upon staining with carbol thionin, there are to be observed along the fine vessels of the mesentery what, from their shape and relationship, can only be the more or less degenerated remains of bacteria. Occasionally a well-formed bacillus is to be recognized. Some are along the lymphatic vessels; some, judging from their nearness to irregularly lobed nuclei, are within polymelear leukocytes; occasionally they are within small blood capillaries.

It is clear, then, that, taken into leukocytes upon the outer surfaces, bacteria may (1) be arrested in the first line of subcutaneous lymph nodes, or (2) may evade these and be arrested in the second line, the mesenteric and retroperitoneal lymph glands, or (3) may pass into the minute radicles of the portal vein.

That such leukocytes as have escaped into the lumen of the gut and have returned can and do pass into the blood stream, has been demonstrated with admirable precision by Prof. A. B. Macallum, of Toronto.[1] In the course of his investigations upon the microchemistry of the cell, studying the fate of iron in the economy, he was led to feed lake lizards (Necturus) with peptonate and albuminate of iron. Taking them when they had fasted for thirty months (to make sure that their intestines were empty), he fed them with the compounds above mentioned, and killed eight hours later. Employing Perl's (the Prussian blue) test, by which means the free iron, if present, takes on a pronounced blue color, he found that:

1. Within the lumen of the intestine were leukocytes full of Prussian-blue granules. These had, therefore, passed out and taken up the iron salts.

2. Between the epithelial cells of the villi were cells of the same order (reëntering leukocytes), along with others quite free (wandering-out leukocytes).

3. Examining the other tissues, he found leukocytes containing the blue granules in the capillaries of the liver and in the spleen; or, in other words, the leukocytes containing the iron had found their way into both the portal and the systemic blood.

And, lastly, not to dwell upon the convincing results of Nocard, Ravenel, and Behring upon the passage of tubercle bacilli and other organisms into the lymph of the thoracic duct of dogs and other animals when fed more especially with fatty foods,[2] Dr. W. W. Ford,[3] in our laboratory at the Royal Victoria Hospital, has demonstrated most conclusively that immediately after death organs like the liver and kidneys of dogs, cats, rabbits, and guinea-pigs are not sterile, but contain some few bacteria, which are capable under favorable conditions of still growing.

[1] Journ. of Physiol., 16: 1894: 268.

[2] It is not an exaggeration to say that during the last two years there have appeared close upon fifty articles dealing more particularly with abdominal infection by the B. tuberculosis, and demonstrating experimentally the passage of solid particles through the unaltered mucosa of the intestine. Fuller data regarding the earlier work are given in an address by me. Jour. Am. Med. Assoc., 33: 1899: 1506 and 1572.

[3] Trans. Assoc. Amer. Phys., 15: 1900: 389, and Jour. of Hygiene, 1: 1901: 276.

Ford's cultures proved that over 70 per cent. of the livers and kidneys of these animals, if removed aseptically within a minute or two after death, and placed with every aseptic precaution in agar-agar, gelatin, or broth, yield cultures of various forms of pathogenic and non-pathogenic microbes, such as are found in the intestinal contents. The interesting point is that the growth of these forms is peculiarly slow. Ford, in general, obtained no growth within three days, but, keeping for several days, he obtained positive results. Evidently (1) the bacteria are attenuated, so that their growth is feeble, and (2) it is arrested until the bactericidal substances of the organs have become inert. There was a striking difference between the flora gained from the carnivorous animals and the rodents, and again between the flora of the different series of animals (dogs, cats, rabbits, guinea-pigs).

Recently, Wroszek has made the further observation that, giving healthy animals cultures of non-pathogenic pigmented bacteria with their foods, these can be obtained in culture from the internal organs, without there being a sign of inflammatory or other lesions along the intestinal tract.

These observations, then, prove conclusively that *bacteria are constantly entering the organism.* But now to turn to another aspect of the subject: If bacteria, and these pathogenic, be injected directly into the blood stream, within fifteen minutes, and even within five minutes, although hundreds of thousands, not to say millions, have been thrown in, the circulating blood affords very few colonies. And, examining the tissues after these intervals, one finds that the bacteria have already been actively removed from the blood by the endothelium of the blood-vessels, more especially of the liver, kidneys, and spleen (splenic corpuscles). Within an hour the heart blood may be found sterile.

(At a later period, however, the blood may again be teeming with the bacteria.)

Bacteria, then, which gain entrance are taken up by the endothelial cells of the bloodvessels. Werigo[1] has observed and figured the endothelial cells in the liver sending out definite pseudopodia, whereby leukocytes and their contained bacteria are arrested. As these processes retract, the bacteria are to be seen lying within the endothelial cells.

As we have pointed out,[2] if one studies a series of livers removed at different periods from rabbits, into whose vessels B. coli have been injected, it is possible to recognize a series of stages of destruction of the bacteria.

At an early stage large, well-formed bacilli are to be seen within the endothelial cells of the liver. Later, these break up into short stumpy segments; later, as the process continues, in place of bacteria, rows of two or three minute dots are observable; later again, the endothelial cells become free from any sign of germs. We are inclined to conclude that minute isolated double and treble dots seen within the liver cells

[1] Ann. de l'Inst. Pasteur, 7; 1893; 593.

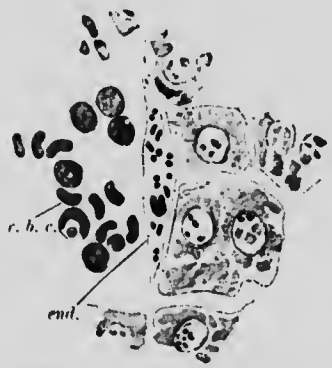
[2] Adami, Abbott, and Nicholson, Journal of Experimental Medicine, 4; 1899; 349.

represent the remains of the bacteria taken up from the overlying endothelium, for similar diplococcoid forms now appear in the bile.

Personally, we incline to the opinion, although we will not lay it down positively, that both the liver and the kidney actively excrete bacteria which have undergone preliminary action by the endothelium. Regarding this matter it is extremely difficult to arrive at an absolute conclusion, and the many observations made since Cohnheim first propounded the view, have been so conflicting—so positive in either direction—that we hesitate to express more than our belief.

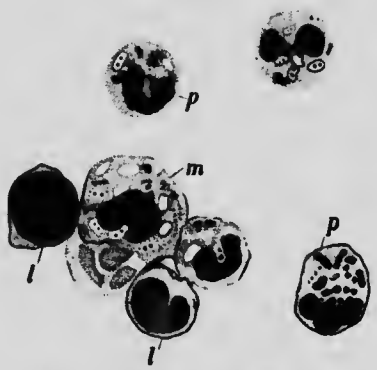
Thus, the observations of Sherrington, Wyssokowicz, and not a few others are wholly opposed to this conclusion; those of Futterer, Wroszek, our own observations, and those of Nicholls support it.

Fig. 109



Swollen endothelial cell of capillary of rabbit's liver containing Bacillus coli in various stages of degeneration, within thirty minutes of injection of the bacilli into the blood stream. Part only of the nucleus is shown in the section.

Fig. 110



Phagocytic cells from peritoneal cavity of guinea-pig, nine hours after intraperitoneal injection of Bacillus coli, to show stages of destruction of the bacilli: *p*, polynucleats; *m*, large mononuclear cell; *l*, lymphocytes (non-phagocytic).

Whether the process continues so far that there is actual excretion of attenuated and destroyed bacteria, this is obvious, that *while the tissues of the healthy body are not of necessity free from microörganisms, they are potentially sterile.* While the mesenteric and other superficial lymph nodes may show abundant bacteria, the mass of these are clearly destroyed, or are undergoing destruction. While the removed liver may show abundant bacterial forms, in its endothelium, and even, as we hold, in its parenchyma, scarce any of these are normal, and cultures from the same organs made immediately after death are either sterile or give only delayed growths of a few forms; here and there throughout the organ a microbe not yet acted upon to the extent of rendering continuous growth impossible may yield a growth.

There are thus many means whereby the organism is prepared to arrest the entrance of microörganisms, and, in the event of such entrance, to inhibit their growth: (1) The physical and bactericidal action of the

bodily discharges; (2) the structure of the surface layer; (3) the bactericidal activities of the wandering cells; (4) the phagocytic and bactericidal action of the lymphoid tissues; (5) the like action of the vascular endothelium; and (6) it may be, the bactericidal and excretory action of the cells of certain excreting glands. Nor is this all: (7) we have, in addition, ample proof that the circulatory fluids of the body have antibacterial properties. There is, however, still some want of accord between different observers as to how far these are in force under physiological conditions. We shall deal with this subject more fully at a later period.

THE MODES OF INFECTION.

We have purposefully dealt with the subject of the normal defences of the organism at some little length, and this because an adequate appreciation of the relationship of the body toward bacteria in health is absolutely necessary for a full grasp of the conditions under which infection may originate. It will be seen that, instead of there being, as is so generally taught, one almost universal method whereby bacteria enter the body, namely, by some (traumatic) solution of continuity of the surface layers, the means are manifold. We may have:

1. Alterations of the surface discharges and secretions, either in amount or in quality, whereby microbes proliferate unduly on the surface, producing sufficiently concentrated toxic matter to affect the surface cells, lower their vitality, and destroy them, with the result that they now gain a focus of growth *within* the tissues.

The foul ulcerous condition of the mouth in certain fevers, accompanied by lessened salivation, is an instance to the point, as, again, is the development of thrush. The accumulation of excreta by closure of the passages of discharge also favors the development of infection. This has been noted especially in the alimentary tract. Posner and Lewin[1] have proved that experimental closure of the rabbit's rectum leads to the presence of the B. coli in the various tissues and excreta in the course of a very few hours; Czaplewsky and Frazier,[2] that experimental closure of the rabbit's cecum rapidly leads to the supervention of peritonitis. Not only do bacteria proliferate excessively under these conditions, but their virulence is definitely exalted. B. coli isolated from the contents of the intestines before such closure may be found harmless for other animals; isolated some forty-eight hours later, are intensely virulent. The main cause of appendicitis is primarily, it would seem, not ulceration or erosion, but kinking or other obstruction of its narrow channel.

2. Traumatic solution of continuity of surface layers. Here we have to deal not only with the destruction of the protective layers, but with the provision of a favorable nidus for bacterial growth in the necrosed cell tissue lining the injured surface.

When Pasteur fed a flock of sheep on a meadow which had been

[1] Berlin. med. Gesell., February 6, 1895, abstr. in Med. Week., 1895; 82.

[2] Contributions from the William Pepper Laboratory, Philadelphia, 1900.

sprinkled abundantly with a virulent broth culture of the anthrax bacillus, scarce an animal succumbed to the disease; when, in addition, he scattered thorny particles and broken glass over the meadow, and then turned out the sheep to graze, the majority of the flock died of anthrax. It is, however, unnecessary to quote individual instances; the marvellous change which has come over surgical results since the application of Lister's method of keeping wounded surfaces free from exposure to contamination is our great object lesson. Little wonder that, with this before them, surgical pathologists regard trauma and solution of continuity as the essential causes of infection.

But here let us point out the significance of Welch's observations. It is not necessarily the destruction of surface layers which allows infection; the lowering of the vitality of the tissues is of almost equal importance. Despite the greatest care in the cleansing of cutaneous surfaces, and in the carrying out of aseptic or antiseptic treatment, suppuration may show itself in a wound. Welch has called attention to the almost universal presence in the lowest layers of the skin of the M. epidermidis—closely allied to, if not an attenuated form of, the pyococcus albus—these in health leading a harmless, saprophytic existence. This form is the common cause of, and is to be isolated from, "stitch abscesses," and may lead to extensive tissue destruction and general disturbances. If ligatures be made too tight, the included tissue is largely deprived of blood supply and nutrition, its vitality is lowered, and under these conditions it is that forms so feebly pathogenic as to be incapable, under ordinary conditions, of growth *within* the tissue, now proliferate, break down the tissues (by their products), with increased growth gain in virulence, and lead to abscess formation.

3. *Growth of bacteria and infection in an internal organ, with no recognizable solution of continuity of a surface—"cryptogenic infection."* It has been usual to regard this as brought about by some local solution of continuity which has undergone healing, or is so small as to be passed over. Such, of course, may occur, but the facts brought forward above show clearly that, through *unaltered* surfaces, bacteria and other microbes may be introduced by the agency of the wandering cells of the organism, and, being so introduced, may be conveyed by the lymph or blood stream to various regions where, coming to rest, they may proliferate and set up infection.

We not infrequently encounter cases of tuberculous cervical glands in children without a sign of tuberculosis of the fauces, active tuberculosis of the mesenteric glands with the mucosa of the intestine showing not a single ulcer, or at times meet with acute localized osteomyelitis, due to streptococci, with no history of, and no sign of, local surface irritation anywhere. Similarly, an acute nephritis or cystitis may suddenly supervene, with no ulcerative lesions found anywhere at autopsy to explain its origin.

It may be asked why, if pathogenic organisms are so frequently present (as we know they are) on the surface of the body, in the mouth and the intestinal contents, and if the leukocytes are thus liable to carry

them into the tissues, cryptogenic infections are not far more common; why, in short, we continue to live. The answer is (1) that leukocytes, in general, taking up very virulent microbes, tend to be destroyed or inhibited, so that they do not make their way back from the surface; or, indeed, through negative chemiotaxis (see p. 378), do not take them up at all. We would not lay great stress upon this, though doubtless it is a factor, for occasionally we find them ingesting distinctly [illegible] forms (*e. g.*, the gonococcus) and showing little obvious arrest of activity. Of more importance, we think, is (2) that, just as one swallow does not make the summer, so a single microbe cannot, according to numerous observations, produce infection (unless it be of extraordinary virulence). A certain minimal number must be at one spot in the tissues in order to produce enough toxic material to counterbalance the opposing cell activities. Ordinarily, therefore, a single microbe-bearing leukocyte coming to rest at any point does not produce disease. One or a few virulent germs introduced at one point are destroyed before they have time to proliferate. Thus isolated bacteria may simultaneously be introduced at various points and simultaneously be rendered harmless. Only when we have a special concatenation of circumstances, is it likely that this method of infection shows itself: (*a*) the presence of an excessive number of virulent microbes at one surface region; (*b*) congestion of a mucous surface, with passage out of an increased number of leukocytes; (*c*) reëntrance at one region of an undue number of the same bearing with them the microbes; (*d*) accumulation at one spot; or recurrent deposit of such numbers of microbes that the bactericidal powers of these cells then become exhausted; and lastly, (*e*) temporary or habitual lowered vitality of the tissues of such a region antecedent to the introduction of the microbes. With all the protective mechanisms, it is unlikely that any one of these conditions alone is liable to set up infection. We must assume the concurrent working of several. Infection, indeed, must be regarded as the outcome of a contest between the protective mechanisms of the organism and the bacteria, in which, for a time at least, the latter gain the upper hand. Whether bacteria grow in the body and set up disease or not depends thus upon two main factors—the resisting power (or susceptibility) of the tissues and the virulence of the microörganism; and both of these are capable of great variation. The first of these we shall consider in a separate chapter, for it has a bearing not merely upon the causation of infections, but of all forms of disease; regarding the latter, it is appropriate that here we should call attention to the more important data.

The Channels of Entry in Relationship to the Modes of Growth of Bacteria.—All pathogenic bacteria, it is needless to say, do not have the same habits of growth. Some are strict parasites, growing on the animal body only, and at the temperature of the body, some, indeed, only on the human body. Such, while they may retain their vitality outside the organism, cannot proliferate there, whence it follows that communication of the bacteria—and of the disease—must be direct, or almost direct, either by immediate contact or by the conveyance of

the virus in the form of *fomites*, in dust, scales of shed skin, etc., or in the discharges from the person from the one individual to the other. The tubercle bacillus and the microbe of gonorrhœa are thus conveyed. Or, insects act as intermediaries; then, it would seem, only in a passive manner (we here refer to bacteria only); although, for example, the typhoid and the plague bacillus can proliferate within the intestinal canal of insects, it is doubtful whether these act as more than passive carriers; certainly they are not essential. Other microbes have a much wider range of growth, and here the process of infecting may be mediate; discharged from the body of the diseased individual, they proliferate in fluid outside the body at the ordinary temperature; here, growing, they may exist for weeks, and through the contaminated fluid it is that the disease becomes conveyed to a second individual. But bacteria which commonly are conveyed by the one means may, with slight change of conditions, be conveyed by the other, and the old and still official usage of classifying certain diseases as contagious (*i. e.*, conveyed by contact), others as infectious, is useless, save as a euphemism. It is better to classify all as infectious, and recognize those properties of growth which render infections more liable to occur mediately in certain diseases, immediately in others. So, too, the term miasmatic, as indicating that certain diseases are brought about by a miasm, influence, or effluvium emanating from the soil, belongs to a past generation and must be allowed to die a natural death. What is of more importance is to recognize how and why specific bacteria gain particular channels of entrance:

1. Organisms floating in the air, whether capable of proliferating outside the body or not, are liable more particularly to gain entrance through the respiratory tract, and especially through the upper respiratory tract, the pharynx, and tonsils.

2. Those, like the typhoid and cholera microbes, which can proliferate in water, are particularly liable to gain entrance through the intestinal tract, although it has to be noted that the mouth and pharynx are common to both the digestive and respiratory systems, and they may here also be implicated. So, also, organisms discharged in the excreta of other animals, and not necessarily propagating in them, if these excreta be used as food (*e. g.*, milk), or contaminate food; or, again, microbes growing in the more sterile tissues of diseased animals used as food, may gain entrance by this channel. In this way, for example, tuberculosis may be conveyed, more especially to young children.

3. Organisms capable of existing in the pores of the skin more particularly are liable to proliferate when there is solution of continuity of the skin. Thus, the pyococci, streptococcus pyogenes, and bacillus pyocyaneus more particularly gain entrance by this means, although, as the skin comes in direct contact with external objects, many other microorganisms, under particular circumstances, may gain entrance in this way; or wounds are inflicted by instruments already bearing pathogenic organisms, such as rusty instruments carrying the spores of the tetanus bacillus.

4. Organisms infecting the genital passages are liable to be conveyed directly to the other sex in conjugation, as also to the child in parturition.

5. Those infecting the placenta pass to the fœtus along the umbilical vein.

We must, however, repeat that the channel of entrance is not necessarily the seat of manifestation of primary growth. We have to note special tissue susceptibility (p. 370), whereby bacteria gaining entrance multiply in certain tissues and not in others.

Virulence.—In the early days of bacteriology it was held that virulence was not so much the expression of active antagonistic processes initiated by the bacteria, as of a disturbance of vital processes, more or less extensive, brought about by the mere mechanical presence of these organisms within the tissues and the abstraction by the same for the needs of their growth of substances equally necessary for the growth and due activities of the tissues. The anthrax bacillus thus was supposed to absorb the oxygen of the blood and to block the capillaries. Nowadays we recognize that it is the expression of the toxic properties of the substances excreted by the bacteria, either in the course of their growth, or, it must be added, of their disintegration. Just as the tissues have their protective mechanisms, so have the bacteria, and these protective mechanisms, so far as we are individually concerned, may be summed up in the one word—toxins; although, as we have already warned the reader under this heading, we clearly include bodies of more than one order, among them the aggressins. Or, in other words, the virulence of a microörganism is the expression of the toxicity of its products. Upon analyzing further, it will be seen that virulence depends upon two factors, namely, the intensity of the toxic action of these products (of a unit of the same) and the amount discharged in a given time. A third factor determines infection, namely, the number of bacteria present affording these toxins. The intensity of action of a given solution of enzyme depends, for example, not merely upon the existence of the enzyme in the solution, capable of converting a given amount of substance in a given time, but upon the amount of enzyme present relative to the amount of material to be converted. This, however, we can neglect for the moment.

It is found that:

1. This virulence is specific, and that in two ways: (*a*) The toxins produced by the different species (*i. e.*, forms differing in morphological and cultural characteristics) are different, so that the results of inoculation constantly vary; and (*b*) the toxins are active for certain species of animals only, and not for others. An organism which will cause disease in one animal may be harmless for another of different species. Regarding the first of these properties, it is to be noted that of recent years facts have accumulated showing that closely allied species may elaborate common toxins; *i. e.*, that they produce multiple toxic bodies, some of which are common to more than one species, but others are specific, and peculiar to the one species. Regarding the other, it is a matter of common knowledge that certain bacteria are specific for man and without

effect on the lower animals (*e. g.*, the gonococcus); whereas others, like the large group of species of organisms of hemorrhagic septicemia, affect particular species of mammals and birds, but are without effect on man.

2. The virulence of a given species is subject to great variation. No two strains isolated from different individuals are of identical virulence.

3. The virulence is exalted or increased for any species by "passage" through members of that species, *i. e.*, by inoculation of a culture into an individual of that species in sufficient amount to set up symptoms of severe infection, and when these symptoms present themselves, killing that animal and inoculating some of the body fluid of that animal in to a second, and of that into a third animal, etc. To this increase a limit would seem to present itself after a certain number of passages, beyond which no further increase is found to occur, but the increase may be so great that a strain of an organism like the Streptococcus pyogenes, which, before passage, will only kill young individuals, and that after a period of three or four days and with the employment of 1 c.c. of a culture, will, by passage, be made so intensely virulent that the thousandth part of a cubic centimeter, or even, it may be, the millionth part, inoculated into an animal will cause death in six hours.

4. While thus the virulence may, by passage, be exalted for the particular species employed, it may be considerably lessened for members of another species. This is not constantly the case, but some notable examples have been noted. Thus, without exception, the virulence of pathogenic organisms is lessened by prolonged growth in or upon media of the laboratory, more particularly when this is accompanied by transfer to new media only at long intervals. It sometimes happens that the rapid transfer of a strain—every twenty-four hours—from one medium to another in rotation will cause a development of virulence in a weak stock up to a certain moderate amount; but if allowed to "stew in their own juice," bacteria tend to become attenuated. Various other agencies lead to lessening of the virulence outside the body, such as growth at a temperature bordering upon the maximum at which the particular species will retain its vitality; exposure to sunlight; action of small quantities of antiseptic or disinfectant substances; subjection to increased atmospheric pressure, etc. Broadly, it may be stated that bacteria exhibit the action of the law that has been made out for the higher forms of life, that within certain narrow limits the struggle for existence brings about the improvement of the race; above these limits, if the race gains too complete a mastery of its environment, it ceases to advance; below these limits the struggle is conducted at a loss—the race becomes enfeebled. So, also, it is in general to be observed that as growth becomes more active, the virulence increases, although as between any two species, or even between two distinct strains of the same species, relative luxuriance of growth is not by any means an absolute criterion of relative virulence.

It is needless to say that in connection with this subject of virulence—as with all others—there is much regarding which we are still ignorant.

We cannot isolate the toxins and study their effects as pure chemical substances; we do not know, and can only infer, their nature. What is more, we are still at a loss to account for the mode of action in setting up infection of the two great groups of pathogenic organisms, namely, those which characteristically discharge extracellular toxins, so that the medium of growth becomes highly toxic, and those, on the other hand, which (grown outside the body, at least) produce inconsiderable amounts of diffusible toxins. Of the former group we have such organisms as those of diphtheria and tetanus, and that of blue pus (B. pyocyaneus); of the latter, the bacillus of typhoid, the B. coli, the anthrax, and tubercle bacilli. It seems evident, in the first place, that if outside the body they produce nothing which we can recognize as toxins, inside the body they discharge or afford something which affects the cells in their neighborhood, for, introduce attenuated anthrax bacilli into the tissues, and the leukocytes rapidly attack them; whereas, virulent anthrax bacilli introduced similarly are left severely alone. The same is true as regards colon bacilli inoculated into the peritoneal cavity; whether they are taken up and destroyed, or not, depends upon their virulence. This group of organisms does not become pathogenic because its members are apparently innocent and inert and gain a footing in the tissues without irritating the cells and simulating them to employ their protective mechanisms. There may be something in this; the unsuspecting scavenger in the mouth or intestines may take up an apparently innocent tubercle bacillus and convey it into the lymph gland, only to discover too late that it has swallowed more than it can digest; but, over and above this, we have to gain more knowledge of the exact nature of the products discharged by the group of bacteria while in active growth before we can feel that we have a satisfactory knowledge of what is the nature of virulence.[1]

Before we leave the subject it is necessary to say a word regarding a matter to which we have more than once referred, namely, the numerical relationship of bacteria to infection. With the possible exception of microbes, which, like the streptococcus already mentioned, have undergone by experimental means an extraordinary increase in virulence, it appears well established that in the individual mammal in normal health a single microörganism cannot cause disease. Even where the vitality is lowered, it probably requires several in close proximity in order to produce so much discharge that the antibacterial substances of the enclosing or surrounding cells become neutralized. We have noted, for instance, Wyssokowicz's observations (p. 184) upon the minimal number of tubercle bacilli which will set up infection. If this be so, it is obvious that the number of bacteria gaining entry to one area at one time is a factor in the setting up of disease. A large number of bacilli of low virulence will as surely cause infection as will a few of exalted virulence. The number entering is very clearly a factor. Your physician—happily of the old days, for

[1] Some light is thrown upon these matters by the recent studies upon the aggressins. (See Section III Chapter VIII.)

such unwise heroism is not called for now—who may have gone through an epidemic of diphtheria, and in so doing must time and again have breathed in the bacilli of the disease without taking the disease, succumbed surely when, sucking the tracheal tube of the little suffocating patient, in order to clear the passages, he introduced a mass of the microörganisms into his own throat.

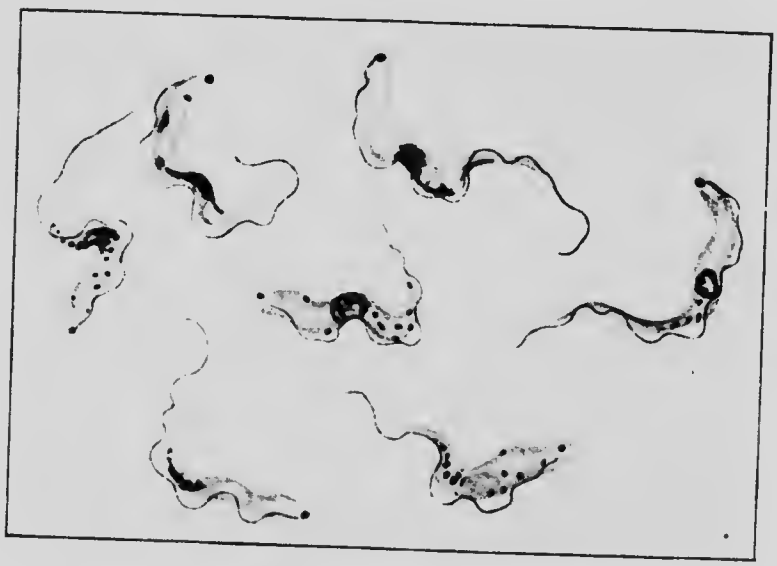
It is well to keep in mind this influence of numbers in attempting to correlate experimental results with the natural course of infectious disease. In the laboratory, that is, we are accustomed to produce disease by the employment of immediate injections of millions of bacteria. It must be remembered that in nature there is rarely any such immediate overwhelming of the tissues. We may thus, at times, obtain positive results with microbes which under natural conditions would be relatively innocuous for the species under observation.

CHAPTER IX.

PROTOZOAN PARASITES AS CAUSES OF DISEASE.

As already noted, active interest has been aroused within the last few years in sundry microbic unicellular forms of animal life as causes of disease, and at the present time scarce a month passes without some investigator announcing the discovery of a new form of protozoan parasite in one or other animal—at times apparently harmless, at times clearly associated with the appearance of definite symptoms of disease.

FIG. 111

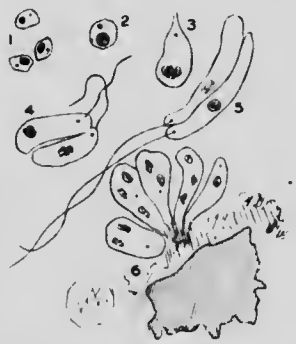


Trypanosomes (T. gambiense) from the blood in sleeping sickness. (× 2000.)

The study is relatively so new and incomplete that it may be the time is not ripe for the broadest generalizations regarding the mode of action of these protozoa as pathological agents. One is tempted, that is, from a study of forms which have been very fully worked out, such as the hematozoon malariæ, to see a broad distinction between the bacteria and these animal forms in the possession by the latter of an amœboid stage, during which the microbes can actively attack the cells of the organism, and in a large number of instances can penetrate and grow within

these cells, that intracellular growth being a definite stage in the life cycle. But with other forms, such as the trypanosomes, we see no local direct action on particular orders of cells, nor are we as yet surely acquainted with the intracellular stage—although the studies of Rogers and other Indian observers upon kala-azar show that the Leishman-Donovan body is an intracellular form of a trypanosome. We do but recognize these forms moving freely in the body fluids. All that can be stated is that at the present time we see obscurely a difference between the nature of the diseases caused by these protozoan parasites and those set up by the vegetable bacteria, in that the latter give origin to powerful toxic bodies having a widespread action, whereas, while we have some evidence, and that definite, of the existence of toxins produced by the protozoan parasites, these would seem to be of a lower order of toxicity, so low that hitherto in most cases it has been impossible to recognize the development of antitoxins and passive immunity by experimental methods. But, if Guarnieri and Councilman[1] be correct in their views regarding the protozoan causation of smallpox and vaccinia, and Mallory, in his regarding scarlet fever, then this distinction must be given up, for the acute exanthemata are clinically the type examples of infections—of diffuse disturbance of all the tissues set up by toxins, resulting either in death or the production of well-marked immunity.

Fig. 112



Development of organism of Kala-azar in citrated spleen blood (Rogers' method); 1, Leishman-Donovan body in fresh spleen blood; 2, after three days' culture; 3, fifth day; 4, sixth day; 5, elongated flagellated forms, sixth day; 6, group apparently developing from intracellular forms, with remains of cell. (After Christophers.)

Under these conditions, the most we can do is to pass in review the different orders of protozoa that have been found causing disease, briefly noting the main features of their growth and distribution in the body. These have been found belonging to all the main orders of protozoa—the sarcodiniæ, or rhizopoda, the mastigophora, or flagellata, the sporozoa, and the ciliate infusoria.

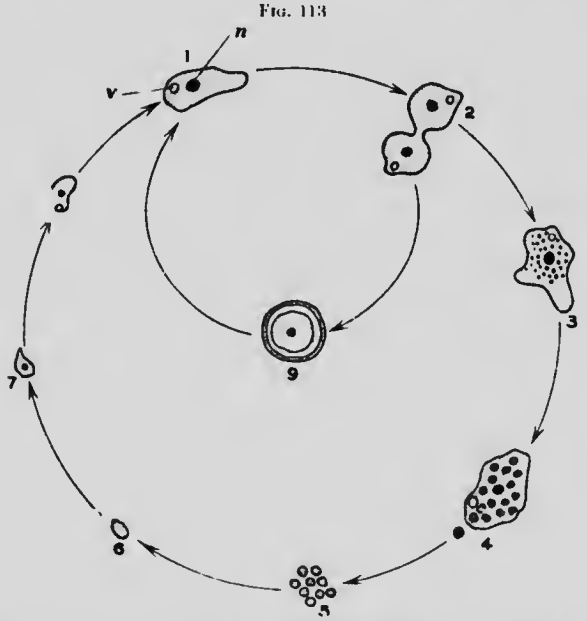
Sarcodiniæ.—Of these the type example is the amœba (or *entamœba*) of dysentery. This exists in a free state in water, and would seem to be capable of multiplying in the colon; it either attacks or passes through the mucous membrane to the submucosa, where it may be found in great numbers, containing ingested erythrocytes and cell debris, *i. e.*, it lives upon and ingests the cells of the part, setting up marked inflammatory swelling, ulceration, and necrosis. A later seat of election may be the liver, in which necrotic abscesses may be set up,

[1] See the series of articles by Councilman and his associates, Jour. of Med. Research, N. S., 6:1904:1.

the amœba being present in abundance in the tissue of the boundary zone of the abscess. Occasional rounded encysted amœbæ are to be made out more particularly in the walls of the colon. Whether the spores developed from these cysts developing into minute amœbæ remain throughout extracellular or exhibit an intracellular stage has not been determined.

It will be seen, therefore, that the indications are that these pathogenic amœbæ live within the organism by attacking and digesting the cells and cell substance. Their action is essentially local, and whether the remote effects seen in dysentery are to be regarded as, in part at

FIG. 113



Schematic life cycle of the *Amaba coli*: 1, the adult amœba with nucleus (*n*) and contractile vacuole (*v*); 2, the same, multiplying by amitotic division; 3, appearance of chromidial granules in cytoplasm, which enlarge and become the spores (*sp.*) in 4; these spores become discharged or liberated (5) and develop (6, 7, 8) into the adult amœba, or (9) under other conditions the amœba passes into an encysted stage. (After E. L. Walker.)

least, due to the effusion of any toxic substances discharged by the amœbæ themselves, or wholly to the products of cell destruction along with the secondary infection of the ulcers in the colon, has not as yet been fully determined.[1]

Mastigophora.—Of these, the trypanosomes may be taken as a type. These form a widely spread class of pathogenic protozoa, numerous species being found as blood parasites in vertebrates, both

[1] An admirable study of the amœbæ parasite in animals has recently been published by Walker, of Boston, Jour. of Med. Research, 17; 1908; 379.

cold and warm blooded, from the fish and frog upward to man himself. The forms most fully studied have been the *Trypanosoma evansii*, causing a disease of horses in Assam, India, and the Philippine Islands, known as surra (Evans, 1880); the *Trypanosoma brucei*, the cause of the n'gana, or tsetse fly disease, affecting horses and cattle in Southeast Africa (Bruce, 1894); the allied form associated with dourine, or mal de coit, in Algeria and Southern Europe, as also recently through importation in the United States and Canada (Rouget, 1896); and with mal de caderas of South America, also affecting horses (Elmassian, 1901). It has recently been fully established that another trypanosome, the *Trypanosoma gambiense*, is the causal agent in the remarkable disease, sleeping sickness, which is spreading rapidly in Western and Central Africa, so rapidly that it is calculated that no less than half a million natives have died from the disease during the last ten years (Dutton and Ford, 1902; Castellani, 1903). Rogers and others have demonstrated that the minute Donovan-Leishman bodies found in the enlarged spleen in the Indian disease of man known as kala-azar, or dum-dum fever, are one stage in the life cycle of another trypanosome; and of the same order are the similar bodies found abundantly in the intractable Oriental sores which go by various names in various regions—Delhi boil, Aleppo button, etc. (Wright, 1903).

Without entering into the full details, for these belong to works devoted to the animal microparasites, it may be recalled that these minute organisms found in active motion in the removed blood possess an elongated, spindle-shaped body, with undulating membrane along one side, whose outer differentiated border, beginning within the head end of the organisms as an offset from a remarkable refractile granule, spoken of variously as centrosome or micronucleus, continues beyond the body as a flagellum. (See Fig. 111.) There is a nucleus; at times a contractile vacuole may be made out. The length may be as much as 30 mikrons, or, in the largest forms, the *T. theileri* of cattle, 50 mikrons; the breadth from 2 to 3 mikrons. Multiplication is by a process of longitudinal fission, in which, in some cases, the nucleus, in others the micronucleus, first undergoes division.

This simple fission is, so far, the only mode of multiplication known; no sexual cycle has been made out, even though the organisms are transmitted through alternate hosts. It is this form also that alone is seen when, as first determined by Novy, the trypanosomes are grown upon the media of the laboratory. In this they differ from the forms presently to be noted. Nor among the blood trypanosomes of typical form has any intracellular stage been determined. Nevertheless, other facts make it doubtful whether we have determined all the stages in the life cycle of trypanosomes. I refer more particularly to the facts determined regarding the curious organism of Indian febrile splenomegaly—kala-azar, or dum-dum fever. Here the only form or organism to be made out in the patient is minute and intracellular, within large endothelial cells of the splenic pulp. It might be urged that, as Leishman first suggested, these are trypanosomes that have undergone degenera-

tion owing to phagocytosis. But curiously similar bodies are made out in a free state in the blood of animals suffering from trypanosomiasis given atoxyl and other drugs that cause a rapid disappearance of the trypanosomes, and against this view is also the singular uniformity of the appearance of the bodies and their great abundance as contrasted with the fact that the numerous observers of kala-azar have not so far detected a single free characteristic trypanosome in the blood; while Rogers has been able to develop from these forms small but undoubted trypanosomes (Fig. 112). We deal, therefore, with a trypanosome in its intracellular phase. This view is supported by Schaudinn's study of the life history of the *Halteridium* of the owl, a parasite of the red corpuscles, which likewise he made out to possess a free trypanosome form in the fluid of the blood, becoming modified into a more amœboid, non-flagellate form within the corpuscles. It has been suggested that

Fig. 11

Piroplasma in red corpuscles of cattle suffering from Texas fever. (Smith and Kilborne.)

Fig. 115

Glossina palpalis ($\times 3\frac{1}{2}$), the carrier of the trypanosome of sleeping sickness

the *Piroplasma* or intracellular parasite of Texas fever in cattle has like relationships.

The striking feature of all this group as disease producers is that they are conveyed to man and warm-blooded animals by the bites of

insects. Specific insects act as intermediate hosts. In n'gana it is the tsetse fly (Glossina morsitans); in sleeping sickness, a closely allied fly, the Glossina palpalis. These act as intermediate hosts, the trypanosomes, sucked into the stomachs, gaining entrance thence into the tissues of the fly and being discharged with the fluid lubricating the mouth parts—thus gaining entrance into the body of a larger animal when that is bitten by the fly.

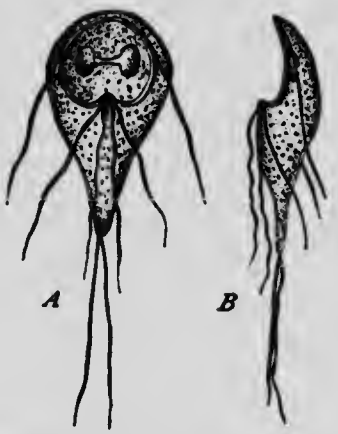
Neither fresh blood, nor warmed, nor organic extracts, nor bile from affected animals have the slightest toxic effect, nor by centrifugalized material, consisting almost wholly of trypanosomes, acted on by alternate freezing and thawing, nor by drying, could Laveran and Mesnil gain any indication of the presence of toxins.

The symptoms produced by trypanosomes are, as a class, essentially those of blood and circulatory disturbances—anemia, with a mild grade of fever; anasarca and ascites, depression of cerebral activity, and coma. The indications are that,

Fig. 116

Trichomonas vaginalis.

Fig. 117



Megastoma enterieum, Grassi, ventral and side views. (Schewiakoff.)

by the very abundance of these parasites in the blood, and their tendency to become agglutinated under certain conditions, they are apt to accumulate in and block capillaries of the brain and other organs, a phenomenon not encountered with the more minute bacteria, save as the result of local proliferation.

Other flagellate infusoria—the *Trichomonas* and *Megastoma* (Lamblia) intestinalis[1]—have been rarely encountered in the intestinal discharges; most often in association with conditions of chronic diarrhœa. Whether they have any causal relationship to the diarrhœa is still a matter of debate.

Sporozoa.—The importance of this group of animal parasites as causes of disease in man may be estimated from the fact that in tropical and subtropical regions one disease of sporozoal origin—ague or malaria—occupies the position assumed by tuberculosis in the temperate zone. It has, indeed, been claimed that this disease brings about an even greater mortality.

[1] The Cercomonas intestinalis used to be regarded as a separate form; Doflein regards it as identical with the Lamblia.

All the organisms of this group are characteristically intracellular in their habits. In other words, the primary disturbance set up by them is that of cell parasitism, the microbes growing within and at the expense of individual cells, arresting the infunction and eventually leading to cell death—the cycle of the life history of the parasites being such that the maturation and spore formation of the intracellular individual coincides roughly with the exhaustion and death of the host cell. The spores, becoming free after a longer or shorter period of incubation, develop into minute amœboid forms, which penetrate other cells and repeat this process of asexual multiplication. This asexual cycle of forms may be repeated again and again. But now, in very many of these sporozoa, it has been determined that a second, sexual, cycle may be intercalated under certain conditions, more particularly (though not in every case) in connection with the transmission of the parasite from host to host, this second cycle being apt to occur in an intermediate host of another species. In ague, for example, the hematozoon malariæ exhibits the asexual cycle in the blood of man, the sexual cycle within the mosquito (various species of anopheles), which, by feeding on human blood, acts as a transmitter of the disease to a second individual, when the sporozoites, the products of the sexual cycle, are introduced into a surface vessel of that individual along with the proboscis of the mosquito. It would seem, thus, that a large number of the sporozoa gain entrance into the systems of animals and are transmitted from individual through the intermediation of biting and sucking insects. Not all, however; others, like the coccidiæ, gain entrance through the digestive tract, and others—if Councilman and Calkins be right regarding smallpox as due to a minute intracellular sporozoon (which is still doubtful)—apparently through the respiratory system.

Several suborders of the sporozoa contribute parasites to man and the higher warm-blooded animals. These we will rapidly note, calling particular attention to those data which throw light upon the mode of causation of disease.

Hematosporidia.—Of these, the type example is the hematozoon malariæ. Other allied forms infesting the red corpuscles are met with in the blood of birds and other animals, and the study of these has elucidated the life history of the malarial parasite. Thus it was W. G. MacCallum's discovery of the process of conjugation between the forms present in the blood of Canadian crows that afforded the clue to the nature of the "flagellate" bodies of the malarial organisms. (See Plate X, 8, Fig. 1, 9, Fig. 2, etc.) Some of these, like the halteridium of the owl, have been shown by Schaudinn to possess close affinities to the trypanosomes rather than to the sporozoa, or otherwise it may be suggested that the trypanosomes and sporozoa are closely allied. There is, however, increasing doubt regarding this observation of Schaudinn's. The main points to be noted regarding the hematozoon in relationship to ague are:

1. The disease, being transmitted by particular species of mosquito, the anopheles, is only endemic where members of these species are present

PLATE X.

Fig. 1.—Tertian Malarial Plasmodium.

1. Hyaline form.
2. Pigmented ring form.
3 to 6. Pigmented forms.
7. Segmenting forms.
8. Flagellate form. (Microgametocyte.)
9. Non-flagellate form. (Macrogamete.)
10. Segmenting form after destruction of red corpuscle.

Fig. 2.—Quartan Malarial Plasmodium.

1. Hyaline forms.
2 to 5. Pigmented forms.
6 and 7. Segmenting forms.
8. Segmenting forms after the destruction of red corpuscle.
9. Flagellate form. (Microgametocyte.)
10. Non-flagellate form. (Macrogamete.)

Fig. 3.—Tertian Æstivo-autumnal Malarial Plasmodium.

1 and 4. Hyaline ring form.
2, 3 and 7. Pigmented ring form.
5 and 6. Pigmented forms.
8. Young intracorpuscular crescent.
9. Segmenting forms.
10. Flagellate form. (Microgametocyte.)
11 to 14. Crescentic forms.

Fig. 4.—Quotidian Æstivo-autumnal Malarial Plasmodium.

1 to 4. Hyaline ring forms. Some cells show infection with more than one organism.
5 to 7. Pigmented forms. In 6 one hyaline form.
8. Segmenting forms. Segmentation complete within infected red blood corpuscle.
9. Flagellate form. (Microgametocyte.)
10, 11, 13 and 15. Crescentic forms.
12. Ovoid form.
14. Non-flagellate forms. (Macrogamete.)

NOTE.—Mark the larger size and greater amount of pigment in the tertian æstivo-autumnal plasmodium.

PLATE X

Fig. 1

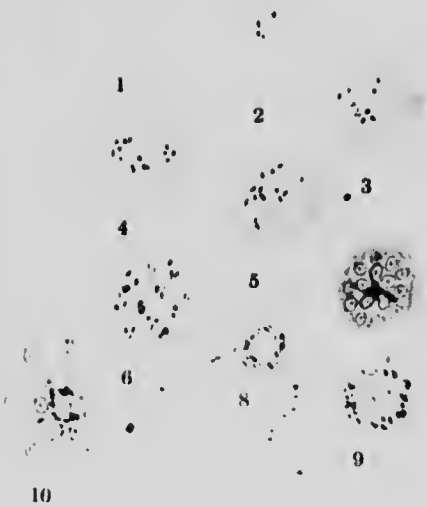


Fig. 2

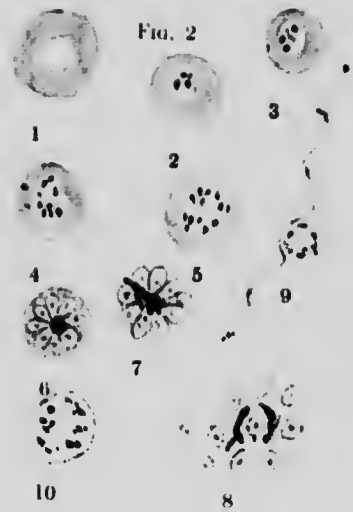


Fig. 3

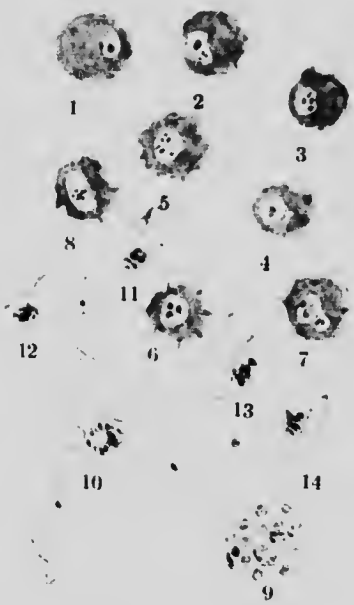
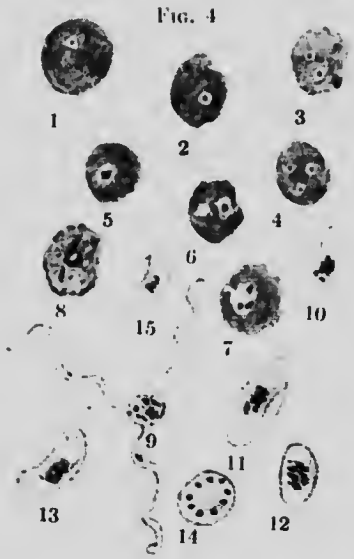


Fig. 4

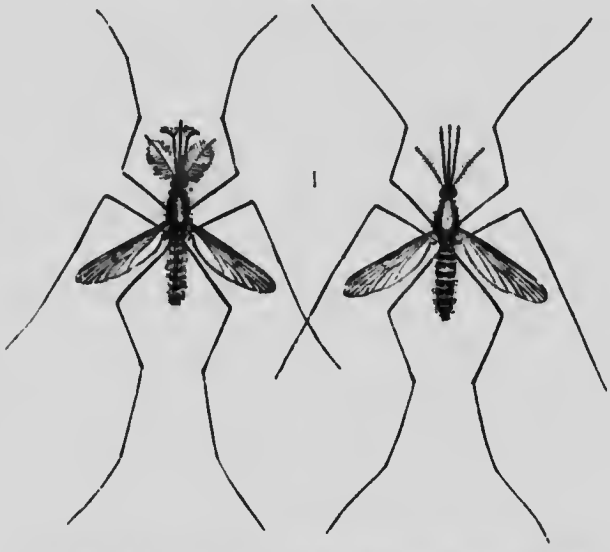


2. The anopheles, like all mosquitoes, lay their eggs in relatively still water, and the larvæ are aquatic. Save under the influence of strong winds, the mosquitoes do not travel any distance from their place of birth and from water. Malaria, therefore, is largely confined to low-lying, swampy, or badly drained regions and the neighborhood of stagnant water.

3. The anopheles bite at night, not during the day; infection, therefore, occurs at night. It may be single or multiple, on different nights.

4. For its development the asexual cycle requires different periods in the different species of hematozoon—forty-eight hours for the organism of tertian fever; seventy-two for that of quartan; forty-eight hours (with irregular variations) for that of the estivo-autumnal type. The

FIG. 118



Anopheles maculipennis; adult male at left, female at right. (Howard.)

periodic attacks of ague are directly determined by these cycles, the chills and fever coinciding with the maturation of the hematozoa and their sporulation. Presumably, it is the breaking down of the corpuscles and liberation of the cell debris and pigment matter rather than any specific toxin (for this has not been determined) that is the cause of the febrile attacks.

5. The clusters of pigment and cell debris are apt to be separated from the blood in the spleen, there setting up those changes which lead to the enlargement of that organ. They may also accumulate in the capillaries of the brain, of the kidney (Ewing), and other organs, setting up disturbances by arrest of the circulation.

6. The observations of Calkins on prolonged asexual multiplication

of protozoa show that this leads to progressive weakening and degeneration of the later generations. Where, therefore, the affected individual removes himself to a region where he cannot be re-infected, it would seem that there is a natural tendency for the malarial organisms to become weaker and weaker, and so for his disease to pass off. Apart from this probability, there is evidence that more particularly young children (Koch) are relatively resistant to the disease, and despite repeated re-infection, gain immunity—*i. e.*, the power of destroying the hematozoa—while in adults improvement in general health, brought about by removal to another climate, etc., would seem to favor the destruction of the hematozoa. This notwithstanding it is evident that, as with many bacteria, certain of the parasites may for long periods lead a latent existence within the body, and after the expiration of months and years take on active growth with the development of new crises of the disease. (*a*) The other members of the sporozoa, while abundantly parasitic and pathogenic in worms, insects, and the lower forms of animal life, are rarely encountered in the higher animals, still more rarely in man. (*b*) The gregarines, for example, are not found in vertebrate forms; (*c*) the neosporidia (including the myxosporidia and the sarcosporidia), while occurring among vertebrates—the former common in fishes, the latter giving origin to Rainey's corpuscles within the muscle fibers of mammals—are almost unknown in man. (*d*) Of the coccidia, one form, the Coccidium oviforme, most common in the rabbit, where it affects more especially the upper part of the small intestine and the liver, has been encountered not half a dozen times in man. As determined by Schaudinn and Siedlecki and Simond, the coccidium and other members of the order exhibit, like the hemosporidia, a sexual and an asexual cycle, though these occur on the one host.

Fig. 119

A, a "Rainey's corpuscle" or colony of sarcosporidia lying between the muscle fibers; *B*, the individual sarcosporidia (sarcoblasts) composing the same. (Perls.)

Forms which curiously resemble certain stages in the sporozoan life cycles have been encountered by Pfeiffer, Guarnieri, and Councilman in the epithelial cells of the vaccinia and smallpox eruption. In the former Councilman and his associates determine out a single intracellular cycle; in the latter they found a second intranuclear cycle. Mallory, likewise, has described a remarkable stellate or rayed intracellular form in the epithelial cells in cases of scarlatina, recalling the

EXPLANATION OF FIGURES IN PLATE XI

Various Stages of Mallory's Intracellular Parasite in the Epithelial Cells in Scarlatina. (Mallory.)

The drawings were made with the Abbe camera lucida; projection on to table. Zeiss apochromatic homogeneous immersion 2.0 mm., apert. 130, compensation ocular 6.

Figs. 1 and 2 show numerous large and small scarlet-fever bodies (stained light blue) in and between the epithelial cells of the rete mucosum. In Fig. 1 is a large body in a lymph space of the corium just underneath the epidermis. Several of the bodies suggest fixation while in amœboid motion.

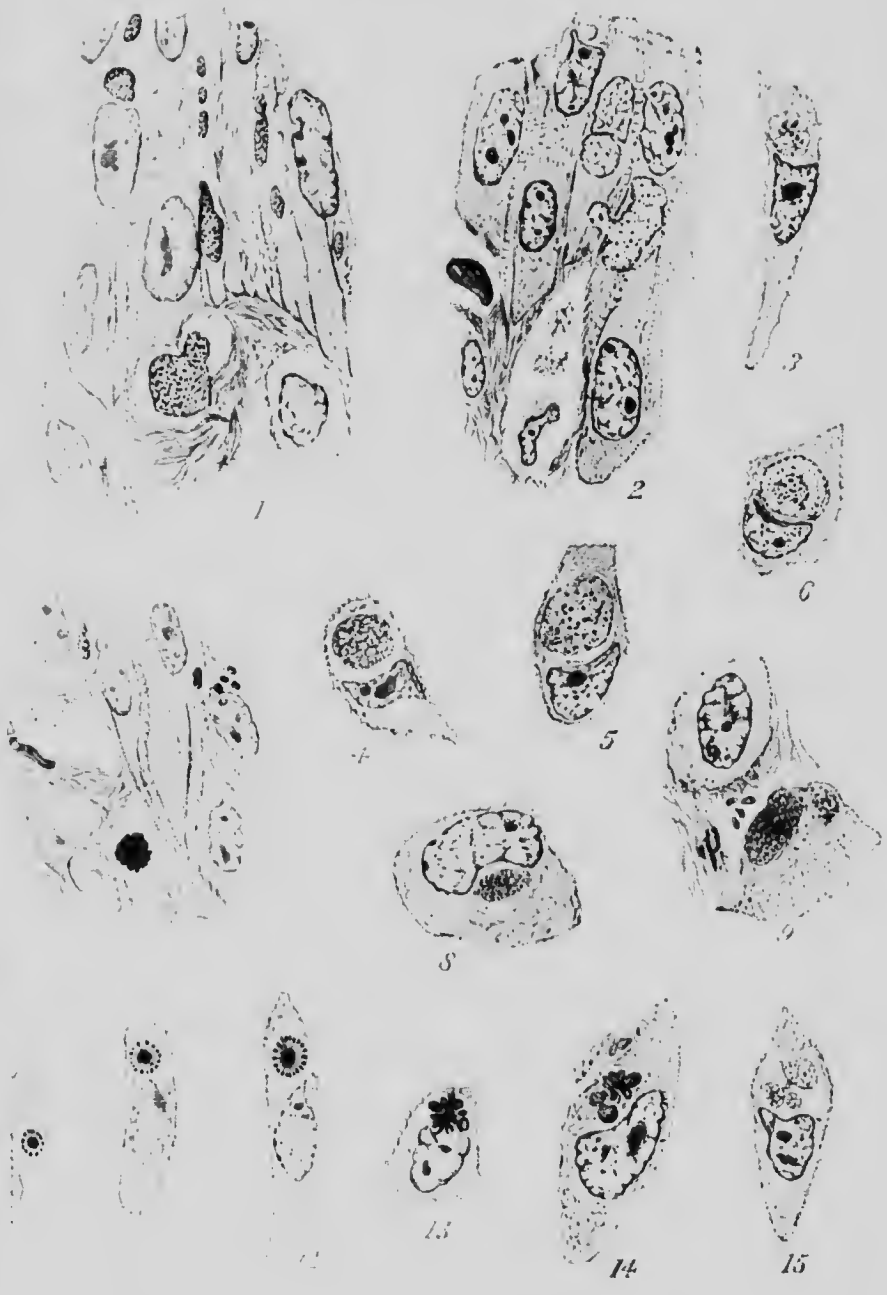
Figs. 3, 5, and 6 are coarsely reticulated forms which may be degenerate forms of the scarlet-fever bodies, or stages in sporogony.

Figs. 4, 8, and 9 probably represent stages preceding the radiate bodies. In Fig. 9 the bodies lie in a lymph space. It shows also four small forms which have just got free from a rosette.

Figs. 7, 10, 11, 12, 13, 14, and 15 show different stages in the development of the radiate bodies.

Fig. 10 is the earliest stage: there is a distinct central body and a definite, regular arrangement of granules at the periphery. Figs. 7, 11, and 12 show a little later stage of development; 11 and 12 are optical sections, while 7 is a surface view. Moreover, in Fig. 7 the body lies free in a lymph space in the corium. The segments begin to show a certain amount of lateral separation from each other. Fig. 13 is a still later stage: the segments are increasing in size and are more or less free from each other, although most of them are still attached to the central body. In Fig. 14 the segments are all free and enlarging, although still grouped around the central body. In Fig. 15 the bodies are still grouped around the central body, which is free and stains deeply with eosin. (Mallory.)

PLATE XI



daisy form assumed by the quartan malarial organism in the process of sporulation and others employing his method have confirmed his findings. The meaning of these forms is still *sub judice*.

During the last decade of the nineteenth century it was held by numerous observers (Sjöbring, Ruffer, Metchnikoff, Soudakewitch, Plimmer, etc.) that bodies seen within the cells of malignant growths—more especially of cancers—were of the nature of sporozoa. That

FIG. 120

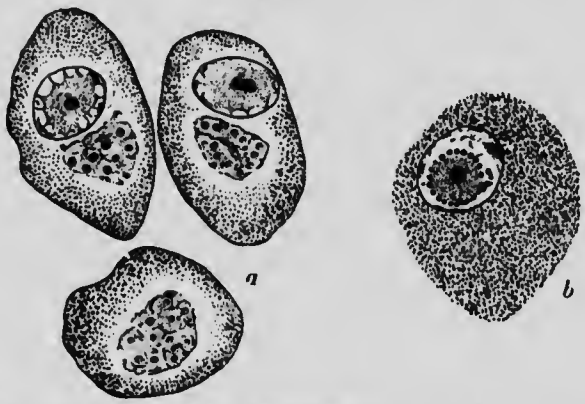
Life cycle of Coccidium schubergi. Sporozoites penetrate epithelial cells, and grow into adult intracellular parasites (*a*). When mature, the nucleus divides repeatedly (*b*); and each of its subdivisions becomes the nucleus of a merozoite (*c*). These enter new epithelial cells, and the cycle is repeated many times. After five or six days of incubation, the merozoites develop into sexually differentiated gametes; some are large and well stored with yolk material (*d*, *e*, *f*); others have nuclei which fragment into many small particles ("Chromidia"), each granule becoming the nucleus of a microgamete or male cell (*d*, *h*, *i*, *j*). The microgamete is fertilized by one microgamete (*g*), and the copula immediately secretes a fertilization membrane which hardens into a cyst. The cleavage nucleus divides twice, and each of the four daughter-nuclei forms a sporoblast (*k*) in which two sporozoites are produced (*l*). (After Schaudinn.)

such is their nature is now generally denied. While certain remarkable bodies are to be observed with fair frequency, sometimes in great abundance, the general opinion nowadays is that these are modified cell and nuclear products, and that they indicate peculiar forms of cell degeneration.

Ciliate Infusoria.—These, the most highly specialized of the protozoa, are the least frequent of all the protozoon parasites. One form

alone has been recorded—apparently with some justification—as possessing pathogenic properties, and this is not found within the tissues, but free in the alimentary canal. This is the *Balantidium coli*, a form not unlike the common paramœcium of pond water, but more oval, and

FIG. 121



a, Guarnieri's bodies in the cytoplasm of epithelial cells in vaccinia (and smallpox); *b*, one stage of the presumed intranuclear cycle of these bodies in the epithelial cells in smallpox. (After Calkins.)

with the oral aperture more definitely at the one pole, the anus at the other; it is abundantly ciliated; this is said to be a normal parasite in the hog. Like the amœba coli, it is supposed to gain entrance into man through contaminated water. It has been found associated with

FIG. 122

Balantidium coli.

extensive catarrhal inflammations of the colon, with dysenteric symptoms. Observers have described a second species, the *Balantidium minutum*, of smaller size, found in association with other intestinal parasites.

Of the most highly differentiated suborder of the infusoria, the Suctoria, no parasitic examples are known in or upon the higher animals.

CHAPTER X.

METAZOAN PARASITES AS CAUSES OF DISEASE.

THE members of a limited number of classes of metazoan or multicellular animal organisms have adapted themselves to growth within the organisms, and, in certain cases, even within the tissues of other higher metazoa. Here I shall not attempt to describe these forms; such descriptions belong properly to works upon parasitology. At most it is necessary to note rapidly the classes capable of this parasitic existence. These are confined to members of the phyla, or groups *Platyhelminthes* and *Nemathelminthes* and rarer members of the *Insecta* and *Arachnidæ*. Among the platyhelminthes, or flat-worms, we encounter members of the *Trematodes*, or flukes, and the *Cestodes*, or tape-worms. The *Nematodes* are the chief representatives of the nemathelminthes, or round-worms.

CHARACTERISTICS OF METAZOAN PARASITES IN GENERAL

Without exception, it may be stated that adaptation to a parasitic existence has been accompanied by simplification and retrogression. Forms that have not to hunt for their food, but receive it in a soluble, assimilable state, prepared by their host; that, further, are largely protected from the effects of external influences by their very mode of life, do not need elaborate organs of locomotion or an elaborate digestive apparatus; do not need organs of protection and defence beyond the means of neutralizing the digestive influence of the juices of their host. Nor do they need weapons of offence beyond those necessary to attach themselves to that host and penetrate its tissues in such a way as to gain therefrom the requisite pabulum. Thus, the organisms of these parasites are apt to become reduced to very simple terms; limbs and organs of locomotion may become rudimentary, sense organs atrophied, and, as in the cestodes, or tape-worms, the alimentary tract may wholly disappear, nourishment being gained purely by surface absorption. The prime necessity is the retention of life of the individual and preservation of the species, so that means have been developed to neutralize the harmful consequences of the host being but mortal and liable to die. Either the parasites are capable of existing for considerable periods outside the body of the host until fortuitously taken up by another, or are capable of living in different forms in a succession of different hosts, or lastly, and most commonly, have enormous reproductive capacity, becoming little more than animated masses of sexual glands, enormous

quantities of ova being produced and discharged, in preparation for the probability that, with rare exceptions, these will fall upon barren ground. More accurately, so precarious is this method of handing on the torch of life that only those species possessing an enormous reproductive capacity can possibly survive. For this retrogression and simplification of structure inevitably carries with it a lessened capacity on the part of the individual to adapt itself to other than a very narrow set of conditions; it has reduced its methods of offence and defence to a minimum, and thus we find, as a general rule, that a given species can only grow actively in a particular species of host, or, when there is alternation of forms, in a particular series of hosts. Or, conversely, each species of animal has its particular set of parasites, which differs from that of other species. At most, certain species of parasites may pass a particular stage of existence in closely allied species of hosts.

How, it may be asked, do these metazoan parasites cause disease?[1] It must be noted, in the first place, that on general principles we should not expect such parasites to set up severe disease. With forms that require a considerable period for the development of their life cycle, forms in which, further, as we have noted, the survival of the species by means of passage into other hosts is precarious, it would be a suicidal policy so to injure the host as to lessen its capacity to obtain nourishment, or to arrest its power of locomotion, and, indirectly, its opportunity to distribute the eggs of the parasite. And, as a matter of fact, we find that these larger parasites tend rather toward symbiosis—to harmonious living together, with minimal disturbance to the host—than toward the production of states of severe disease. Nevertheless, the symbiosis is in no sense voluntary on the part of the host, nor have we any indication that the presence of parasites is an advantage to that [illegible] We no longer hold, as did Jordens, in 1801, that intestinal worms are "the good angels and unfailing helpers of children." The indications are to the contrary. If, in general, the disturbance set up is slight, it is nevertheless there, and we have indications of definite reactive processes on the part of the host. The injury set up and the evidences of disturbance are of five orders:

1. That of actual presence in some organ, leading to displacement and pressure.

2. Disturbance due to migration of the parasites from one organ of the host to another.

3. Direct destruction of tissues.

4. Loss of foodstuffs diverted by the parasite and used up by it.

5. Disturbances induced by the excretions of the parasites.

These we may pass rapidly in review:

Injury Caused by the Mere Presence of the Parasite.—This, in general, is *nil*. There are, however, exceptions. A *Filaria nocturna*

[1] For the arrangement of the following paragraphs and the data therein contained we are largely indebted to a valuable summary of the subject by Messrs. Shipley and Fearnsides, Journal of Economic Biology, 1·1906: No. 2.

PLATE XII

The Kidney Worm, Dioctophyme Renale (Eustrongylus Gigas) of Man, from a Specimen in a Dog. Natural size. (Stiles.)

in a lymph vessel or gland may set up little disturbance, but if it, or its eggs, blocks the vessel, elephantiasis or chyluria may ensue. *A Cysticercus cellulosæ* in the muscle is without obvious effects; in the brain, by pressure upon important nerve centres, it may cause fatal results, and in the eye may lead to blindness. In this respect

FIG. 123

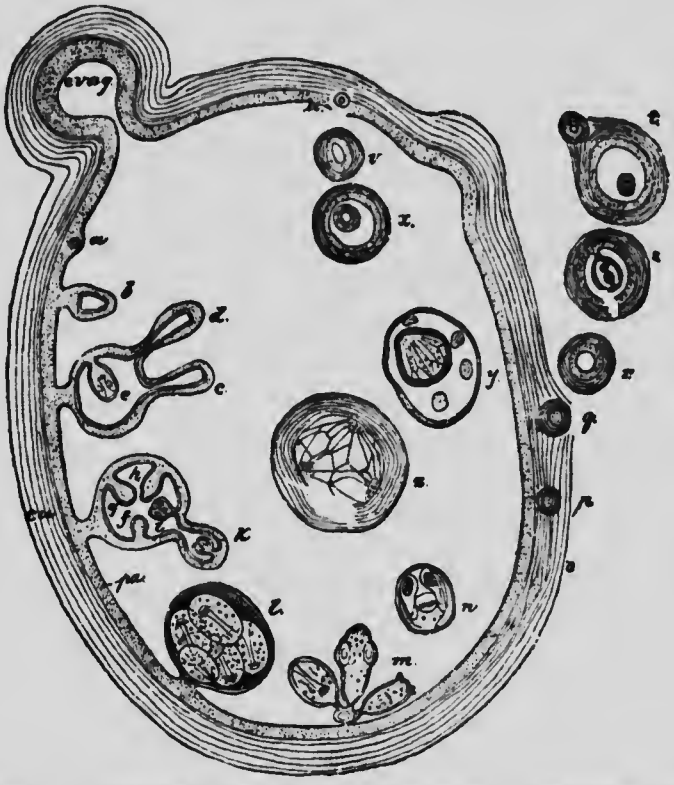


Diagram of an Echinococcus hydatid: *cu*, thick external enticle; *pa*, parenchymal (germinal) layer; *c*, *d*, *e*, development of the heads according to Leuckart; *f*, *g*, *h*, *i*, *k*, development of the heads according to Monez; *l*, fully developed brood capsule with heads; *m*, the brood capsule has ruptured, and the heads hang in the lumen of the hydatid; *n*, liberated head floating in the hydatid; *o*, *p*, *q*, *r*, *s*, mode of formation of secondary exogenous daughter-cyst; *t*, daughter-cyst, with one endogenous and one exogenous granddaughter-cyst; *u*, *v*, *x*, formation of exogenous cyst (after Kuhn and Davaine); *y*, *z*, formation of endogenous daughter-cysts (after Naunyn and Leuckart); *y*, at the expense of a head; *z*, from a brood capsule; *evag*, constricted portion of the mother-cyst. (R. Blanchard, slightly modified.)

the larval form of the *Tænia echinococcus* is the most dangerous human parasite, the size attained by the cysts in the liver and elsewhere being so considerable. In the dog, the *Eustrongylus gigas* (or Dioctophyme renale), growing slowly and attaining great size, may eventually, by pressure atrophy, replace the whole of the kidney substance.

Injury Caused by Migration.—This, again, may be infinitesimal. The minute larvæ of *Filaria nocturna* make a nightly migration from the deep-seated bloodvessels of the internal organs to the peripheral vessels without causing disturbance. The *Filaria medinensis*, the longest of the roundworms in man, may, without symptoms, make its way through the tissues of the body until it comes to lie under the skin of the leg, and then only sets up disturbance when it pierces the skin to allow escape of its ova, or if, in this situation, it becomes ruptured. The disturbance may, on the contrary, be very marked; most severe are the fever, myositis, and muscular pain, set up by the migrating *Trichina* larvæ prior to encystment. A common cause of irritation and itching is the nocturnal passage outward at the anus of the *Oxyuris vermicularis* (Fig. 125). The observations of Looss and others of late years upon the life histories of the *Ankylostoma duodenale* and the *Strongyloides intestinalis* have demonstrated that the larvæ hatched from the eggs in water or moist earth gain entrance into the human host through the skin, where they set up a dermatitis, known by diverse names in different localities—"ground itch," "coolie itch," etc.

Fig. 124

Larva of Filaria bancrofti in the blood of man, in Egypt; *Nerv.*, nervous system; *Ex.*, excretory; *An.*, anus. × 511 (Looss.)

Injury Set Up by Active Destruction of Tissue.—According to Looss,[1] the ankylostomes feed upon the mucous membrane of

Fig. 125

Fig. 126

Fig. 127

Fig. 125.—Oxyuris vermicularis, the pin-worm, natural size; male smaller, female larger form with sharply pointed tail.

Fig. 126.—Ankylostoma duodenale, the old world hook-worm, natural size; the female is the larger and more curved.

Fig. 127.—Trichocephalus trichiurus, the whip-worm, natural size, male and female.

[1] Reports of the Egyptian Government School of Medicine, 3: 1905.

the small intestines, and only suck in blood when by chance they pierce an underlying capillary. It may be, and has been, questioned whether the anæmia of ankylostomiasis is not a secondary result of this erosion—not from loss of blood, but from absorption through the damaged mucosa of toxic intestinal contents, if not from increased passage into the tissues of intestinal bacteria and the production of a state of sub-infection (p. 290). A similar and more severe anæmia is set up by another parasite, the *Dibothriocephalus latus*, which attaches itself to the intestinal wall and in so doing injures the mucous membrane. We shall refer shortly to another view regarding the mode by which these parasites induce anæmia. Of late, Metchnikoff[1] and Giard[2] have called attention to the fact that, by its long, whip-like anterior end the *Trichocephalus trichiurus* (*T. dispar*) (Fig. 127) can bore through the wall of the intestine, and have suggested that the escape of the intestinal bacteria along the fine passage thus made is a probable cause of some cases of peritonitis and appendicitis; may, would look upon this as a common cause of appendicitis. The examination of thousands of sections from cases of appendicitis without once encountering in them anything corresponding to a trichocephalus must negative this view.

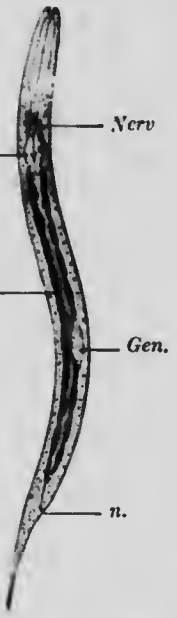


Fig. 128

Larva of Strongyloides stercoralis as found in fresh feces; *Ner.*, nervous system; *Es.*, œsophagus; *Int.*, intestines; *Gen.*, genital primordium; *An.*, anus. × 228. (Looss.)

With these exceptions, the internal parasites cause singularly little destruction of tissue; to the passive destruction by pressure atrophy we have already referred.

Injury by Loss of Foodstuffs.—As pointed out by Shipley and Fe[illegible]sides, this, in general, is so slight as to be negligible. "A female round worm, *Ascaris lumbricoides* produces 42 grains of eggs every year, and must also extract from the host a certain amount of nutriment for herself besides the amount that goes to build up the ova. When present in large numbers—and Francomeau Dufresne describes a case in which a boy got rid of 5000 (worms) in less than three years, and on one day evacuated 600—the loss is certainly serious. *Strongyloides intestinalis* (vel *stercoralis*) at one time thought to be the cause of Cochin China diarrhœa, exists in such numbers that

[1] Bull. Acad. de Méd., Paris, 45: 1901: 301.
[2] Ann. de l'Inst. Pasteur, 15: 1901: 440.

it is not uncommon for 100,000 to be expelled at one time. Such a number is said to weigh 200 grams." Others have described the evacuation of as many as a million at a time. Despite the small size, such numbers indicate a severe strain upon the host. Blanchard regards the anemia caused by the liver fluke, *Fasciola hepatica* (*Distoma hepaticum*), as due to the fact that these nourish themselves in the blood which they suck from the small capillaries of the bile ducts inhabited by them. Shipley and Fearnsides doubt whether there can be any great loss of blood from this source, and ascribe the anemia to toxic action.

Morbid Conditions Caused by Excretions: Toxic Action of Metazoan Parasites.—The very definite symptoms which accompany the presence of the metazoan parasites, and the difficulty of explaining those symptoms by the extent of the lesions seen to accompany their presence, have led pathologists during recent years to surmise that, like bacteria, these discharge toxins which, diffused into the tissues and blood, are the essential cause of these symptoms. And they have been encouraged to hold this view by Weinland's[1] intensely interesting demonstration that cestodes defend themselves against the action of the digestive juices by the elaboration and excretion of an antibody (see Section III, Chapter VIII)—an antitrypsin, according to Weinland and Hamill, an antikinase, according to Dastre and Stessano—a body comparable with that elaborated by the cells of the intestinal mucous membrane, whereby it also prevents digestion. The demonstration of the existence of these defensive bodies favors the supposition that the parasites excrete also offensive substances. As a matter of fact, we have abundant proof that the tissues and body fluids of many of the parasites are themselves distinctly toxic. The cyst contents of *T. echinococcus* and other echinococci have been found toxic, setting up in the lower animals, when injected, peritonitis and urticaria.[2] Disturbances of a similar order have been noted to follow the rupture of echinococcus cysts in man. The *Dibothriocephalus latus* sets up a most pronounced form of pernicious anemia.[3] Schaumann and Tallquist have produced a like anemia in the dog, by injecting extracts of the bothriocephalus. While there is little evidence of the existence of these body poisons in the trematodes, in the nematodes it is abundant and convincing. The body cavity fluid of *Ascaris megalocephala*, spurted accidentally into the eye, has set up violent corneal inflammation, and Charlton Bastian, Miram, and von Linstow have experienced uncomfortable, and even severe, effects from the mere emanation from this parasite when dissecting it—sneezing, conjunctival irritation, paroxysmal asthma, etc.; while 2 c.c. of the expressed body fluid has been

[1] Zeitsch. d. Biol., 44, 1903: 1.

[2] Blanchard, Traité de Zoöl. Méd., Paris, 1885–89; Delbove, Compt. rend. Acad. des Sci., 105: 1887: 1285; Mourson et Schlagdenhaussen, Bull. et Mém. de Soc. Méd. d'Hôp., Paris, 5: 1888: 113.

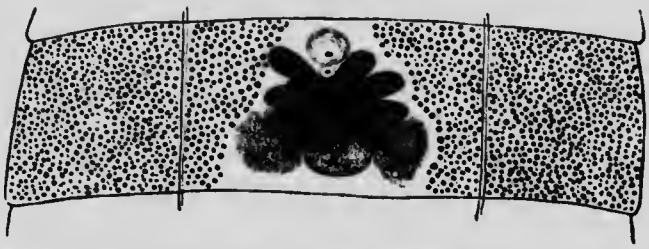
[3] Deutsche med. Woch., 24: 1898: 312. Schaumann is the author of the classical work upon Bothriocephalus anaemia (Z. Kenntniss der sog. Bothriocephalusanämie, Berlin, 1894). See also Askanazy, Zeitschr. f. klin. Med., 27: 1895: 492.

found to kill the guinea-pig within forty hours. Cattaneo[1] has gained like results with *Ascaris lumbricoides*.

But the mere existence of toxic substances in the bodies of these animals is no evidence that they excrete toxins. It may, for instance, be pointed out that the blood of one species of warm-blooded animal is toxic for other species; that is no proof that these excrete actively toxic substances. At most, the irritative effect of the emanations from the *Ascaris megalocephala* suggests that toxic substances may be discharged. Nor have we adequate evidence of the existence of toxins gained from a study of the discharges of these metazoan parasites.

Of bodies which, perhaps, should not be included among the toxins, we possess some evidence. Thus, Leo Loeb and Smith have demonstrated that there is to be obtained from the anterior body region of the hook-worm (Ankylostoma) a discharge possessing pronounced effects in arresting the coagulation of blood. Their observations—contrary

FIG. 129



Gravid segment of Dibothriocephalus latus, showing the rosette uterus in the median line. × 6. (Leuckart.)

to those of Looss, already noted—would suggest that these parasites are prepared to pierce the intestinal capillaries; and secondly, that the continued minute hemorrhages are a factor in the production of anemia in those cases.

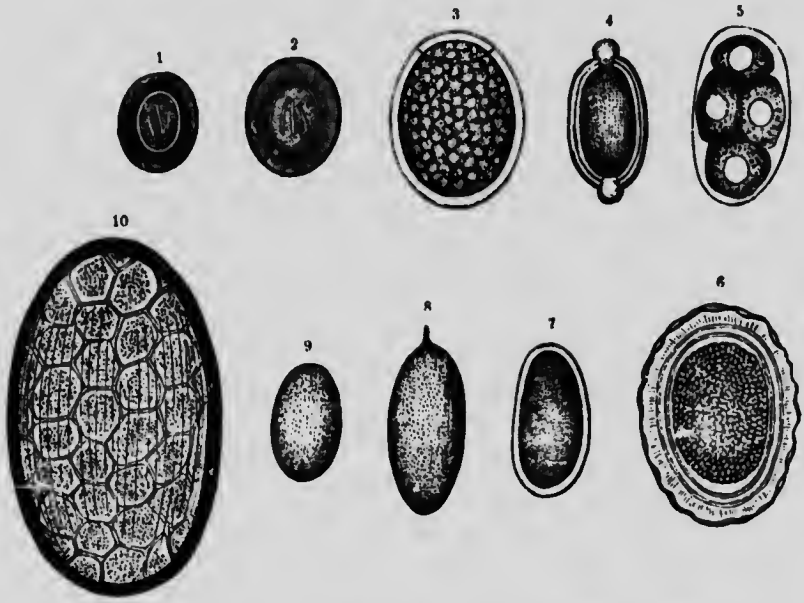
We possess, however, what is the clearest evidence from another quarter. I refer to the *eosinophilia*, or increase in the number of eosinophile leukocytes in the blood, which characterizes the presence of almost every vermiform parasite. That eosinophilia cannot be explained save on the assumption that there diffuses from the parasites into the tissues, and so into the blood, some substance which, conveyed to the bone-marrow and other seats of origin of the eosinophile cells, there stimulates the proliferation and increased production of these cells. Müller and Riedel[2] would seem to have been the first to call attention to this remarkable phenomenon, in the case of two patients infected with ankylostoma. Bucklers,[3] in 1894, first showed that eosinophilia characterizes all forms of helminthiasis. All kinds of parasitic worms,

[1] Abstr. in Arch. ital. de Biol., 42: 1904: 496.
[2] Deutsch. Arch. f. klin. Med., 48: 1891, 96
[3] Münch. med. Woch., 41: 1894: 21.

from the harmless oxyuris upward, induce eosinophilia, and, accompanying this, as shown by Leichenstern, there is constantly the presence of Charcot-Leyden crystals in the feces (a frequent finding in eosinophilia in general).

Whereas, the normal percentage of eosinophiles, compared with the other leukocytes of the blood, is between 1 and 4 per cent. (25 to 500 per cmm.), in 50 cases of Bilharzia disease Douglas and Hardy found an average of 16.48 per cent., a maximum of 40 per cent. In trichinosis, T. R. Brown, of Johns Hopkins, has called attention to the marked eosinophilia, the proportion of eosinophiles in his first case

Fig. 130



Relative size and characters of the eggs of various species of intestinal worms: 1, Tænia solium; 2, Tænia mediocanellata; 3, Dibothriocephalus latus; 4, Tricocephalus trichiurus; 5, Anchylostoma duodenale; 6, Ascaris lumbricoides; 7, Oxyuris vermicularis; 8, Schistosoma (Bilharzia) hæmatobium; 9, Distoma lanceolatum; 10, Distoma hepaticum. × 250. (Heller.)

rising from 37.0 to 68.2 per cent.; in other cases he obtained percentages of 42.8, 45.0, and 48.0, respectively—observations which have since been abundantly confirmed, Harlow Brooks gaining a count of 84.0, and Kerr one of 86.6 per cent. In guinea-worm disease the same phenomenon is observed; in 6 cases Balfour found an average of 19.6, the figures varying from 6.4 to 36.6. So, also, with ankylostomiasis; here all recent observers call attention to eosinophilia as a constant feature, while percentages as high as 72.0 (Leichenstern), 66.0 (Boycott and Haldane), and 53.5 (Ashford) have been recorded. In cestode disease, various forms of filariasis, in ascariasis, and to a less extent in infection

with Oxyuris vermicularis, eosinophilia shows itself in well-marked cases, though never to the same extreme extent as in the conditions already noted.

The intimate relationship between the parasites and the eosinophilia, as noted by Ward,[1] is shown by the following facts: (1) The increase and decrease of eosinophiles in the peripheral blood coincident with the appearance and disappearance of the *Filaria bancrofti* in the superficial capillaries; (2) Opie's experiments upon the induced trichinosis of the guinea-pig. It was found that the increase of eosinophiles dates from the beginning migration of the embryos, and that the eosinophilia reaches its maximum when the majority of the embryos are in the process of transmission from the intestinal mucosa by way of the lymphatics and the blood to the muscular system; (3) Sabrazes has also noted the accumulation of eosinophiles in the neighborhood of hydatid cysts. I am informed by Dr. Told that at the site of attachment of ankylostomes to the mucosa of the small intestines a marked accumulation of eosinophiles is to be detected. All these observations indicate a positive chemiotactic influence leading these cells toward the source of the stimulus.

As we have said, it is difficult, when we consider the different modes of life of these different forms, to arrive at any other conclusion than that the parasites afford a diffusible irritant, or toxin, which stimulates the proliferation and increased entry into the blood of the eosinophile cells. If we accept this, then the frequent accompanying anemia is most rationally ascribed to a like cause.[2]

INSECT AND ARACHNID PARASITES.

Little need be said regarding the insect and arachnid parasites. These produce local disturbances (1) by puncture and the introduction of irritative salivary secretion, (2) by burrowing, as in scabies, or (3) by the deposit of eggs within the tissues and germination of the same, as in *Myiasis*, and (4) by affording means for secondary entrance of infective microbes. (5) Koch, I am informed, is of the opinion that the chigger, or sand flea (*Sarcopsylla penetrans*), gains entrance into the corium of the foot not through the action of its mouth parts, but through the digestive action of an excretion.

Science, 25: 1907: 201. A thoughtful article on the effects of parasites on their host.

[2] A very full bibliography and analysis of cases of the eosinophilia of helminthiasis is afforded by Shipley and Fearnsides (loc. cit.). The observations to which we have more particularly referred are: Douglas and Hardy, Lancet, 1903: ii: 1540; T. R. Brown, Johns Hopkins Hospital Bulletin, 8: 1897: 79; Journal of Experimental Medicine, 3: 1898: 315, and Medical News, Philadelphia, 7: 1899: 12; H. Brooks, Medical Record, 59: 1900: 885; Kerr, Philadelphia Medical Journal, 6: 1900: 346; Balfour, Lancet, 1903: ii: 1649; Leichenstern, quoted by Ehrlich and Lazarus, Histology of the Blood, translated by Myers; Cambridge, 1900: 151; Boycott and Haldane, Journal of Hygiene, 3: 1903: 95; ibid., 4: 1904: 437; Ashford, New York Medical Journal, 71: 1900: 552, and American Medicine, 6: 1903: 391.

CHAPTER XI.

THE ENDOGENOUS INTOXICATIONS.

INTERNAL SECRETORY.

By Disturbance of the Internal Secretions.—An adequate recognition of the part played by the internal secretions of the economy has only come about during the present generation. Previous to this, attention had been almost wholly directed to the external secretions and the disturbances associated with or leading to alterations in excretory glands; this, although Claude Bernard, in his brilliant studies upon the liver and its glycogenic properties (1855–57), had demonstrated the existence and importance of the internal secretions, and, indeed, had given this name to substances which, formed through cell metabolism, become discharged, not externally, but into the blood and lymph; substances, which, while from the point of view of the cells that form them they may be regarded as waste products, are by no means such for the rest of the economy, being essential to the proper carrying out of one or other function of one or other tissue, and affording most instructive examples of the mutual interdependence of the cells of the organism.

After Bernard's impressive demonstration that the liver cells convert into glycogen the sugar brought by the portal veins, and yield this glycogen (as sugar) to the blood, according to the needs of the muscle and other tissues, there came a long pause, broken in the late "eighties" by Brown-Séquard's bizarre campaign in support of injections of ovarian and testicular extracts as a cure for declining vigor. There is now no doubt that these gland extracts have some tonic effect; considerable doubt as to whether they have the specific effects claimed for them by Brown-Séquard and his followers. It has to be admitted that the use of organ extracts suffers even to-day from the suggestion of charlatanism, which inevitably accompanied the Brown-Séquard treatment. In the meantime the quiet work of other medical men and physiologists —Reverdin, Ord, Schiff, Horsley, Kocher, and others—was establishing the fact that the thyroid, a ductless gland, incapable, therefore, of affording an external secretion, played a very essential part in the organism, and that removal of this gland, or lack of development, or atrophy of the same, was followed by the appearance of a very remarkable train of symptoms—a train which might show itself as "cachexia strumipriva," cretinism, or myxœdema, respectively. The doctrine of the internal secretions may be said to have come into its own when George Murray demonstrated that injections of extracts of the healthy thyroid gland of the domestic animals causes the disappearance of all

the distressing symptoms of myxœdema. Very soon it was shown that administration of the extract by the mouth is followed by equally good results; that the administration to healthy animals brings about the symptoms of hyperthyroidism, which in many respects resembles those of exophthalmic goitre, a condition which already, from histological considerations, Greenfield, of Edinburgh, had recognized as associated with overgrowth and overactivity of the gland. Next came the isolation by Baumann, of Freiburg, from the thyroid gland substance, of a compound protein, which he termed, first, thyroiodin, and later, and more appropriately, iodothyrin; he showed that this possessed the characteristic properties of the thyroid extract.

Here, then, has been afforded a full and scientific demonstration that disease is capable of being caused (1) by deficiency, (2) by excess of the specific internal secretion of a gland, or of particular constituents of the same.

While this is the most striking example, it is far from being the only one. We have evidence of one or other order, not merely of the development of internal secretions by glands, and those both ductless and affording external secretions; the indications, indeed, are now that the medulla of the adrenal bodies, which, although originating in connection with the sympathetic system, we are accustomed to regard as "glandular," and also the sympathetic ganglia in other regions afford an internal secretion. Nay, more, the valuable work initiated by Bayliss and Starling, upon the pancreatic secretion is leading us to see that in a large number of cases certain portions of the mucous membrane of the alimentary tract afford *hormones*,[1] or internal secretions, which are necessary for the full activity of other digestive glands at a distance.

Here we have to deal with the internal secretions as causes of disease; it would be out of place to describe *in extenso* the various morbid states associated with a disturbance in the internal secretion; at most, I can adduce briefly the evidence we possess associating these morbid conditions with such disturbances.

The Thyroid.—Myxœdema and Cretinism.—Myxœdema is a condition appearing in adult life in which there develops characteristically a loss of expression, associated with a thickening of the skin, or, more accurately, a subcutaneous infiltration of the face and body generally. At first this is due to a mucoid œdema (hence the name); later, this gives place to connective-tissue overgrowth. The skin is dry, the hair badly nourished, tending to drop out; the nose and lips become thick and bloated. With this the mental processes become slowed and undergo progressive failure, with a defective memory and, it may be, final dementia. Cretinism, on the other hand, is congenital; it is characterized by a striking retardation and imperfection of development. The adult of forty is mentally an infant, often an imbecile, and his body retains infantile or childish features. Dentition is delayed; the

[1] From ὁρμάω, I excite or arouse.

sexual organs and functions do not attain maturity; the extremities are short and thick; the abdomen swollen; the features coarse and lacking expression. The evidence that these conditions are due to lack of thyroid secretion is:

1. Myxœdema, even after many years' duration, and cretinism, in the child, can be cured by administering thyroid extract. The cure is not complete, *i. e.*, to preserve the normal state it is necessary to continue giving the extract from time to time.

FIG. 131

Cretin, male, aged twenty-one years. (Bourneville and Bricon.[1])

2. As first shown by Kocher,[1] symptoms identical with those of myxœdema follow a complete removal of the human thyroid (cachexia strumipriva).

3. Histologically, in all cases of myxœdema and cretinism we encounter either extreme atrophy or grave lesions of the thyroid.

It is interesting and, at first thought, paradoxical, that in a certain number of cases of both conditions we find enlarged thyroid as also that upon operative interference in this latter order of cases symptoms of the very opposite condition—of exophthalmic goitre—are apt to show themselves. We have here, in my experience, examples of colloid goitre, *i. e.*, of great distension of the vesicles of the thyroid, with thickened, inspissated, firm, gelatinous secretion. The normal thyroid is extremely vascular, a network of capillaries surrounding each vesicle, and these both hemic and lymphatic. I have suggested[2] that here, as in the expansion of the air-sacs in emphysema of the lungs, the distension of the vesicles results in such a flattening and compression of the vessels that circulation in and absorption of the thyroid secretion by these vessels is arrested, and symptoms of athyrea show themselves as a result. Acute congestion of the organ will thus lead to sudden absorption of large amounts of the secretion, and symptoms of hyperthyroidism manifest themselves. Similar considerations help to explain how overaction of the thyroid and exophthalmic goitre may give place to myxœdema.

Exophthalmic Goitre, or Graves' Disease (1835), **Basedow's Disease** (1840), **or Parry's Disease** (1825).—In this we have an unmistakable collection of symptoms: (1) Exophthalmos, or protrusion of the eye-

[1] Arch. de Neurologie, 12; 1886; 137 and 292. [2] The Practitioner, 64; 1900; 56

balls; (2) tachycardia, or great rapidity of heart-beat and pulse; (3) enlargement of the thyroid; (4) tremor and nervousness. Flushing and abundant perspiration and increased pigmentation of the skin may also be present.

That this is caused by excessive secretion from the gland is shown by: (1) The cure of the disease by partial thyroidectomy; (2) the production of some of the most striking symptoms (tachycardia, tremors, and nervous irritability) by the administration of too large doses of thyroid extract to previously healthy men or animals (hyperthyroidism); (3) the increased nitrogenous output seen both in exophthalmic goitre and in hyperthyroidism; (4) the histological indications in typical cases of Graves' disease (as shown by Greenfield, and later by Halsted), of hyperactivity of the gland; the cells lining the vesicles are large; there are indications of overgrowth in the form of infoldings of the epithelium; the gland is found very vascular; the vesicular contents thin and fluid. The atypical form supervening upon colloid goitre has already been noted.

What is behind these states? What are the causes of athyrea and hyperthyrea? That is another matter. Here, for the time, we must be satisfied to recognize that these remarkable sets of symptoms are brought about essentially by defect and overproduction, respectively, of the internal secretion of the thyroid. This statement holds in connection with all the other instances to be brought forward.

The Parathyroids.—Associated with the thyroid, either embedded in the lateral lobes or in their immediate neighborhood, are certain small bodies, the size of a pea or thereabouts. Of these there are usually a superior and an inferior pair. There is still debate regarding their functions. Some would regard them as rudimentary thyroid tissue;[1] but clearly they are functional, and their activity differs from that of the thyroid. Removal, in dogs, lends to muscular twitchings, giving place to tetany, exophthalmos, and rapid breathing, with death within a few days.[2] The symptoms are preëminently those of irritation of the nervous centres.

The brilliant observations of MacCallum and Voegtlin, published as this work is passing through the press,[3] show that in the parathyroidectomized dog there is a rapid fall of the calcium salts to about half the normal amount, and that the intravenous injection of a calcium salt (the lactate or the acetate) almost instantly removes the violent symptoms produced by removal of these bodies—muscular twitchings, and rigidity, tachypnœa, fibrillary tremors, increased rapidity of heart beat. It would seem thus that the parathyroids in some way control the calcium metabolism, so that their removal is followed by a rapid excretion of the calcium salts. The observations further suggest that the toxic symptoms may be due to the unantagonized action of potassium salts upon the nerve centres, for in tetany the injection of potassium salts was found to intensify all the symptoms.

[1] Kishi, Virch. Arch., 176: 1904: 260.
[2] MacCallum, Medical News, 1903: 820
[3] Johns Hopkins Hosp. Bull., 19: 1908: 91.

It is still unsettled what is the exact causation of the *exophthalmos* of Graves' disease. It is not reduced by injections of parathyroid extract; nor, on the other hand, has it been satisfactorily reproduced by injection of thyroid extract into normal animals. Here may be noted Macallum and Cornell's observation[1] that where the dog's head is removed from the body (and so all influence removed of orbital congestion) stimulation of the cervical sympathetic results in an exophthalmos as pronounced as any produced in the living dog, and their demonstration that this is brought about by contraction of the so-called musculus orbitalis of Müller (1859), a case of smooth muscle and elastic fibrous tissue, enclosing the fatty bed of the eye, and having its apex posterior. They were unable to produce exophthalmos in the human being by sympathetic stimulation, so would leave the matter open; but Jonnesco[2] employing strong stimulation had previously reported definite protrusion of the eyeball. We are thus inclined to attribute the exophthalmos of Graves' disease to sympathetic irritation.

FIG. 132

Normal skull. Skull from case of acromegaly. (Osborne.)

The Pituitary Body, or Hypophysis Cerebri.—There is evidently a relationship in function between the glandular portion of the pituitary and the thyroid. According to Wells,[3] this, like the thyroid, contains iodine. Several observers (Rogowicz,[4] Boyce and Beadles,[5] etc.) have observed a compensatory enlargement of the organ following upon atrophy of the thyroid, and Ponfick[6] and others have noted the accumulation of colloid material within the gland vesicles in cases of myxœdema. In a case of endothelioma of the hypophyseal region, under my colleague, the late Dr. James Stewart, in which I performed the autopsy, there were distinct symptoms of myxœdema, without recognizable thyroid change. One remarkable set of symptoms is associated

[1] Med. News, N. Y., October 15, 1904.
[2] 13th Internat. Med. Congr., Paris, 1900.
[3] Jour. Amer. Med. Assoc., 1897: 1011
[4] Ziegler's Beitr., 4: 1889: 453.
[5] Journ. of Pathol., 1: 1893: 222 and 359.
[6] Zeitsch. f. klin. Med., 38: 1899: 1.

with disturbance of the pituitary, forming the condition known as *acromegaly*. The face becomes enlarged, the enlargement especially involving the superior and inferior maxillary bones; the ears become of great size, the nostrils broaden, the eyelids thicken. The hands and feet are characteristically hypertrophied and of great size as compared with the other portions of the extremities. Later, the spinal column may be affected. The condition develops in adult life and is of slow development, extending, it may be, over twenty or more years. Autopsy upon such cases shows commonly a condition of tumor, involving the gland, either endothelioma or adenoma, as also that the hypertrophy affects particularly portions of the bony framework. In several cases of irregular gigantism, enlargement of the pituitary has also been recorded.

By analogy it would seem evident that acromegaly is associated with some disturbance of the internal secretions of the pituitary. Beyond this we cannot surely extend much farther. It is far from clear, from the published descriptions, whether the gland tissue is replaced by tumor growth, or that growth is of the nature of a hyperplasia of the specific elements of the glandular portion of the organ. It is usual to regard the state of acromegaly as due to hyperactivity of the organ, but there is no sure ground for this conclusion. The condition is characterized by retention of nitrogen and phosphorus; feeding animals with pituitaries leads, on the contrary, to loss of weight and increased discharge of nitrogen and phosphorus.[1]

In some cases there is no evidence of increase in the glandular elements. Feeding those affected with extract of the pituitaries of animals has been found to be without effect. But on the other hand, as shown by Harvey Cushing and Reford and others, removal of the pituitary in the dog is succeeded by fatal results within four days, while Schäfer's studies demonstrate that the gland, small as it is, possesses a most active internal secretion.

The Adrenals.—Addison, of Guy's, in 1855, was the first to call attention to the remarkable association between disease or atrophy of the adrenals and the peculiar affection which now is known by his name. This, Addison's disease, presents a progressive great muscular weakness, with feeble heart action and very weak pulse, pigmentation of the skin, nausea, vomiting, and other indications of gastric disturbance, and, according to Addison, anemia, although this is not usual. The pigmentation is deepest upon exposed parts and in regions normally pigmented, and tends to be diffuse, varying from a yellowish color to deep brown. The asthenia is very striking, and is out of all proportion to the apparent nourishment of the individual and the size of the muscles.

The commonest lesion of the adrenals found in these cases is a chronic fibrocaseous tuberculosis, replacing the tissue, generally of both organs, though cases are on record with only one involved; simple atrophy is more rarely encountered; primary and secondary malignant growth of the organs, hemorrhagic extravasations (which, in children, very often leads to relatively sudden death), and diffuse interstitial

[1] Thompson and Johnson, Journal of Physiology, 33: 1905: 189.

inflammation have still more rarely been noted. Lastly, some cases have shown no recognizable increase of the adrenals, but inflammation of the semilunar or other sympathetic ganglia.

Here the matter rested until Schäfer and Oliver (1894) demonstrated that extract of the medulla of these organs leads to an extraordinary increase in blood pressure. What the constituent is that has these effects has been actively studied, isolated (Takamine, Abel, etc.), and even synthesized (Dakin),[1] the synthetic body, though differing in being optically inactive, having the same physiological effects.

It is related to pyrocatechin. It acts directly on muscle, both striated and plain. Langley and Elliott[2] have shown that it is effective even when the nerve endings of a muscle have undergone degeneration. Klotz and others have called attention to its specific action upon the muscle cells in the media of arteries. Clearly, therefore, the asthenia of Addison's disease and the lowered blood pressure would seem associated with the inadequate secretion of this substance, and in partial support of this view is the fact that in a certain proportion of cases, though not in all, the administration of adrenals, or of adrenal extract, has ameliorated the symptoms of the disease.

It is the medulla that furnishes the adrenalin, and we know, from embryological studies, that this portion of the gland is a derivative of the sympathetic system. Recent studies have demonstrated that from the sympathetic ganglia an extract can be obtained having an identical action upon the blood pressure. We appear here to be gaining light upon those aberrant cases in which Addison's disease is found associated, not with adrenal disease, but with disturbances of the abdominal sympathetic ganglia.

Dissecting out the solar plexus, etc., but rarely, we are apt to obtain a false idea of the relative volume of the sympathetic ganglia and the medulla of the adrenal. As a matter of fact, the latter is of small extent; the deep pigmented layer seen in sections toward the middle of the gland is often mistaken for medulla. But that is the zona reticulata of the cortex; the central pale area alone is medullary. If, then, both sympathetic and adrenal medulla afford adrenalin, it is not difficult to realize that disturbances of the one or the other may lessen the normal production to such a degree that circulatory disturbances and asthenia become manifest.

A striking fact, to which Langley and Starling call attention, is that the presence of this body seems to be a necessary condition for the normal functioning, by ordinary reflex means, of the whole sympathetic system. The effects of adrenalin upon a part are identical with the results of stimulating the sympathetic fibers distributed to that part. These studies seem to be leading us toward the recognition of a chemical, and not merely a physical, basis of nerve excitation. However, the fact that adrenalin directly excites muscle must make us proceed very cautiously in reaching any such conclusion.

[1] Proc. Roy. Soc., B., 76:1905:491.

[2] Journal of Physiology, 32·1905:401, and 33:1905:374

Regarding the other symptoms of Addison's disease and their relationship to disturbances of the adrenals we are not so clear. We know, in the first place, that complete removal of these organs leads to death in a few days, with extreme asthenia; in some cases, in animals, time has been afforded for the development of a certain grade of pigmentation of the palate and other regions. The cortex, by its structure, suggests much more strongly a secreting organ than does the medulla, and is extensively involved in the common tuberculous form of the disease, but of its mode of activity we know next to nothing. At most, some relationship has been noted between it and the glandular system. No obvious changes follow administration of this portion of the gland or of extracts from the same.

Ovaries and Testes.—It is a matter of familiar knowledge that capons and other castrated animals, in which the active organs of generation have been removed prior to puberty, differ materially in build and character from "entire" animals of the same sex and species; the external and secondary sexual features are imperfectly developed, the vocal organs do not reach adult development, the general bodily build approximates more to that of the other sex. Is this due to lack of nerve stimuli proceeding from the ovaries or testes to the higher centres of the brain, to lack of removal from the blood of substances necessary in the elaboration of the ova and spermatozoa, or, lastly, to absence of an internal secretion? It cannot be said that we know the complete answer; it is, indeed, difficult to see how it can be obtained by experimental means.

The full demonstration that these changes are due to lack of internal secretion must be obtained by removing ovaries and testes and then showing that ovarian or testicular extracts lead to full development of one or other sexual type. We deal here with growth. Now, normally, if this be due to the influence of internal secretions, these secretions must be continuously elaborated in small quantities over long periods of time. Experimentally, we cannot reproduce the process; we can only make periodical injections of uncertain quantities. At most, using these faulty methods, there is a possibility of obtaining approximate results, and this has been done in part.

Thus, Ancel and Bouin[1] have proved clearly that the secondary sexual characters in the male are due to the internal secretion of the interstitial cells of the testes—certain fairly large cells lying in the stroma, between the tubules. Remove the testes entirely, and the secondary characters do not develop. Ligature the vas deferens, and so bring about atrophy of the seminal tubules, the interstitial cells still persist and the secondary characters make their appearance. It is not, then, the secretory tubules of the organ that are responsible, but these interstitial cells, which, it may be added, are embryologically of like origin, although, as a result of position, their function becomes widely different. Shattock has confirmed and extended these observations.

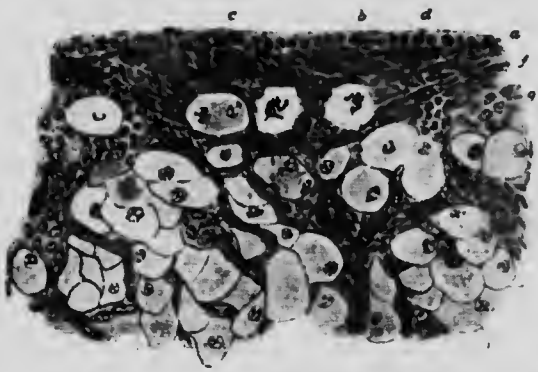
In the ovary there are homologous interstitial cells, derived, as shown

[1] Compt. rend. Soc. de Biol., 55:1903:1397; and 56:1904:81.

by Miss Lane-Claypon,[1] from the common germinal epithelium, which gives rise indifferently to follicular epithelium, ova, and the intermediate cells. The indications are that these cells have equally important influence upon sexual life and growth, although, confessedly, it is difficult to distinguish between their effects and those of the follicular epithelium. Menstruation and "heat" depend upon the presence of the ovaries. It has been shown by Fränckel[2] and by Marshall and Jolly[3] that, in castrated animals, heat can be produced by the injection of ovarian extracts.

The corpus luteum has functions of another order. This develops rapidly after discharge of the ovum. These observers have shown that if the ovaries of an animal be removed within six days after coitus the ova do not become adherent in the uterus. Fränckel obtained the same results by destruction of the corpus luteum alone. To the internal secretion of the [illegible] cells of this little organ must be ascribed the stimulation of the [illegible] mucosa so that it responds to the presence of

FIG. 133



Cells in ovary of young rabbit, derived from the germinal epithelium (*a*), which give rise to (*b*) primordial ovum; *c*, multinucleated interstitial cell; *d*, interstitial cell becoming isolated; *f*, connective tissue; *g*, modified germinal cells. (Lane-Claypon.)

the ovum and develops the maternal sections of the placenta and decidua. It is the interstitial cells lying external to the Graafian follicle that form, it would seem, the main cell layer of the corpus luteum and that supply the hormone.

The Fœtus, and its Bearing on the Growth of the Mammary Gland.—That the development of the mammary gland during pregnancy is not due to nervous reflex has been shown by more than one observer. The whole lumbosacral cord may be extirpated in a pregnant bitch, but pregnancy will continue, and the gland enlarge, and the bitch suckle its pups. Ribbert transplanted a mammary gland in the guinea-pig to the region of the ear. With pregnancy, the gland underwent hyper-

[1] Proc. Roy. Soc., B., 77: 1905, 32.
[2] Arch. of Gynäk., 68, 1903: Pt. 2
[3] Phil. Trans. Roy. Soc., 1905.

trophy, and when the young were born milk could be expressed from it. Lane-Claypon and Starling[1] have shown that the stimulus to the hypertrophy of the gland comes not from ovaries, or uterus, or placenta, but from the developing fœtus. Injections of watery extracts from rabbit fœtuses into a virgin rabbit every one to three days, over a period of three weeks led to the glands, which were at first almost invisible, becoming markedly hypertrophied, with enlarging ducts and epithelium, and discharge of a thin fluid; in multiparous rabbits, similar injections led to the discharge of true milk. They draw the conclusion that the amount of the substances leading to the glandular hypertrophy is greatest during the latter part of pregnancy, and lactation would seem due, we would add, primarily to the removal of these substances, the cells which had under its influence manifested anabolism and growth, in its absence proceeding to break down, and so form milk. These observations would appear to explain the cessation of lactation with the onset of a renewed pregnancy.

Eclampsia.—We are still wholly at a loss where to place eclampsia, that most dangerous combination of disturbances which may result from pregnancy. The kidneys are profoundly involved; indeed, the danger signal is found in the appearance of albuminuria during the last weeks of pregnancy; there is a relatively large proportion of globulin with low urea content, suggesting a relationship of the condition to uræmia, which is strengthened by the convulsions and coma, leading to death. But anatomical studies show disturbances elsewhere, and notably in the liver, which are wholly foreign to the uræmic state. The liver changes are remarkable; in typical cases there occur abundant necroses in this organ; where slight, these recall the focal necroses seen in many infections and toxic conditions, but they may be so extensive as to give the appearance of that wide destruction of the hepatic parenchyma seen in acute yellow atrophy. Schmorl and others have ascribed these to liberated placental cells becoming blocked in the portal vein and hepatic arteries, but, while placental cell emboli do occur, they are incapable of explaining the widespread eclamptic disturbances. No positive or consonant results have been obtained from bacteriological studies, and the tendency nowadays is to regard the condition as an intoxication set up by abnormal or excessive substances diffusing into the maternal blood from either the placenta or the fœtus. Inasmuch as the condition may first become acute, it may be some days after the fœtus has been removed, the tendency on the part of many is to regard the placenta as originating the irritant, and this view gains some support from Hitschmann's[2] case, in which eclampsia showed itself in a woman, the bearer of a placental mole (a mole is an aberrant growth of the chorionic villi placenta, the embryo having died or aborted). Opposed to this view is the fact that extract of placental tissue produces singularly little disturbance when injected, although Liepmann states that eclamptic placentas are definitely toxic. This awaits fuller con-

[1] Proc. Roy. Soc., B., 77: 1906: 505.

[2] Centralb. f. Gyn., 28: 1904: 1089. Quoted by Wells.

firmation. The most that can at present be said is that it is along these lines of investigation that attention is at present being directed, and that the tendency is to recognize two orders of cases, in one of which the main histological lesions are hepatic, in the other, renal.

The Digestive System.—A great step forward in the comprehension of the internal secretions and their mode of action was made by Bayliss and Starling in their already classical observations upon the secretion of pancreatic juice. Everyone should be familiar with Pawlow's[1] notable advances in the study of digestive secretions. His studies established the existence of nervous reflexes as setting in action the flow of, more particularly, the gastric juice, just as, years previously, Ludwig had shown the nervous paths whereby salivary excretion is brought about. Bayliss and Starling went farther; studying the increased flow of pancreatic juice which follows the introduction of acid into the duodenum (it must be recalled that the chyme when it enters the small intestine is acid), they found that this occurred even when pancreas and duodenum were separated, and even when the acid was introduced into a loop of the upper jejunum that had been deprived of all nervous connections. The reaction could only be chemical, and further study demonstrated that, by scraping off the mucous membrane of the duodenum and upper part of the small intestine, pounding this with sand, and adding 0.4 per cent. HCl, they could, by boiling and neutralizing the fluid, extracting with alcohol, and evaporating the latter, obtain a substance, *secretin*, which, dissolved in water and injected into the veins of a mammal, leads to an abundant excretion of clear pancreatic juice. That acid in the small intestine leads to discharge of secretions from the mucous membrane into the blood, by which it is carried to the pancreas, stimulating that organ, has been further demonstrated by Wertheimer; establishing a cross-circulation between two animals, he found that acid introduced into the duodenum of the one led to increased secretion of pancreatic juice in the other. The indications are that, while there exists a nervous mechanism for the secretion of the digestive juices, as shown by the mouth watering at the sight, smell, or thought of food, and by Pawlow's demonstration of the pouring out of "appetite juice" in the stomach, there exists also a series of secretins developed by the mucous membrane of one segment of the alimentary canal after the others, which, passing into the blood, stimulate the specific glands of a neighboring segment. Thus, Edkins has proved the existence of a gastric secretion elaborated by the pyloric glands leading to the discharge of hydrochloric acid from the cardiac end of the stomach. Hemmeter describes removal of the salivary glands as leading to dyspepsia and arrest of the cardiac secretion. Bayliss and Starling found that the duodenal secretion also influences the flow of bile. In other words, *the various forms of indigestion, dyspepsia, absence of pancreatic juice, of biliary excretion, and of digestion in the lower portion of the small intestine, may, in the absence*

[1] The Work of the Digestive Glands. Well translated by W. H. Thompson, London, Griffin, 1902.

of gross obstruction and disturbance, be due to imperfect development of one or other secretin. We thus open a new chapter of the pathology of digestion.

It may be added that, like adrenalin and iodothyrin, and unlike toxins, the secretins are not modified by heat or by alcohol, in which they are readily soluble.

The Pancreas, the Liver, and Diabetes Mellitus.—As shown by von Mering and Minkowski (1889), complete removal of the pancreas in the dog is followed within twenty-four hours by glycosuria, by the appearance of abundant sugar in the urine, and this not temporarily, but of the diabetic type, *i.e.*, it persists. There may, in a few days, be as much as 8 to 10 per cent., and this although the food contains no carbohydrates; and in diabetes mellitus, in many cases, the animal exhibits increased appetite and excessive thirst, with abundant discharge of urine; progressive asthenia and emaciation show themselves, and the urine comes to contain acetone, diacetic and oxybutyric acids. The phenomenon is not confined to dogs, but results in all vertebrates, even down to eels (Capparelli), when the greater part of the pancreas—seven-eighths and more—is removed.

That the ordinary external secretion of the organ plays no part in the sugar regulation is evidenced by the facts: (1) That glycosuria does not supervene when the pancreas is transplanted into the abdominal wall (Lépine), and (2) that no diabetes occurs when a pancreatic fistula is made draining away all the secretion so soon as it is elaborated.

There are thus the alternatives: (1) That the organ furnishes an internal secretion, affording something of the nature of a glycolytic ferment, in the absence of which the sugar is not transformed, but accumulates in the blood, and (2) that under normal metabolism there is produced a substance which hinders the above transformation, this substance being taken up and destroyed by the pancreas. When this organ is removed or diseased, the substance in question accumulates in the system and glycosuria results.

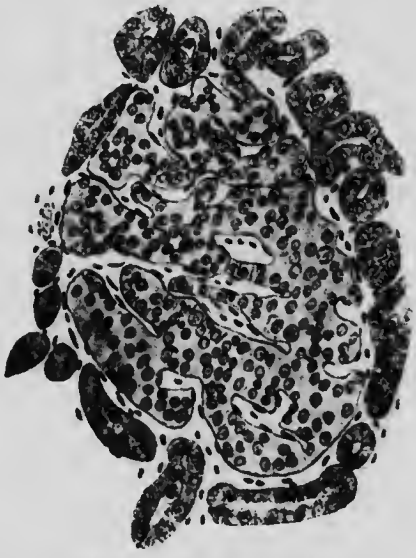
Beyond this, for long years, despite abundant experiments, no advance was made, no extract could be obtained from the pancreas having an action upon the sugar in the blood. It is true that Lépine, Bail, and others demonstrated the existence of glycolysis in normal blood, and that the former found this absent in cases of diabetes, but these observations could not be confirmed. Only in the last few years has Otto Colnheim[1] afforded what appears to be the correct solution. Muscle and liver, it will be remembered, normally contain glycogen. Colnheim expressed the juice from pancreas and muscle; adding each separately to a solution of glucose, there was no reaction; but when to the muscle juice he added a small quantity of the pancreatic extract, there followed a rapid conversion of the glucose into alcohol and CO_2. Rahel-Hirsch independently announced the same results, as also that the other tissue, the seat of active carbohydrate metabolism, viz., the liver, gave corresponding results, the difference being that liver juice

[1] Zeitsch f. Physiol Chem., 39:1903:338, and 42:1904:401.

normally is able to act to some extent upon glucose; if, however, a little pancreatic extract be added, the decomposition is greatly accelerated.

Now, this substance produced by the pancreas withstands boiling, and is soluble in alcohol without loss of activity; it has properties allied to those of adrenalin and the secretins. We thus arrive at the conclusions: (1) that the normal pancreas affords a body of the nature a secretin; (2) that the liver and muscle are the main seats for the deposit and utilization of carbohydrates; (3) that these two tissues can convert soluble carbohydrates into insoluble glycogen, and *vice versa;* (4) that unaided they cannot to any extent break down these carbohydrates; (5) that for glycolysis to ensue, these tissues need to be activated by

FIG. 134



Section of island of Langerhans from pancreas of human adult. × 200. (Dewitt.)

a "hormone" elaborated in the pancreas. Just as the pancreatic juice is unable to act upon proteins alone, but requires the addition of enterokinase before the trypsin is complete, so this hormone of pancreatic origin is necessary before the full glycolytic ferment is evolved in liver or muscle.

Were this all, our comprehension of the causation of diabetes would be easy, but there are many riddles still remaining to be solved. Diabetes in man, in the first place, is not always associated with pancreatic disease. In most cases the organ or its specific cells are greatly reduced through congenital aplasia (rare), interstitial fibrosis with atrophy of the glandular elements (the commonest cause), cancerous growths, etc.; but in the majority of these the reduction does not approximate to that which experimentally is found necessary to produce glycosuria. Opie and, later and independently, Ssobolew have

laid down that it is not the pancreatic tissue in general, but the remarkable little "islands of Langerhans" scattered through the organ that are at fault; that these act as ductless glands (elaborating, we would now say, the hormone), and that diabetes is due to degeneration of the same. And certainly, as Opie has shown, in many cases there exists a form of hyaline degeneration of these bodies. But Dale, working under Starling and, more recently, Swale Vincent and Mrs. Thompson,[1] have shown conclusively that the islands are not separate organs; that they vary in number according to the state of nutrition and activity of the gland, becoming converted into active acini, and *vice versa*. At most, then, changes in these islands are to be regarded as indications of changes involving the pancreas in general, and in quite a number of cases of diabetes in my experience no histological alteration is to be made out in these islands; the pancreas is of normal size and weight.

Then, again, Naunyn, Pavy, and others call attention to an hepatic form of the disease, in which, more particularly, the liver is enlarged and hyperemic; again, experimentally, by the exhibition of phloridzin, without there being any hyperglycemia, or excess of sugar in the blood, the urine comes to contain large quantities of sugar, and Zuntz has shown that if phloridzin be injected into one renal artery, the urine from the corresponding kidney contains sugar, that of the other remaining wholly free therefrom. Evidently, also, there is an adrenal glycosuria (Blum, Herter, etc.) produced by subcutaneous, intravenous, or peritoneal injection of adrenalin, or even (Herter) by painting adrenalin over the pancreas. Herter would explain this by the pronounced reducing powers of adrenalin, whereby the function of the pancreatic cells becomes arrested; other reducing agents, he found, have the same effects.

Lastly, alimentary and nervous glycosuria have to be taken into account. Excessive consumption of carbohydrates is apt to be followed by the appearance of sugar (glucose) in the urine, while injuries to the head and neck, organic lesions of the brain, cerebral hemorrhage, cerebral tumors, more particularly involving the pons, cerebellum, medulla and posterior fossa, recall Claude Bernard's well-known "piqure" experiment, in which he established a transient glycosuria by puncture of the floor of the fourth ventricle between the vagus and auditory centres.

The causes and forms of glycosuria are, therefore, numerous, and no single theory, so far, suffices to explain all cases.

Conclusions.—Nevertheless, we think it possible to harmonize and bring into a common scheme the greater number of these diverse facts, and what is here said applies not merely to diabetes, but to all the group of conditions caused by disturbances in the discharge of the internal secretions.

1. As will be laid down more fully later (p. 449), it must be recognized that if, in general, the function of the nervous system is to control and

[1] Proc. Physiol. Soc., Jour. of Physiol., 34: 1906, ibid. 35: 1907, and Trans. Roy. Soc., Canada, 1907.

coördinate the various bodily functions, there are conditions under which it can stimulate one or other function in excess. Your drunken coachman may whip up the horses to a reckless and wholly unnecessary gallop. We must be prepared, for example, to find that glycosuria may present itself in the absence of any primary disturbance in the organs concerned in carbohydrate metabolism.

2. The elaboration and discharge of internal secretions has its limits. It is, therefore, possible to have an intake or production of the substance acted on by those internal secretions, over and above the capacity of the internal secretions to convert or neutralize them, and this, again, without primary disturbance of the organs producing those internal secretions. An alimentary glycosuria is thus to be expected in case of excessive intake of carbohydrates.

3. The morbid states here discussed are not the outcome of one, but of the interaction of at least two factors; they represent a want of balance between amount of internal secretion and amount of the substance upon which that acts. These two must always be kept in mind. Myxœdema, we find, is the series of signs and symptoms associated with insufficient discharge of thyroid secretion; but if animals with removed thyroids be kept on a vegetable diet, and so the substance or substances are not elaborated which, under ordinary conditions, are neutralized by the thyroid secretion, then, notwithstanding the absence of the thyroid, no symptoms of myxœdema show themselves. The same symptoms may be brought about:

(*a*) By diminution of the internal secretion in the presence of normal production of the substratum or substance upon which it acts; and

(*b*) By no diminution in the amount of internal secretion elaborated and discharged, but by excess of the substratum upon which it acts.

In the first of these cases we may expect to find morbid changes in the organ affording the secretion; in the latter, none; in the first, the tissues, if any are known, affording the substratum may be perfectly normal; in the second, they may be diseased. In other words, we may expect to find an identical syndrome in two cases, which, from the point of view of morbid anatomy or histology differ widely.[1] That this must be so appears to be too often overlooked.

4. Where, as would seem to be the case in connection with glycolysis, we have the additional element of a hormone, the case becomes yet more complicated. The same syndrome, it would seem, may be set up (*a*) by excessive development or intake of the substratum; (*b*) by lesion of the organ or organs in which that substratum undergoes disintegration preventing that disintegration; and (*c*) by lesion in the organ affording the hormone without which the disintegration cannot be effected.[2]

[1] Adami, The Internal Secretions, Trans. Congr. of Am. Phys. and Surg., 4:1907:103.

[2] For fuller study of the pancreas and of diabetes mellitus, the reader is recommended to Opie, The Pancreas; Williamson, on Diabetes, and Futcher's article "Diabetes," in Osler and McCrae's Modern Medicine, vol. i. Starling's Croonian Lectures, Lancet, London, 1905:i and ii, give an admirable grasp of the trend of recent investigations on the internal secretions

CHAPTER XII.

ENDOGENOUS INTOXICATIONS—(CONTINUED).

DISINTEGRATIVE INTOXICATIONS.

Autolysis.—There will be frequent occasion to refer to autolysis in discussing the various morbid processes and the part played in them by the self-digestion of the tissues; there is less to say regarding this action as a cause of morbid states. Nevertheless, to make ourselves clear, it is necessary to explain here in a little detail what we understand by this term and what we know regarding the extent of the process.[1]

It has long been known that proteolytic ferments are liberated in certain forms of cell disintegration. Thus, Leber, in the "eighties," showed that aseptic pus produced around copper filings had the power of dissolving white of egg and fibrin. Filehne, in 1877, Stolnikow, Fr. Müller, and others long ago obtained proteolytic ferments from gangrenous and pneumonic sputa. But the wide extent to which the tissues in general are capable of self-digestion (or autolysis) only became recognized after the publication of the works by Salkowski (1890), and more especially of Jacobi (1900). Hauser had previously noted that liver tissue, kept in a perfectly aseptic condition, underwent softening, the cells breaking up and becoming granular. These observers studied the phenomenon from its chemical aspect, and demonstrated that the process was of the nature of a proteolytic change. They showed that it still progressed when chloroform or toluol was added to the broken-up tissue, whereby bacterial activity was with certainty prevented, and when all that could happen was the result of enzyme action; as, also, that all the soft tissues of the body undergo this autolysis, although at varying rates, the softening and disintegration of normal liver substance being most active, that of renal cortex the next; skin and brain substance (contrary to expectation) being among the slowest to be affected.

Very many different enzyme actions evidently take place in this process; that which is the most evident is the conversion of protein from an insoluble to a soluble state. In fresh liver tissue, 90.4 per cent. of the nitrogen in a given example, which had been boiled and kept for several days, was found to be in an insoluble form, 9.6 soluble. An emulsion from the same liver after digesting itself for twenty-two days, and then being boiled, afforded only 39.4 per cent. of insoluble

[1] The fullest and clearest *résumé* in English upon this subject is by Wells (Chemical Pathology, p. 86 et seq.), who himself has made material contributions to the study.

nitrogen; 60.6 per cent. was soluble and contained in the filtrate.[1] But the nucleoproteids are broken down by nucleases; the purin bases are liberated, and, in their turn, acted upon by guanase and adenase; the fats are split up and fatty acids liberated, presumably by the action of lipase; the glycogen gives rise to glucose, and this, in turn, undergoes further splitting, being absent from the products of long-continued autolysis; lecithin is split up, and jecorin and allied bodies make their appearance, while, further, there is a marked increase in cholin and in cholesterin. What is interesting is that there is, as shown by Hildesheim and Leathes, a marked increase in the fatty acids, suggesting, at first, that these are developed from proteins; the probability is that a large proportion of the fat in organs like the liver, kidneys, and muscle exists in a masked condition—whether in a state of loose combination with the proteins, or how, has not surely been determined.

This process proceeds most rapidly at, or slightly above, the body temperature, and in a slightly acid medium. Wiener has shown that the process does not begin until the normal alkalinity of the tissues has been neutralized by the production of organic acids (lactic, butyric, etc.), which takes place in all dying tissues. We deal, that is, not with ordinary tryptic digestion (which proceeds in an alkaline medium), although the products of the proteid cleavage are of the same type; nor do we deal with peptic digestion, for they are far more advanced than those effected by peptic activity. For us, what is of immediate importance, is that, as demonstrated by Jacobi and others, this process of autolysis can take place in the living organism; cut off the blood supply to a section of the liver and the central part softens and affords leucin, tyrosin, and the other cleavage products found in autolysis outside the body. The outer part does not show change to the same extent, autolysis being evidently arrested by the diffusion of the alkaline lymph. Thus, it is only in the more central portions of relatively large areas of necrosis or cell death that autolysis manifests itself—save where there is invasion by leukocytes. As shown by Opie and others, the leukocytes possess enzymes, proteases, which differ markedly from those of the tissues; those act mainly or almost entirely upon the cells in which they are developed, but, once liberated, the leukocytic enzymes act indifferently upon various tissues. These properties explain the softening of septic infarcts and of the outer zone of simple infarcts, as the result of the migration of leukocytes into them; they explain, also, as Fr. Müller has shown, the softening and absorption of the consolidated exudate in the pneumonic lung, that exudate being, in the stage of gray hepatization, little more than a dense mass of leukocytes.

There is, however, another factor, as determined by Opie,[2] which regulates the autolytic action of leukocytes, viz., the presence in normal blood serum of an antibody, neutralizing the leukocytic protease. In

[1] Quoted from Wells, loc. cit.

[2] Journal of Experimental Medicine, 7: 1905: 316, and 8: 1906: 410.

pathological exudates the amount of this antibody exhibits variation; thus, an exudate which, although containing abundant leukocytes, is at first fibrinous, may eventually show disappearance of that fibrin through diminution of the antibody and unrestrained digestive activity of the enzyme liberated from the leukocytes. Jacobi would distinguish this solution of dead matter by the agency of wandering in leukocytes as *heterolysis*.

There are, however, conditions under which autolysis—not heterolysis—may obviously manifest itself in individual cells or groups of cells. The conditions under which the process manifests itself are not wholly understood. The liver, again, affords the clearest example, and that in a curiously assorted group of cases—acute yellow atrophy, phosphorus and arsenic poisoning, chloroform necrosis, and, to a slighter degree, in the pernicious vomiting of pregnancy.[1] In all these cases we obtain histological evidence of death of cells throughout the organ, others in the immediate neighborhood still retaining their vitality. The death is not immediate, but is preceded by indications of profound nuclear and cytoplasmic disturbance; it leads to a breaking down and disappearance of the affected cells. Coincidently, as pointed out by Salkowski, the liver tissue and the urine come to contain the products of autolysis—leucin, tyrosin, etc. In the livers of cases of phosphorus poisoning, Waldvogel and Tintemann[2] obtained increased amounts of cholesterin, jecorin, neutral fats, protagon, and fatty acids, with diminished lecithin, just as in the earlier stages of experimental autolysis. With Wells, we must conclude that in all these cases we have a death of the individual cells without inhibition or destruction of the intracellular enzymes; that just as chloroform, for example, kills bacteria, but leaves their ferments unaffected, so it acts also when exhibited in excess to the cells of the organism.

A partial explanation of this intravital autolysis is probably to be found in the coincident condition of acidosis. As already noted, the autolytic enzymes act best in a slightly acid medium; an alkalinity equal to 0.04 per cent. NaHO arrests their action.[3] Now, as will be pointed out (p. 348), it is in just this group of conditions that the alkalinity of the blood is diminished and acetonuria is apt to manifest itself. It is not that the mere acidity of the blood kills the cells; in diabetic coma, for example, we do not have this acute destruction of the hepatic parenchyma; some toxic agent must be present having a specific action on the liver cells, and the coincident acidosis favors the autolysis.

Turning now to a more immediate discussion of autolysis as in itself a cause of morbid states, it will be recognized that three possible orders of disturbances may exist: (1) Disturbances due to liberation of the enzymes and diffusion of the same; (2) those due to possible toxic action of the diffused products of autolysis; and (3) alterations in the excretions due to discharge of these products. This last is but a sub-

[1] See Williams, Johns Hopkins Hosp. Bull., 17: 1906: 71.

[2] Cntlbl. f Path., 15: 1904: 97. [3] Wiener. Centlbl. f. Physiol., 19: 1905: 349.

group of the second; it is not so much a morbid condition in itself as an indication and outcome of the existence of such, and we may dismiss it first.

Albumosuria.—Wherever there is extensive suppuration, with its attendant heterolysis, we gain indications in the urine by the development of what used to be termed *peptonuria*, but which now we know to be more correctly an *albumosuria*. This is most marked in the resolution of pneumonia, and in cases of empyema. A similar albumosuria, due to autolysis, has been noted in the case of large tumors undergoing softening and necrosis. In the case of diffuse autolysis of the liver, what is more marked is the appearance of amino-acids in the urine, with reduction of the urea.

Fever.—With reference to the liberated enzymes, it was demonstrated years ago by Hildebrandt that ferments of all orders injected into the blood set up marked *fever*, and the hyperpyrexia which is noted as following the development of an infarct, which follows internal hemorrhages and burns, and even that accompanying suppuration, might be ascribed to liberated intracellular enzymes. The fact, though, that there exist antibodies, or anti-enzymes, in the normal blood serum, which must tend to neutralize such enzymes, and that, save in the case of the leukocytes, we obtain no other evidence of action of these enzymes outside the organs which give origin to them, is, on the whole, against this supposition. Rather we must regard the fever, which may show itself even in experimental aseptic suppuration, as due to the intermediate products of metabolism poured into the blood. We know that peptones and albumoses injected into the system set up high fever. To bodies of this order the pyrexia is best attributed.

Some of these bodies are distinctly hemolytic. The anemia and cachexia accompanying malignant growths are by some attributed to the extensive breaking down and autolysis of the new-formed tissue that accompanies these states. A similar anemia accompanies all old-standing cases of suppuration.

Of the production and diffusion of acutely toxic substances we have little evidence save that of liberation of cholin in the autolysis of nerve substances. Cholin itself is but slightly toxic, but would seem to be easily convertible into the highly toxic neurin. Mott and Halliburton have found cholin in the cerebrospinal fluid in cases accompanied by nerve degeneration and softening, and have suggested that it is responsible for the convulsions and other toxic symptoms seen in these cases.

Burns.—The careful histological researches of Bardeen[1] and of my colleague, J. McCrae,[2] upon cases of extensive burns have shown that, even where death occurs before there has been time for adequate infection of the burned surfaces, the internal organs exhibit indications of an intense intoxication. Degenerative changes are seen in the liver, kidneys, and heart muscle, while the lymph glands present endothelial

[1] Johns Hopkins Hosp. Repts., 7; 1899; 137.
[2] Trans. Assoc. Am. Phys., 16; 1901; 153.

swelling and proliferation (McCrae) identical with that seen in typhoid, diphtheria, and other acute infections. The cell destruction has thus led to the formation, or liberation, from the burnt cells of bodies having an action resembling that of bacterial toxins. The rapidity with which these disturbances manifest themselves indicates that it is certain products of thermal disintegration of the cells that are directly responsible, rather than the secondary products of autolysis. Whether these are the liberated enzymes, or modified proteins, or yet other substances, is not surely known.

Coagulation and Thrombosis.—Closely associated in origin with heterolysis is the coagulation of blood, either outside the vessels (*coagulation* proper), or within them (*thrombosis*), and this because everything points to these processes being due to the production of an enzyme or active discharge of the same from the leukocytes contained in the blood, and its action upon the fibrinogen of blood plasma. We shall have more to say regarding these processes elsewhere.

It is still a matter of debate whether, in breaking down, the leukocytes liberate a kinase (thrombokinase), which activates a prozymogen present in the blood plasma, or *vice versa*, or what part the blood platelets play in the process. What is pertinent in this connection is that an essential factor in the formation of fibrin is a body liberated from the disintegrating leukocytes.

It is generally accepted that in the sudden death of a mass of tissue cells within the organism there is a like discharge of a body leading to *coagulation necrosis*, or coagulation of the whole of the dead area. (See Section III, Chapter XXXII.)

IMPAIRED METABOLISM AS A CAUSE OF DISEASE.

It is well to bear in mind that the instances brought forward in the last chapter in connection with the internal secretions are not those of primary causes of disease. It is to the relative excess or deficiency of one or other internal secretion that the particular signs and symptoms are to be attributed, but behind this excess or deficiency are the causes which bring about the same, and these may be very various—inherited, or acquired. So, also, some of the signs and symptoms may not primarily be due to the direct toxic effect of relative excess of either internal secretion or of the bodies neutralized by the same, but may be secondary, due to imperfect metabolism, brought about by want of due amount of the internal secretion. There is, however, a group of cases of disease in which, so far as we at present see, wholly apart from internal secretions and their excess or deficiency, the cells of certain organs (once again from antecedent causes of varying nature) do not carry out the metabolic processes to their normal termination; as a consequence, there are discharged from these cells substances possessing a more or less toxic action, or, through deficient oxidation, there accumulate in the system bodies not themselves toxic, but obstructive to the proper activity of

the tissues. These cases must be distinguished from another group in which it would seem that the intracellular metabolism proceeds aright, but the metabolites fail to be excreted, and, accumulating, give rise to disease. We make this distinction provisionally, or, more accurately, our knowledge is not sufficient to make it with absolute precision; nevertheless, it is well to attempt the separation. In the same rapid manner we must glance at the cases coming under these two categories.

Morbid Conditions Due to Various Products of Proteid Metabolism.—(1) **Gout.**[1]—This is a condition characterized symptomatically by attacks of acute arthritis and other constitutional symptoms; clinically, further, by the presence of excess of uric acid in the blood; and anatomically, by the deposit of sodium biurate in the joint cartilages and elsewhere.

Here we shall not consider the underlying causes predisposing and indirect (sex, heredity, alcohol, high living, lead poisoning), but consider the metabolic disturbances which everything indicates as underlying the symptoms of this disease, these disturbances being associated with the nitrogenous metabolism. The presence of urates in the joints (Wollaston, 1797), and of an excess of loosely combined uric acid in the blood (Garrod, 1848), led naturally to this conclusion, that either excess in production of uric acid or deficient elimination of the same, is the cause of the disease. We are now convinced that this is not so. As first shown by Galvani, in 1766 (before Scheele discovered uric acid), and confirmed by Kionka, ligature of the ureters in birds leads to extensive gouty deposits in the joints, without, however, other gouty symptoms. There is excess of uric acid in the blood in leukemia and during the resolution of pneumonia, without a sign of the gouty syndrome manifesting itself. Further, large amounts of uric acid and the urates may either be given by the mouth or injected without setting up recognizable disturbance, save, possibly, slight necrotic change at the site of inoculation. They are, in fact, curiously inert bodies. At most, *the urates are an indicator*, or, in other words, while they do not themselves cause disease, the faulty metabolism which leads to their accumulation produces simultaneously other bodies having toxic effects. What these other bodies are has not been determined with absolute precision, but the study of the conditions under which uric acid is formed is that most likely to lead to their detection. As a matter of fact, this study has been pursued with great vigor of late years, and the researches of Emil Fischer and Kossel in one direction, and Jones, of Baltimore, and his colleagues, of Schittenhelm and Burian, in another, have very greatly increased our knowledge.

In the first place, it has been shown that uric acid is one of a group of substances termed *purin bodies* by Fischer, inasmuch as all are derived from, or have as nucleus, the compound $C_5H_4N_4$, or purin, the members

[1] For an admirable study of the modern theories regarding gout, the student is directed to the article on this subject by Futcher, in Osler and McCrae's Modern Medicine, vol. 2.

of the group being derived from this by the replacement of the H atoms by hydroxyl, amide, or alkyl groups.[1]

These bodies are uric acid, $C_5H_4N_4O_3$; xanthin, $C_5H_4N_4O_2$; hypoxanthin, $C_5H_4N_4O$; guanin, $C_5H_5N_5O$; adenin, $C_5H_5N_5$; heteroxanthin, $C_6H_6N_4O_2$; paraxanthin, $C_7H_8N_4O_2$; episarkin, $C_4H_6N_2O$; carnin, $C_7H_8N_4O_3$, and epiguanin, $C_6H_7N_5O$. Uric acid is thus trioxypurin; xanthin, dioxypurin; and hypoxanthin, oxypurin. Adenin is amino-oxypurin. Kossel terms them the *alloxuric bodies*, on the ground that each is made up of an alloxan and a urea nucleus, and (with the exception of uric acid) they are also referred to as the *xanthin*, *purin*, or *alloxuric bases*. As already noted in the first part of this work, members of this group are obtainable from nuclein. This in itself is a point of considerable importance. It indicates that in the body it is not from the ordinary cell proteins that they are derived, but from nuclear disintegration, the mother purin substance being present in the nucleic acid, combined, it is held, with phosphorus. Food, like milk, containing no purin bodies, gives rise to a minimal excretion of uric acid and purin bodies; on the contrary, feeding animals with nuclein, or substances like the thymus and pancreas (which are rich in nuclei and nucleins) leads to a great increase in uric acid excretion. There are, indeed, the two sources for the urinary purin bodies, the *exogenous* from the food undergoing assimilation, and the *endogenous* from the tissues. The excretion of the latter is relatively constant in amount for the individual, being derived from the normal disintegration of nuclear matter, and, it would appear, of muscle substances. Hypoxanthin is a constant product of muscle metabolism, and with increased exercise there is increased output of uric acid (Burian). The greatest discharge of this endogenous uric acid is encountered in leukemia, in which there is excessive production and breaking down of the leukocytes and their nuclei, as also in the resolution of pneumonia, through absorption of the autolyzed leukocytes.

We have already implied (in the statement regarding muscle hypoxanthin and urinary uric acid) that the conversion of one purin body into the other takes place within the organism. *In vitro*, this conversion can be readily produced. Thus, if finely divided sterile pancreas be allowed to act upon guanin for some hours at 40° C., the guanin is converted into xanthin. As pointed out by Jones and Partridge, there is, obviously, a ferment present, by which the transformation is accomplished. This they term *guanase*. In like manner, Jones and Winternitz have found that through the action of *adenase* present in thymus, adrenals, pancreas, and liver, adenin is converted into hypoxanthin. Continuing these researches, they have discovered that the different glands contain different ferments or groups of ferments. The thymus, subjected to autodigestion, yields abundant xanthin, a little hypoxanthin and uracyl, but no guanin or adenin; the spleen, similarly

[1] I here follow Futcher's account of the relationship between these bodies, that being quite the clearest yet given

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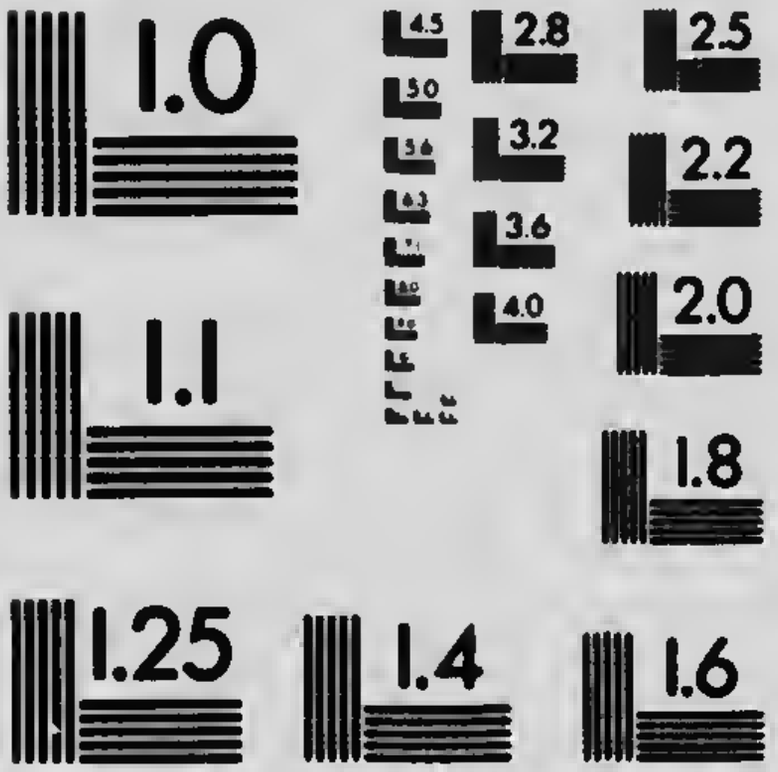

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treated, affords abundant hypoxanthin and guanin, but no adenin or xanthin. In both cases ammonia is split off; the ferments are typical de-amidizing agents (Chittenden).

$$\underset{\text{Guanin}}{C_5H_5N_5O} + H_2O = \underset{\text{Xanthin}}{C_5H_4N_4O_2} + NH_3$$

$$\underset{\text{Adenin}}{C_5H_5N_5} + H_2O = \underset{\text{Hypoxanthin}}{C_5H_4N_4O} + NH_3$$

It will be noted that in these reactions uric acid does not make its appearance. Its development, as shown by Schittenhelm, is due to another ferment, an *oxidase*, present in the liver, lungs, muscles, and spleen, whereby the alloxur bases are oxidized to uric acid. The same observer has found another oxidase in the kidneys, liver, and muscle, which is capable of oxidizing uric acid into urea. Lastly, we have evidence of the existence of an intracellular *nuclease* (Sachs, Ivanoff), by the action of which nucleoproteids are disintegrated with the liberation of the purin or alloxur bases; and, even further, enzymes liberating the nucleoproteids from other proteins.

We thus have the following steps:

1. Nucleoproteids, exogenous, (of nuclei) of foodstuffs taken up by the cells; or endogenous and part of the cell structure, acted on by *nuclease*, yield.
2. Purin bases, which, acted on by deamidizing enzyme (*guanase*, *adenase*), yield
3. Xanthin and hypoxanthin, which, acted on by an *oxidase*, yield
4. Uric acid, which, acted on by an *oxidase*, may yield
5. Urea.

It need scarcely be said that this is neither the only, nor more than an insignificant, source of the urea normally excreted. We mention it here, as it throws light upon the variations in the amount of uric acid that, under different conditions, may be derived from the same diet. Nay, more, it offers a suggestion as to the cause of the accumulation of urates in the blood and tissues in the gouty state.

What is requisite now is a fuller study of the toxic effects of the purin bases. The evidence is that these are distinctly more toxic than the urates: they cause fever independent of the presence of any infective agent (Mendel),[1] and the administration of adenin to dogs and rabbits leads to degenerative changes in the kidneys, with deposits of spherolithis of uric acid (or quadriurate) in the tubules, and of ammonium urate in the kidney substance. This recalls the condition of chronic nephritis, which so commonly accompanies gout. We can, at most, say that the trend of modern work is to the conclusion that the presence of the deposits of sodium urate in the joints and elsewhere, and the presence of loosely combined uric acid in the blood, indicates disturbed purin metabolism. An interesting observation in this direction is that of Beebe, working with Chittenden. Alcohol taken with a purin-

[1] Amer. Jour. Physiol., 10:1904:452.

free diet leads to no increased output of uric acid. Given with a diet containing a definite quantity of purin, there is an immediate increase in the excretion of uric acid. We know that alcohol is one of the factors leading to the gouty state; we know also that it reduces oxidation.

It would seem indicated that *gout is the outcome of insufficient oxidation*, whereby, in the first place, the precursors of uric acid are not wholly oxidized, and so, accumulating, set up morbid changes; while what uric acid is formed is in its turn imperfectly oxidized, and so tends to accumulate in the blood, and that *this diminished oxidation is due to a constitutional deficiency of oxidases, whether inherited or acquired.*

What leads to the formation of *tophi* and urate deposits in the joint cartilages is still an open question, although, contrary to the view of Ebstein, that originally maintained by the English workers is gaining ground, viz., that the deposit is primary, the necrosis secondary. It is still an open question, also, regarding the form in which the uric acid is present in the blood. The acid itself is most insoluble; it is a dibasic acid. The biurate, or acid sodium urate NaHU, ($U=C_5H_4N_4O_3$), is deposited in the joints and tophi; the neutral urates, Na_2U, have never been found in the body. Sir William Roberts, following certain work of Bence-Jones, held that the form present in the blood is the soluble, but easily decomposed *quadriurate*, $NaHU.H_2U$, and made a series of observations strongly supporting the view, but it has not gained complete acceptance.

These, however, are matters not wholly bearing upon causation.

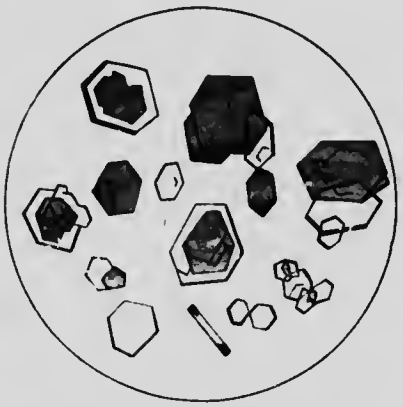
(2) **Cystin and Cystinuria.**—There is a rather remarkable condition, frequently of an hereditary nature, being observed in members of the same family, and, it may be, for successive generations. It is relatively harmless, save for the disturbance set up by calculus formation, in which *cystin* is excreted in the urine. This cystin is a sulphur-containing amino-acid—

$$\begin{array}{l} S - CH_2 - CHNH_2 - COOH \\ | \\ S - CH_2 - CHNH_2 - COOH \end{array}$$

It occurs in the urine in hexagonal crystalline plates, which, as above indicated, may accumulate into concretions. There has been considerable debate as to its origin, whether exogenous and due to abnormal disintegration of proteins in the alimentary tract, or endogenous and due to some aberrant intracellular metabolism. The fact that it may be present in the absence of products of intestinal putrefaction, such as *cadaverin;* that it shows itself in the absence of proteid diet, and is excreted over long periods independently of variation in the amount and nature of the food taken, together with the hereditary nature of the change, all indicate that we deal with an abnormal disintegration or conversion of the sulphur-containing portion of the protein molecule. It is possible that, normally, through the action of some special enzyme, this is in part converted into taurin, appearing in the bile as taurocholic acid; in part into the neutral sulphur of the urine.

(3) **Alkaptonuria.**—A condition in many respects parallel to the last is alkaptonuria, in which, over long periods—in fact, through life—and with little apparent effect upon the health of the individual, the urine turns dark upon exposure to the air. The phenomenon has been found due to the presence of two aromatic substances, *homogentisic* and *uroleucic* acids. These evidently are due to incomplete burning up of the aromatic constituents of the protein molecule—*tyrosin* and *phenylalanin*. When those exhibiting this condition are fed with these two substances there is a marked increase in the amount of the two acids excreted; whereas, in normal individuals, similarly fed, not a trace of either acid is to be found. The same is true in feeding with homogentisic acid. The alkaptonuric individual is incapable of carrying out the final stage of oxidation. By analogy it would seem that here also we have to deal with the deficiency or absence of a specific intracellular oxidase. The normal steps would seem to be: (1) separation of the tyrosin and phenylalanin from the protein molecule (alanin side chain); (2) oxidation of the tyrosin and phenylalanin into homogentisic and uroleucic acids; (3) further oxidation, with splitting up of the benzene (aromatic) ring. It is this last stage which is not carried out in the alkaptonuric.

FIG. 135



Crystals of cystin spontaneously voided with urine. (Roberts.)

There are, it may be noted, yet other causes of darkening of the urine, *i. e.*, the presence of a chromogen (melanogen) in cases of melanotic new-growths, and the absorption and excretion of phenol.

Morbid Conditions Due to Impaired Metabolism of Other Orders.—Liposis, or Obesity.—Here, in passing, we may note another condition which, like alkaptonuria, is morbid, though not of a toxic type. We refer to the accumulation of fat in the tissues. At most, where extreme, this hinders activity, and, doing this, brings about diminished oxidation, thus setting up a vicious circle. For, primarily, this accumulation of fat must be regarded as brought about by inadequate oxidation of the foodstuffs. The result may be impaired locomotion, dyspnœa, and palpitation. How much fat may be stored up is shown by Meyer and Falta's observation that the body of an individual 111 kilograms in weight afforded 51 kilograms of fat, or 38 per cent. of the total weight.

To what are we to ascribe this storing up of fat? The normal fate of fat is to be burnt up, CO_2 and water being the ultimate products. From this it follows that in obesity we have to deal either with: (1)

excessive absorption of food, either fats themselves, or substances which, like carbohydrates, afford fat in the process of katabolism; or (2) inadequate combustion of the fats so acquired; in other words, diminished oxidation. There is a certain amount of clinical evidence that liposis may be due to both of these causes; we have the plethoric type of corpulency, occurring in those with blood rich in corpuscles and hemoglobin, and the anemic type, in pale individuals, with reduction in the amount of hemoglobin and corpuscles. In the latter, at least, the indications are those of lowered oxidative powers. Of the former, we can distinguish two groups, one largely yielding an hereditary history in which a normal diet is associated with progressive obesity. In these two explanations afford themselves: (1) That these individuals have such excellent absorptive powers, that the digestive availability of the food consumed is in them rendered much above the normal, the excess absorbed becoming stored up in the form of fat. In a second group there is excessive feeding. As regards the first, the fact that the obese heredity is, in a very large percentage of cases, associated with the gouty diathesis suggests that more is present than mere excessive consumption. (2) If gout be an indication of imperfect oxidation of one group of metabolites, so, probably, in these cases also a lack of oxidase is connected with the lack of fat consumption.

Acetonuria.—While thus, normally, we have no indication of disturbances other than mechanical, set up by inadequate metabolism of fats, there are morbid conditions best explained on the supposition that the toxic substances accumulating in the system are products of intermediate fatty katabolism. In diabetes, the peculiar odor of the breath —like that of an apple cupboard—is due to acetone, and this is found in the urine, in severe cases, in considerable quantities. Acetone itself is productive of little disturbance.[1]

But associated with this in diabetes, the acetone bodies appear in the urine—*β-oxybutyric acid* and the oxidation product of the same, *diacetic acid*. These acetone bodies might be derived from any one of the three main groups of foodstuffs and cell constituents—from the amino-acids of the protein molecule, from the fatty acids and from the carbohydrates. Their excretion in cases of diabetes mellitus naturally suggests abnormal carbohydrate metabolism. But they may also show themselves in a group of other conditions—in high fever, wasting diseases, in cancer and in starvation, in which the store carbohydrates of the system —the glycogen—have become used up; the fact that the administration of sugar lowers their discharge is against the theory of impaired carbohydrate metabolism. We know so little regarding the normal stages of fat disintegration that it is not possible to formulate how these bodies are derivable from the fatty acids; we can only suggest that just as β-oxybutyric acid by oxidation becomes converted into diacetic acid, and then into acetone, so the higher fatty acids may similarly become

[1] In 1886, at the instigation of the late Professor D. J. Leech, the writer took progressively increasing doses with no ill effects.

changed into these acetone bodies by progressive oxidation. Eppinger's[1] observation that the administration of amino-acids to rabbits arrests the appearance of acidosis would suggest that normally the ammonia evolved in ordinary protein metabolism combines with these lower fatty acids and prevents their appearance in the urine. It may be that their appearance in starvation is due to the fact that the fats of the organism are disintegrated at a greater rate than are the proteins. Nevertheless, it has to be admitted that if we accept this progressive disintegration of the fatty acids we must also recognize the possibility that the aminated fatty acids—the amino-acids of the protein molecule—are capable of undergoing a like series of disintegrations. In other words, the matter of the origin of the acetone bodies is still very largely an open question.

The symptoms, it may be added, are those common to acidosis—they are those of a grave intoxication, with air hunger, and nervous symptoms passing into coma and death.

Acidosis.—That the accumulation of β-oxybutyric and diacetic acids in the blood is the cause of the main symptoms of diabetic coma is evident from the fact that almost identical conditions follow the treatment of animals, especially herbivora, by repeated doses of inorganic acids. They become stuporous, their gait is unsteady, the breathing extremely rapid, the blood is bright red, containing much less CO_2 than normal, and with this there is a marked diminution in the alkali of the blood. Administer alkalies, and these symptoms pass away. The explanations would seem to be that, normally, the alkalies of the blood take up the CO_2 as it is formed in the tissues, convey it to the lungs, where, aided by the oxidase present, the CO_2 is split off and the salt, once more rendered basic, is prepared to join with another molecule of CO_2 in the tissues. Where there is an excess of other acid in the blood, it is this that combines with the alkaline salts, and as a result the CO_2 accumulates in the tissues, symptoms of asphyxia ensuing.

In carnivorous animals the combination affects not only the alkalies proper, Na, K, etc., but also ammonia. There is in these cases a diminution of urea in the urine, with great increase in ammonia compounds, indicating that in the disintegration of proteins there is an ammonia antecedent of urea, and that this in the blood combines with and neutralizes the excess of acid present.

As already noted, there are other conditions besides diabetes which afford these symptoms of acidosis with discharge of acetone bodies—starvation, fevers, cachectic conditions and, we should add, the pernicious vomiting of pregnancy, chloroform anesthesia, retained placenta and fœtus. These last conditions have this in common, that they may exhibit profound hepatic disturbances. Whether here the glycogenic function is gravely disturbed, or the lipolytic, must be left an open question.

Another acid which has been detected in the urine in increased quantities is *lactic acid*—in rheumatism, osteomalacia, and rickets. This is

[1] Wien. klin. Woch., 1906; 111.

never in quantities sufficient to set up the extreme changes produced by the acetone group, and, as regards the effects on individual tissues, there is so much debate and contradiction as to display our almost complete ignorance of its action as a cause of morbid states.[1]

Dyspnœa and Asphyxia.—These conditions may now strictly be included among the acidoses. For long there was debate as to whether the main symptoms were due to lack of oxygen or excess of CO_2. The researches of Haldane and Priestley appear to have finally answered the question.

It is well established that muscular exercise most materially leads to a using up of the oxygen in the blood and to an active discharge into the same of corresponding increased amounts of CO_2. In the circulating blood the above observers have shown that the amount and tension of the oxygen may be altered from 20 to 8 per cent. without any increase in the depth or frequency of the respiratory movements, but that relatively slight increase in the amount, and more particularly the tension of the CO_2 in the blood, finds the respiratory centre extraordinarily sensitive, increasing its activity, whereas diminution of the tension of the gas depresses the activity of the centre and causes slowing of the respiration, or even apnœa—total arrest of respiratory movements. A rise of only 0.5 per cent. in the tension of the carbon dioxide in the air in the alveoli, and so in the blood circulating around those alveoli and supplying the brain, was found to increase the volume of air respired 100 per cent.

This may appear contradictory to what has just been noted regarding the air-hunger of diabetic coma, in which the amount of CO_2 in the blood has been found greatly decreased (in one case Minkowski found it reduced from normal 36 to 3.3 per cent.). It must be remembered that, as Haldane and Priestley show, the phenomena depend not upon the total amount of CO_2 which can be extracted from the blood, but upon the tension of the (free) CO_2. In diabetic coma other acids combine with the alkalies present in the blood plasma. Very much less CO_2, in consequence, is taken up; but it still diffuses into the blood, and is present in a free state.

In this connection might well be discussed the subject of *impaired carbohydrate metabolism*. It has, however, seemed more serviceable to take up the main example of this—diabetes mellitus—in the previous chapter in connection with the internal secretions.

THE INTERMEDIATE INTOXICATIONS.

Gastro-intestinal Intoxications.—Constipation.—It is a familiar experience to those regular in their habits, or, in other words, to all

[1] To this lactic acid Zweifel attributes the acidosis of pregnancy, finding this acid both in the urine and in the blood of eclamptic cases. For a criticism of modern views on this form of acidosis see Leathes, Proc. Roy. Soc. of Medicine, 1: 1908: No. 5.

healthy adults, that failure to pass the morning evacuation is apt to be followed by a certain amount of heaviness and feeling of being "out of sorts," with mental dulness, accompanied, it may be, later in the day by slight headache and malaise. It is true that a habit of constipation may be developed, and may continue for years without grave lesions being manifested. The late Sir George Humphry, in his lectures, was accustomed to cite the case of two elderly maiden ladies, patients of his, who, living abstemious lives, indulged with regularity in but a monthly evacuation! We do not imagine that those two old ladies were cheerful; the common experience is that habitual constipation is associated with irritability and depression of spirits, other symptoms of a low toxic state showing themselves in lack of energy, muddy skin, and tendency to "spottiness."

It is more particularly in those cases in which there is a sudden or complete obstruction of the upper bowel that pronounced indications of intoxication show themselves. The subnormal temperature, vomiting, muscular weakness, and actual collapse encountered in these cases of ileus can only be attributed to a resorption of intestinal contents, and this is proved by the appearance in the urine of considerable amounts of the products of imperfect or abnormal metabolism of the foodstuffs, of indol, and other sulphuric acid nitrogenous compounds.

The graver and more immediate results ensuing upon obstruction of the upper intestine, as compared with the lower, indicate one of two things: either that normally in the digestive process toxic bodies are elaborated in the stomach, which undergo modification into harmless compounds lower down the digestive tract, or that the result of obstruction is to lead to abnormal fermentations in the upper portion of the canal, to the growth of bacteria there not normally present, and to the production of toxic products of their activity. There is a certain amount of evidence in favor of each of these suppositions. It has been shown by Magnus-Alsleben[1] that the contents of the stomach and duodenum of the normal dog are distinctly more toxic than are those of the lower part of the bowel. On the other hand, we know that in the healthy individual, while abundant bacteria may be taken into the stomach with the food, they undergo in the main a fairly rapid destruction, and that in the duodenum of the healthy animal that has been starved for a short time absolutely no bacteria may be present. The case is very different in the rest of the small intestines, whose alkaline contents favor the rapid proliferation of bacteria, so that in the neighborhood of the end of the ileum they reach their maximum abundance and activity; that, passing into the colon, with the concentration of the feces, their number now undergoes rapid diminution, so that from the stools of a healthy individual it may be that relatively few colonies are obtainable, although other observations demonstrate that quite a considerable proportion of the matter constituting the healthy stool is in the form of bacterial remains. We know, further, by experiment, that obstruction to any

[1] Hofmeister's Beitr., 6:1905:503.

part of the alimentary canal leads to active proliferation of bacteria above the point of obstruction and to the assumption of definitely increased virulence by those bacteria. Thus it is more than probable that the toxic effects of obstruction are associated with this increased bacterial activity. Granting all this, it has to be admitted (1) that the substance or substances setting up the particular train of symptoms seen in ileus has not yet been isolated, and (2) that intestinal bacteria grown outside the body have not, so far, been shown to produce substances setting up these particular symptoms. We are, in short, only at the beginning of a knowledge of the intestinal intoxications.

Indol.—Of the known products of the putrefactive or bacterial decomposition of proteins, but one, or one group, stands out with any prominence, and this more as an indicator of intestinal putrefaction than, it may be, as an active toxic agent. This is indol, and with it other substances derived from the aromatic radicals of the protein molecule. We know that what is the commonest of the bacterial inhabitants of the intestine—the B. coli—is capable of forming this from peptones outside the body. We detect it in the urine in these cases of obstruction. Indol, as shown by Herter,[1] has distinct and suggestive toxic properties. It is capable of setting up irritability, mental dulness, and headache—symptoms, it will be seen, closely resembling those of constipation. The amount found in the urine of well-marked cases of obstruction is, however, so small, compared with that necessary to induce these symptoms when administered by the mouth, that it is gravely debated whether this can be regarded as the agent setting up these particular symptoms in obstruction. Our inclination is toward accepting Herter's view, and this from the fact that when indol is administered *per os* in quantities sufficient to produce definite symptoms, only a very small proportion can be regained in the urine; it would seem, therefore, quite possible that in obstruction there may be absorption of amounts of indol adequate to induce symptoms, and yet there be little excretion in the urine. But something more would seem necessary to account for the graver symptoms of ileus.

Other decomposition products of the aromatic radicals are skatol, phenol, paracresol, indolacetic acid, paraoxyphenylacetic acid, and paraoxyphenylpropionic acid. All these may be detected in the urine.

Ptomaines.—For a time great expectations were based upon these bodies, not only as affording an explanation of the intestinal intoxications, but also as explaining the specific toxic effects of pathogenic bacteria. As regards the second of these, we now know that the ptomaines are not specific—*i. e.*, particular species of bacteria do not lead to the formation of ptomaines peculiar to those species; wherefore, to the ptomaines cannot be attributed the specific toxic symptoms of the different diseases; and secondly, that the amount of ptomaines present in bacterial culture fluids is inadequate to induce the toxic effects of these fluids. As regards intestinal intoxication, it may be, as we shall point

[1] New York Medical Journal, 68: 1898: 89 and 116

out, that one group of ptomaines is responsible for certain disturbances. If animal matter of various orders be allowed to undergo putrefaction for several days, the product was found by Gautier to contain small but definite quantities of nitrogenous bases, allied chemically to the vegetable alkaloids. To these Selmi, in 1881, gave the name *ptomaines* (*πτωμα*, a corpse). We owe the fullest study of the substances and their properties to Brieger. The active and abundant studies of the "eighties" demonstrated the existence of a large group—some two score—of these bodies; among them may be noted:

Methylamin	$CH_3 - NH_2$
Dimethylamin	$CH_3 - NH - CH_3$
Trimethylamin	$CH_3 - N - CH_3$, or $N(CH_3)_3$
	$\mid$ CH_3
Cholin	$CH_2 OH - CH_2 - N(CH_3)_3 - OH$
Neurin	$CH_2 - CH - N(CH_3)_3 - OH$
Muscarin	$CH(OH)_2 - CH_2 - N(CH_3)_3 - OH$

Certain basic substances, such as the tyrotoxicon separated by Vaughan from putrefying cheese and milk products, while intensely toxic, have not yet been obtained in sufficient amounts to permit full analysis. While the majority of these bodies are non-toxic, a few are intensely toxic, having properties and constitution very similar to those of muscarin and other vegetable alkaloids; muscarin itself has, indeed, been isolated by Brieger from the cod. The central radicals of these bodies are amino groups; this fact and the mode of origin indicate that they are penultimate[1] products of the disintegration of proteins. Nevertheless, it may be that these are not in all cases directly derived from the proteins. Among the most widespread components of the cell are the compound fatty bodies, the lecithins, compounds of fatty acid molecules with phosphoric acid and cholin. The disintegration of these bodies will afford cholin, and this, indeed, has been isolated from brain matter that has undergone putrefaction (which affords much lecithin). Cholin itself has relatively slight toxic powers; in la doses, however, it has muscarin-like effects. Mott and Halliburton were the first to call attention to the presence of free cholin in the cerebrospinal fluid in degenerative conditions of the brain matter. Donath[2] and Rosenheim[3] have confirmed their work. The former finds that, introduced directly under the dura, cholin has a powerful action upon the nerve substance, setting up severe convulsions, tonic and clonic. He suggests thus that cholin may be responsible for the development of epileptic attacks.

On the other hand, introduced into the alimentary tract, cholin is found relatively harmless; the case is very different with neurin and muscarin, of which the former can be gained from cholin. As shown by the formula already given, it differs from cholin by the loss of a molecule of H_2O; it is intensely toxic. That neurin is formed in the organism

[1] Penultimate, because if putrefaction be continued beyond a certain limit they diminish in amount, giving place to nitrates and ammonium compounds.

[2] Zeitschr. f. physiol. Chemie, 39: 1903: 526.

[3] Journal of Physiology, 35: 1907: 465.

is indicated by Kutscher's detection of it in human urine. It is thus well within the bounds of possibility that some of the depressant effects of constipation are due to the development and absorption of bodies of the neurin and muscarin type from fermenting fecal matter. But if such be present, it must be purely as the result of bacterial activity, and the same is true of the aromatic derivatives, indol, skatol, etc. Investigators have been unable to gain either category of bodies by the action of the digestive ferments upon foodstuffs in the absence of bacterial growth.

Here a word of caution should be introduced against the acceptance of not a few of the results announced by workers, more particularly of the Bouchard school. Toxic effects have been ascribed to not a few products of protein disintegration recognized as present in fecal matter, the urine, and other excretions, which now we are assured have been due to accompanying potassium salts.

It would appear to be bacterial fermentation more than the action of the digestive ferments that leads to the production of irritative and noxious products of carbohydrate disintegration. Foremost of these are the series of organic acids: lactic, butyric, formic, etc. Little is known regarding the deleterious effects of these in individual cases, but, on the other hand, it has been shown by Boix and others that the administration of them in repeated doses leads to very definite disturbances in the different tissues, of a chronic type; such as, for example, cirrhosis of the liver.

Besides cirrhosis, many of the more chronic or constitutional disorders have, indeed, been ascribed to absorption of the products of abnormal gastric and intestinal fermentations: chlorosis, pernicious anemia, rheumatoid conditions, Graves' disease, myxœdema, migraine, and epilepsy—and the series could be greatly extended. It is, indeed, well within the bounds of possibility that the ascription is in many of these cases correct, but indubitable evidence is wanting. It is also possible, as I have pointed out elsewhere,[1] that in some of these, at least, we deal not with intestinal absorption: excessive growth of one or other form of intestinal bacteria and the resulting irritative conditions of the mucosa being followed by increased carriage into the portal circulation of bacteria of low virulence, the destruction of the same, and liberation of their endotoxins within the vessels and tissues, causing hemolysis and hepatic irritation.

It will be seen that these considerations all tend to point in the one direction—that the gastro-intestinal intoxications are, strictly speaking, exogenous, and in no sense auto-intoxications.

OBSTRUCTED ELIMINATION OF THE PRODUCTS OF KATABOLISM AS A CAUSE OF DISEASE.

Two closely related conditions may be considered under this heading: (1) The failure of excretory organs to eliminate, in consequence of

[1] Jour. Am. Med. Assoc., 33: 1899: 1565 and 1572

disease; and (2) the retention of the eliminative powers by these organs but subsequent resorption of constituents of the excreta, owing to obstruction in the ducts.

The results of the two processes are not necessarily identical; there is, for example, a marked difference, as pointed out by Rose Bradford, between the results of removal of the two kidneys, and ligature of the two ureters, a difference showing clearly that certain, at least, of the final metabolic processes are conducted by the gland cells of the excretory organ. But in other conditions, as in obstructive jaundice, there are indications that the metabolites, the results of the cell activities of the excretory organ, may, as the result of the obstruction, not necessarily be excreted and then reabsorbed, but may pass direct from the excretory cells into the blood and lymph. Thus, no sharp line is to be drawn between the two conditions.

The Resorption of Excretions.—Excretions, or certain constituents of the same undergo resorption under normal conditions to a far greater extent than is generally realized, and this as a physiological process. The solidification of the feces in the colon is in itself evidence that the watery constituents of the digestive juices become reabsorbed; the view nowadays most generally accepted regarding the mode of secretion of urine is that the urine becomes concentrated in its passage down the urinary tubules by resorption; the remarkable increase in the solid constituents of gall-bladder bile, as compared with that collected direct from the bile ducts, indicates a similar absorption. Not only this, but the complete disappearance of certain constituents from the intestinal contents is most simply explained in the supposition that they undergo resorption there. Nay, more, as shown experimentally by Aschoff, if the full gall-bladder be occluded, within a few days it may be found empty, all the constituents being taken up again. As I point out elsewhere, we are compelled to recognize a *reversibility* not merely of enzyme action, but also *of cell activity*. According to the influences acting upon either side of a secretory cell, so will it in certain cases either secrete or absorb. So long as the resorption is within limits, little or no disturbance is set up. Serious results are apt to occur if the process be long continued, and this with greater ease if the excretory products be taken up by cells other than those which have discharged them.

The most striking example of such resorption occurs in *obstructive jaundice*. There has been, and continues to be, debate as to the exact process which occurs here. Both Harley and Ziegler conclude that the liver cells may, in consequence of the obstruction, discharge the substances elaborated by them, not into the bile duct, but into the system; they differ as to the details of this discharge. The former, by coincident ligature of the common bile duct and the thoracic duct (which receives the lymphatics from the liver), shows clearly that the onset of jaundice is delayed for several days over cases in which the bile duct alone is ligated, and concludes, therefore, that the bile constituents pass from the liver cells into the lymphatic system of the organ. The

latter demonstrated equally surely by histological methods that the bile can be seen making a direct entry into the hepatic blood capillaries. The probability is that both are right and both wrong; that neither process is exclusive; and it may be that one or other predominates, according to the activity of the liver cells. But over and above this where the obstruction is not in the bile capillaries, but lower down, the intrahepatic ducts are found widely distended, with signs of irritation around them, and, as Ford[1] more particularly has shown, working in our laboratory, this irritation may lead to the development of a characteristic type of duct cirrhosis. It is evident that in these cases there is resorption from the bile ducts.

A fuller description of jaundice is given in the discussion of the various forms of pigmentation in Section III, Chapter XVII. Here it need only be said that jaundice is more than a mere pigmentation; accompanying this are cerebral symptoms, slowed pulse, itching of the skin, lowered coagulating power of the blood, with tendency to hemorrhages. The more important of these symptoms, cerebral dulness, slowed pulse, and even hemolysis, can be reproduced by the experimental injection of the bile salts. It is those that are in the main responsible for the symptoms other than the jaundice itself.

The indications are that these bile salts, under physiological conditions, undergo resorption in the intestines, setting up there no disturbance, and that because, as Sir Lauder Brunton has pointed out, taken up thence into the portal system and conveyed once more to the liver, they are there again taken up and discharged by the liver cells, and so, as it were, undergo a lesser circulation. There is a like intestinal resorption of the bile pigments, but this after they have in the bowel been converted into hydrobilirubin. Neither icterus nor cholemia would ever seem to be set up by absorption of these bodies from the alimentary canal.

The Pancreas.—Opie has called attention to the deleterious local effects of resorption of the pancreatic juice.

If the pancreatic ducts of a cat be ligated and the animal killed at the end of two or three weeks, the gland is found to be the seat of chronic interstitial inflammation. Schulze and Ssobolew have performed similar experiments with similar results. The inflammation specially shows itself around the ducts.

As Opie,[2] Halsted, and others have shown, obstruction of the ampulla of Vater by a biliary calculus may, under certain conditions, lead to the obstructed bile making its way into the pancreatic duct, and then its absorption leads to the more acute condition of hemorrhagic pancreatitis.

The Kidneys and Uremia.—Under the heading Uremia we include all the symptoms associated with retention in the system of the urinary constituents. Such retention may be of more than one order. It may

[1] American Journal of Medical Sciences, 121: 1901: 60.

[2] Am. Jour. of Med. Sci., 121: 1901: 27 and Diseases of the Pancreas, 1903: 71.

be due (1) to disease of the kidneys and renal incompetence, so that these constituents fail to be abstracted from the blood; or (2) to ureteral obstruction, so that, primarily at least, the kidneys perform their function, and, as in the case of the obstructed bile duct, in part we deal with resorption of the urine, in part with return from the renal epithelium of the products of their metabolism into the blood or lymph; or (3) it may be due to resorption of the urine from the bladder, where there is a prostatic or urethral obstruction. In this last case more particularly there is apt to be infective and fermentative change in the urine, and it is the modified constituents that are resorbed. German authorities have spoken of this condition as *ammoniemia*, the earlier idea being that the symptoms were more particularly due to the absorption into the system of the ammonia salts, the result of decomposition of the urea. It is true that ammonium carbonate has certain toxic properties, and that its absorption in considerable quantities may possibly set up disturbances; it has not been shown that this produces the symptom complex seen in vesical obstruction; it would seem more probable that intermediate products of protein metabolism are here to blame.

The symptoms are most marked and most characteristic in the cases of the first order, which are the most frequent; it is in these that we are most apt to have pronounced headache, nausea and vomiting, convulsions of an epileptic type, passing on to coma, dyspnœa, with asthmatic attacks and Cheyne-Stokes breathing, and evidence of gastric and intestinal catarrh, going on to ulceration. It is remarkable and suggestive as to the nature of uremia, that where the kidneys have not been primarily at fault, then, in case of urethral or vesical obstruction, there may be complete anuria for several days without uremia showing itself; when in these cases it does supervene, it suggests itself that the back pressure has eventually led to renal disturbance; in other words, the most satisfactory view is that uremia is due to the heaping up in the blood of substances not acted upon duly by the renal epithelium. This view is supported by the experiments of Rose Bradford upon the different effects of complete removal of the kidneys in animals, as compared with the fact that nephrectomized animals may be kept alive for several days and uremia be warded off by injecting extracts of healthy kidney substance. Such kidney extract cannot excrete and discharge urea and its precursors; they must still tend to accumulate in the blood; but it may convert certain of these substances from a toxic into a relatively harmless state.

What the substance or substances may be that are responsible for the nervous and other symptoms has been the source of abundant debate, experiment, and theory. One theory after another has been propounded, only to be shown inadequate; the present standpoint is one of a healthy agnosticism. As above stated, ammonium carbonate does not suffice, neither does ammonium carbamate (a possible precursor of urea). The potassium salts which should be discharged are toxic, but if they accumulate slowly in the organism they set up little

disturbance. Bouchard has described toxic substances present in normal urine, possibly ptomaines (diamines), differing in the overnight and daily urine. Stadthagen has wholly denied his findings. There is, as von Jaksch showed, a distinct accumulation of urea in the blood of most (but not all) uremic cases, but urea is curiously inactive, save upon the kidney itself. The same observer finds also an increase of uric acid, but the yet greater amount of this in gouty blood sets up no uremia. Kreatin and kreatinin have been invoked because the latter applied to the cerebral cortex causes convulsions; but these are not increased in the uremic blood. The family likeness of the conditions to diabetic coma has suggested that acidosis is the cause. von Jaksch calls attention to the diminished alkalescence of the blood; A. E. Taylor denies that there is any such.

CHAPTER XIII.

BODILY STATES AS DIRECT AND PREDISPOSING CAUSES OF DISEASE.

OVERSTRAIN.

A CONDITION that of late years has come in for not a little study, either as directly causing morbid states or as rendering the organism more susceptible to disease, is that of overwork and fatigue. It is necessary that we should call attention to the more important data bearing on the subject.[1]

It may, at the outset, be noted that there is some little latitude in the employment of terms—some would limit fatigue to the physiological result of work, and would speak of exhaustion, surmenage, or overstrain, as a severer and pathological state, resulting from overwork. Others, on the contrary, would speak generally of fatigue as resulting from overwork. For ourselves, the meaning implied by "overstrain" is so obviously that of a pathological state that we are prepared to employ this term in a pathological sense, and "fatigue" to indicate more physiological states.

It does not need the evidence of exact studies upon the action of isolated muscles of cold-blooded animals to inform us that work within natural limits is followed by fatigue, so that what at the beginning was done with ease, with repetition of the act demands increasing effort for its accomplishment. Whereas such fatigue passes off if followed by adequate rest, and what is more, given such adequate rest, the individual is benefited by the work, and finds himself as the result of successive periods of work and rest, able to perform a particular act with greater ease and over longer periods without experiencing the sensation of fatigue; if adequate rest be not taken between successive work periods; or if, again, a given action is continued over too long a period, so that the sensation of effort and of fatigue becomes excessive; or, lastly, if a sudden violent effort be made and continued, then the result is overstrain; and, if return to the normal be gained—which is not always the case—it is after a period of rest wholly out of proportion to that needed after mere fatigue. What is more, at the end of this period the organ that had been overstrained, instead of being found stronger from the exercise, is definitely weaker—less capable of responding to a given demand.

[1] Two valuable articles may be especially commended for fuller study, that on "Surmenage," by Marfan, in the first volume of Bouchard's "Pathologie Générale," p. 445; and that on "Fatigue," by Professor F. S. Lee, Journal of the American Medical Association, May 19, 1906.

The results of such overstrain are various, according to the organ or tissues involved, and according to the grade of work or intensity of the effort that has led up to the state. As already noted, there may be either direct production of morbid states or the development of a state of susceptibility to disease. It is in connection with the most widespread tissue of the body—the muscular—and with overwork of this tissue, that, both clinically and experimentally, the fullest observations have been made. This, then, may be considered in the first place and in more detail, other tissues of necessity receiving briefer consideration.

Direct Effects of Physical Overstrain.—With Marfan, we may divide these into (1) superacute; (2) acute and subacute; and (3) chronic.

1. Into the first of these categories enter the cases of sudden excessive muscular action. Of these, we observe various degrees, from the painful dyspnœa of the man who makes a spurt to catch his morning train, who suffers from violent heart action and a breathlessness that is almost suffocating—through a severer stage of extreme dyspnœa, cyanosis, temporary cardiac dilatation, and irregular pulse—up to fatal asphyxia with death within a few minutes. Such may occur during or at the culmination of bursts of speed or violent effort, the classic example being that of the soldier who dropped dead when he reached Athens with the news of Marathon. Cases have not been unknown in recent times among "sprinters" and other athletes.

It may well be that in this series we deal with two categories; it suggests itself, that is, that the symptoms in the slighter cases are largely referable to cardiac inadequacy, the heart being unable to pass on the blood as rapidly as is demanded by the muscles, so that pre-existing cardiac weaknesses or disease may be regarded as the efficient cause. But these conditions may show themselves in those who, before and after, afford no indications of cardiac disease, the only noticeable condition being that they have been unaccustomed to and untrained to "sprint," while, again, identical conditions are exhibited in the lower animals. It has been suggested that where death occurs as the result of prolonged intense effort, we have to deal with more than mere cardiac inadequacy, and with a state of intoxication. It is striking that animals hunted to death enter almost immediately into a state of cadaveric rigidity. Authentic cases are on record in which similar immediate rigidity has shown itself in man. During severe engagements, headless cavalrymen—their heads shot off—have retained their seat and been carried over the field by their horses, rigidity developing so immediatly that the lower limbs continue to grip the saddle. This rigidity passes off rapidly and gives place to very early putrefaction, indicating that the antibodies of the organism have been neutralized. Similarly, as noted by Hunter, the blood, dark and venous, fails to coagulate, and, according to Arloing, the capillaries are widely dilated, as though by some vasodilator drug. These facts all point to the presence in the muscles and discharge into the blood of products of muscle activity and dissociation. What those products are we will discuss later. But,

granting all this, it must be admitted that cardiac inadequacy, with its attendant asphyxia, dominate the scene.

2. Muscular overwork of a less violent but more prolonged type while leading to no noticeable cardiac irregularity or symptoms of asphyxia, may set up disturbances of another type. Such cases, for example, we meet with in those going straight from their city life into the country, and indulging, without due training, in the ascent of a mountain or a brisk twenty-mile walk. The symptoms then are extreme and prolonged lassitude, with pains in the muscles that have been most used, sleeplessness at night, and, it may be, next day anorexia and a definite low febrile state. Cases are on record in which the fever has been of the typhoidal type, lasting some five or six days and then suddenly disappearing, though usually it terminates in twenty-four or forty-eight hours, and with its termination the urine, previously diminished in amount, containing a large amount of urates, phosphates, and chlorides, becomes abundant and loaded with urea.

3. In addition, there is a certain class of cases in which no one act or series of acts may have seemed excessive, in which, nevertheless, individuals performing muscular exercise above the normal eventually experience symptoms which can only be referable to overwork. Such, in those having to walk about and keep on their feet for a large part of the day, are: pains in bones and joints, with slight periarticular swelling, pains in the tendons, and, as seen in adolescence, among boys and young adults in active exercise without adequate rest, as also in soldiers, what is known as the "irritable heart," a condition of cardiac hypertrophy, with palpitation and more or less marked irregularity of pulse, with signs pointing to mitral incompetency.

In this category, it would seem, are also to be placed the various occupational paralyses which may follow the excessive employment of particular groups of muscles—writer's and pianist's cramp, to mention the most familiar forms, labioglossal paralysis of players upon the flute and other wind instruments. The myopia which is apt to follow excessive use of the eyes is essentially due to exhaustion of the muscles of compensation. The earlier view, that these conditions are primarily nervous, due to exhaustion of particular nerve centres, has given place to the opinion that these states are essentially the outcome of muscular overstrain.

Overstrain as a Predisposing Cause of Disease.—It is a familiar experience clinically that overwork favors infection, that those engaged in hard labor, with late hours and inadequate periods of rest and recuperation, are apt to succumb to tuberculosis, pneumonia, influenza, etc. The difficulty in determining the importance of overwork as a factor in the development of such cases lies in the fact that most often there are associated conditions which also tend to be predisposing factors—inadequate nourishment, foul air, etc. Experimentally, however, as demonstrated more particularly by the studies of Charrin and Roger, it can be shown:

(1) That animals subjected to forced labor over long periods (turning

a wheel, etc.) are apt to die with naturally developed infections, either through secondary infection of abrasions, or from intestinal infection, it being presumed that pathogenic microbes of low virulence, which, in the healthy animal, live on the skin and mucous membranes without gaining entrance, now in the lowered state of the system manage to gain a foothold. Thus, Charrin and Roger, taking four guinea-pigs, placed them in a cage so constructed with a rotary cylinder that, to keep their balance, they were forced to keep moving; of these four so treated for one or two days, three died in from two to nine days after the experiment. Smears made from the livers and spleens and cultures from these organs and from the blood gave positive results.

(2) That animals subjected to forced labor succumb more rapidly to the effects of the injection of pathogenic microbes than do resting animals, or are killed by doses of the same, which resting animals resist. It is suggestive in this connection to note that sundry organisms of little virulence, which, injected into normal animals, undergo destruction, will gain a foothold, grow, and produce their specific effects if there be simultaneously injected along with them a small quantity of lactic acid. It may well be that this greater liability of exhausted animals to infection is associated with the increased acid production accompanying muscular activity.

Predisposition of another order is well exemplified in these effects of overstrain. It may be laid down as a broad principle that such overstrain is apt to tell especially upon the parts which bear the brunt of the strain. The most familiar and striking example of this principle in action is seen in connection with the heart. During fœtal life the burden of the circulation is borne by the right heart; in postnatal existence, by the left. We find, accordingly, that fœtal heart disease affects the valves of the right heart, postnatal heart disease those of the left. With the greater intracardiac pressure, greater strain is thrown upon the valves of the one or other side, and these, in consequence, are more liable to become damaged, and, as a result, lesions, whether of an infective or of a purely mechanical origin, are apt to develop. The greater number of the conditions already noted in connection with the direct chronic disturbances set up by overstrain strictly come under this category. Those lesions, in one sense, are directly set up by the action of some strain upon one or other tissue especially involved; in another sense, it is the strain that has predisposed to the lesions, which, it may be noted, as affecting any particular tissue, may be of more than one order; *i. e.*, diverse noxæ, acting upon a predisposed tissue, lead to different manifestations.

A second principle deserves notice, namely, that tissues already weakened by other agencies are particularly susceptible to overstrain; or, in other words, what is a simple strain for normal tissues becomes overstrain for those that are damaged. Here, again, the circulatory system affords well-marked examples. It is in the subjects of chronic intoxications, by syphilis, alcohol, tobacco, etc., that muscular effort, accompanied by increased intravascular pressure, is peculiarly liable to

cause the production of aneurysms and extensive arteriosclerotic changes. Here, of course, it is the overstrain that acts as the immediate cause of the disturbance, the intoxication as the predisposing.

The Physiological Basis of Muscular Fatigue and Overstrain.—For long years it was held that muscular fatigue was the criterion of nervous exhaustion, and that the grave conditions of writer's cramp and other occupational palsies were similarly of central origin. More recent studies by Woodworth,[1] Joteyko,[2] and others have profoundly modified our ideas. It has been shown, in the first place, that the peripheral nerve fibers are practically inexhaustible, and that the extent of the fatigue is identical in a pair of muscles, one of which is stimulated directly, the other through its nerve. Joteyko's experiments indicate also that the reflex centres in the cord are not capable of exhaustion. Accepting these views, there are those who hold that the nervous system must be wholly left out of account, that fatigue shows itself in the muscle fibers themselves. Nevertheless, Sherrington has shown that this cannot wholly be accepted. Selecting a motor centre in the spinal cord influencing a particular muscle, a centre acted upon by several afferent tracts, he has shown that, setting up reflex stimulation of the muscle along one path, he can bring about exhaustion so that the muscle no longer responds, and when this happens, by stimulating along another path to the same centre, the muscle responds as actively as at first. . From the earlier studies, we know that the nerve fibers are not exhausted; we see that the muscle fibers are not exhausted. What is "exhausted," says Sherrington,[3] is the "synapse," or membrane of junction between the first afferent tract and the motor neuron. It may be recalled that according to the neuron theory the individual cells, or neurons, are independent units; there is no true junction between them; that thus, when a stimulus passes from one to the other, it must be, at most, by contact action between the processes of one neuron and the body or processes from another. It is, suggests Sherrington, at this membrane of contact that repeated stimuli lead to physical and chemical changes, whereby the conducting power is modified and the nerve current encounters increasing difficulty in its transference from the one cell to the other.

Sherrington is so sound an observer that his experiments must be accepted, and from them it is difficult to arrive at any other conclusion than the above; nay, more, his conception of the cause of the difficulty in passage of the nerve current is in harmony with what we know regarding the hindrance to the passage of the electric current through an arc formed of different elements. While in his experiments there resulted no direct muscular exhaustion, we know, from abundant experiments, that it is possible to fatigue muscle fibers by direct stimulation.

[1] New York University Bulletin of the Medical Sciences, 1: 1901: 133.

[2] Art. "Fatigue," Richet's Dict. de Physiol., Paris, 1904.

[3] Schaefer's Text-book of Physiology, 2: 1900: 831; and Journal of Physiology, 34: 1906: 12.

The only satisfactory conclusion, therefore, is that there are two orders of fatigue: (1) The immediate or direct muscular fatigue, brought about by the using up of muscle substance in the course of its activity, or, more exactly, due to the inhibiting action of the products of contraction; and (2) what we may term "conductive" fatigue, the neurons, as such, not being worn out, but increased obstruction being established at the synapses, or, more broadly, at the sites at which the neurons come into closest communication.

Here, however, as regards the first of these, we must clearly distinguish between two allied but distinct conditions: muscular exhaustion and the *sense of fatigue*. Through overwork, undoubtedly, the contraction of the muscles becomes hindered by the products of metabolism. This can be demonstrated by repeated direct stimulation of a muscle until it fails to respond. If such a muscle be now washed out with blood, or even with salt solution, it very rapidly responds to further stimulation. In such cases the muscle is put out of action by the products of its own activity. On the other hand, the increasing difficulty in voluntarily repeating a given muscular act—the sense of fatigue—is of central origin, and due to the action of the products of muscular activity, whether directly or reflexly on the nervous system. As Mosso[1] has shown if a dog be fatigued by a long run and his blood be transfused into another dog, that second animal exhibits all the phenomena of fatigue—dyspnœa, rapid heart action, etc. It is clear that the blood comes to contain substances having a deleterious effect on the nervous system and the tissues in general. Experiments by Zuntz, F. S. Lee, and others show that these products are largely of an acid nature—that sarcolactic acid, potassium monophosphate, and carbonic acid produce similar effects upon the isolated muscle and the organism in general; in other words, that the sense of fatigue is brought about by a mild form of acid intoxication. More particularly, it would seem that in muscular activity it is the glycogen of the fibers that is used up, and from this the sarcolactic acid and the carbonic acid would in the main appear to be derived.

Absence of glycogen, as in the diabetes produced by phloridzin poisoning and inhibition of further glycogen metabolism by the presence of products of muscle activity, leads to a like muscular weakness and exhaustion.

Conclusions.—Thus far, then, it would seem that we must accept the following conclusions:

1. The nerve fibers as such are incapable of fatigue.

2. By direct repeated stimuli muscles can be made fatigued, their lessened response being due largely to the accumulation of the products of active function.

3. The progressive difficulty, in response to successive reflex stimuli, may, under certain conditions, not be due to exhaustion, but to increased resistance to the passage of stimuli from one neuron to another.

[1] Verhandl. d. Internat. med. Congr., Berlin, 1890: 2: Pt. 2: 13.

4. The *sense* of fatigue is due to the accumulation of the products of muscle activity in the circulating blood and the action of the same on the higher centres.

Can we accept unreservedly Joteyko's observations that stimuli may pass through a nerve cell without leading to its exhaustion, to indicate that there is no such thing as nervous fatigue?

Personal experience tells us that the mental activities are capable of being overworked; not merely does attention become fagged (which might be ascribed to fatigue of the accessory muscles of eye, ear, and other sense organs—and not necessarily, therefore, to fatigue of the nerve centres themselves), but even in the domain of pure reason the philosopher also is apt to exhaust himself. Nor would this appear to be wholly a matter of synaptic resistance. The one definite series of observations we possess bearing on this nervous fatigue is that initiated by Hodge,[1] and expanded and confirmed by Vas,[2] Gustav Mann,[3] Lugaro,[4] and others. Histologically, that is, it can be shown that the nerve cells controlling the wing muscles of the bee present recognizable differences between their state in early morning, after the night's rest, and at night, after hours of active flight. Like distinctions are to be made out between resting motor cells of higher animals and those that have been repeatedly stimulated to induce muscular activity. (See Fig. 11, p. 43.)

If, therefore, recognizable differences can be made out in the size and appearance of the cell body, the Nissl granules, and even the nucleus, it is difficult to believe that the nerve cell itself is incapable of fatigue, even if the nerve fibers are; there must be exhaustion of the cell and nuclear matter, which, beyond a certain point, makes itself felt.

As regards glandular and other organs, so little has been determined along these lines that, at most, we can apply by analogy like conclusions.

CELL DISUSE AND LACK OF ACTIVITY AS A CAUSE OF DISEASE.

In an earlier chapter, discussing the states of cell activity, it was pointed out that cell disuse, equally with cell overwork, led to alterations in cell constitution. Here it may be added that we have indications that this disuse predisposes to disease, just as it may be a direct cause of morbid conditions. We shall but call attention to these matters as briefly as possible.

Cell Disuse as a Direct Cause.—We have in the chapter just referred to pointed out that continued disuse of functional cells tends eventually to complete atrophy and death of the same. Such atrophy

[1] American Journal of Psychiatry, 1:1888:479 and 2:1889:376, and Journal of Morphology, 7:1892:95.

[2] Archiv f. mikroscop. Anatomie, 40:1892:375.

[3] Journal of Anatomy and Physiology, 29:1894:100.

[4] Lo Sperimentale, Sez. biol., 49:1895:159.

and death, if widespread, is apt to destroy the equilibrium between the different tissues of which the organism is composed. Atrophy of a part, in short, has the same effects as removal of that part, and, in the case of organs supplying an internal secretion, induces identical metabolic disturbances.

The state of the cells in disuse atrophy approaches closely to that seen in simple atrophy resulting from reduced blood supply; indeed, it is difficult to say whether, in the atrophies of inanition, the reduction in the size and the number of the cells of different tissues is to be attributed primarily to impoverished nutrition, or, on the contrary, to lack of functional activity; for, while adequate blood supply favors adequate nutrition, so also functional activity leads to improved circulation through a part, as also, within normal limits, it leads to a healthy state of the nourishing medium—the blood. It is, however, more particularly in these cases in which the nerve supply of a part is cut off, that we in the main encounter disuse atrophy. An organ, such as a muscle not stimulated by nervous influences, affords the most striking example—and commonest—of this type of lesion.

Disuse as a Predisposing Cause of Disease.—The last word has still to be said regarding the means whereby disuse predisposes to disease. For a considerable period this was ascribed in the main to the action or want of action of trophic nerves, which were supposed to govern the general nutrition of the tissues. To this, for example, was attributed the inflammation of the cornea following section or paralysis of the fifth nerve. But no incontrovertible demonstration has been afforded of the existence of such trophic nerves; the above noted keratitis may more satisfactorily be ascribed to the resulting insensibility of the cornea, whereby irritant dust, etc., settling on its surface, is allowed to remain and is not reflexly swept off by the eyelids or by increased flow of the lacrimal fluid. Experimentally, it is found that where the eyelids are kept closed, or the surface of the eyeball is protected by covering over the orbit with a watchglass, no keratitis results. In herpes zoster, which involves the area of distribution of particular cutaneous nerves, it is found that there is a lesion of particular posterior root ganglia. This association does not necessarily demand that we deal here with either irritation or paralysis of trophic nerves. Lack of coördination between nutrition, vascular supply, and cell activity under the influence of direct stimuli, together with the lowered condition of cell vitality resulting from this want of coördination of the cells of a tissue cut off from central control, would appear sufficient to explain the liability for such tissues to become more easily subjected to inflammations and infections.

This lowered vitality from disease, it must be laid down, appears effective in increasing the susceptibility to infection in parts also in which the nerve supply is intact. It may be pointed out that it is in those regions of the lungs which, from their position, are least in action, namely, the apices, that the tubercle bacillus most easily gains lodgement and growth.

CHAPTER XIV.

PREDISPOSITION AND SUSCEPTIBILITY.

All living matter depends upon its environment for its continued existence; upon the stimuli which act upon it from without, whether these be of a chemical or a physical nature, and from its constitution it is so adjusted to that environment that life is only possible within a comparatively narrow range of intensity of stimuli. If this be increased beyond a certain point, it becomes irritation, causing injury; beyond this, again, it renders life impossible, and death ensues. But, in the course of their development under varying environments the different forms of life have come to respond to different agencies in varying degrees—a temperature, for example, which is a stimulant for one form, favoring increased metabolism and increased growth, may be fatal for another; and when we come to the members of the same species, we note at times similar differences; in fact, it may be laid down that no two individuals respond identically to influences acting upon them from without, from the grosser chemical influences of food-stuffs absorbed to the intangible influences of psychical impressions. And even in the individual himself the different tissues present different grades of reaction to stimuli or irritants of one and the same order. Such heightened sensitiveness to stimuli or irritants above what is normal for the species, the tissue, etc., we speak of as susceptibility, or, more narrowly, as predisposition, by this last term indicating that, constitutionally, there is a liability to be more affected by particular influences than is usual; and, pathologically speaking, whenever either of these terms is employed it indicates an abnormal liability to be so influenced that the development of morbid conditions is favored.

Such predisposition may be either (1) inherited or (2) acquired. In our discussion of inheritance we have already referred to this (pp. 141 and 188), and here need but briefly note that inherited predisposition may be: (*a*) *Specific* or *ex-specie* (*e. g.*, cattle are peculiarly susceptible to contagious pleuropneumonia; dogs to distemper; gonorrhea, typhoid, and the main exanthemata affect man alone). (*b*) *Racial* (*e. g.*, those of European origin are susceptible to yellow fever, the Hebrew race, predisposed to diabetes, etc.). (*c*) *Familial*, as to scarlet fever, measles, tuberculosis, to particular neuroses, and weaknesses of individual tissues (Friedreich's disease, pseudohypertrophic paralysis, etc.), to metabolic disturbances, gout, etc.

We have so fully discussed the subject of heredity that here it is unnecessary to enter again into the principles involved. But we would in passing note that, as regards all these forms of inherited predis-

position, more particularly the susceptibility to infectious diseases, we have to weigh with some caution the evidence that is presented to us: the specific susceptibility may not be so marked as on the surface it appears to be. That there is such specific susceptibility, we do not for a moment pretend to question. Certain influences tell more upon the cells of one species and of one family than on those of another, and the "survival of the fittest" is fitted, to some extent, to explain how races long accustomed to liability to infection by one disease may eventually show but a small percentage of cases of infection, and those of a milder type. What we would more especially point out is that, where a disease is endemic in a region, it is probable that a certain proportion of the inhabitants do not exhibit inherited, but acquired, immunity; that these inhabitants have suffered from transient, unrecognizable, or unrecognized, attacks of the specific disease, which have thereafter protected them. They may not even have had definite "attacks." As Meltzer has pointed out, if the wandering cells are constantly passing in from mucous surfaces, bearing with them individual bacteria, which bacteria tend to be destroyed, even if virulent, provided the number at one focus or place be not too great; then immunity may be brought about, not by the supervention of a mild attack, but by accustomance of the tissues to repeated minimal doses of the toxins of the specific microbes thus introduced. The negro, for example, may not owe his immunity to yellow fever entirely to heredity. Indeed, this has of late years been conclusively shown by Koch and others in connection with malaria, that the apparent immunity of the natives of malarial regions is explicable by the fact that the young children become extensively affected; the malarial organism may abound in the blood without there being pronounced indications of an acute infection. To such a gradual process of immunization, without definite attack, Sir James Paget explained the freedom of the hardened frequenter of the postmortem room from the blood poisoning which may overtake the infrequent performer of autopsies. To it, also, we may add, is to be ascribed largely the immunity of the practitioner to epidemic disorders.

In this connection, certain observations of Hankin are, at least, suggestive. Rats as a species are refractory to anthrax: even young rats are little influenced. Taking a brood of newly born rats and feeding one moiety with the ordinary mixed food of these animals, with relatively large amounts of meat, the other moiety with bread and milk, he found the former moiety relatively insusceptible, while all the members of the latter succumbed to the disease. Here we have the influence of diet upon the bactericidal properties of the tissues. It may well be that diet and state of nutrition are factors helping to explain the relative incidence of diseases among various races.

(*d*) *Individual.* While many forms of individual predisposition are inherited (p. 188), it is not at all times easy to distinguish between these and acquired conditions. Here it will be more serviceable, not so much to seek to attempt to distinguish between these two orders, as to classify the different forms of individual predisposition.

We note thus predisposition according to:

1. **Sex.**—It need but be remarked that the sexual life of the female exposes her to the liability to contract a special series of disorders in connection with menstruation, childbirth, and the menopause.

2. **Life Period.**—The liability to the incidence of particular disorders at different life periods may be briefly expressed in the following table, the brackets indicating the year or period at which the condition in question is most fatal:

Infancy.—Disorders of maldevelopment and inanition (to the end of first year); athrepsia, various forms of enteritis with diarrhœa; meningitis.

Childhood.—Rickets, measles, scarlatina, diphtheria.

Puberty and Adolescence.—Chlorosis (in female); acute rheumatism and rheumatic heart disease (ten to fifteen); typhoid; tuberculosis.

Adult.—Typhoid (twenty to twenty-five); tuberculosis (twenty to thirty).

Middle Age.—Gout, lithiasis, and chronic Bright's disease (thirty-five onward); arteriosclerosis, aneurysms (thirty to fifty); cancer (forty to sixty).

Old Age.—The same continued along with atrophic conditions; cerebral apoplexy (fifty-five to seventy-five); low infections.

The immaturity of the cells and tissues, the fact that they have not become immunized, coupled with the fact also that particular tissues are undergoing either great strain or very rapid growth, would seem to explain to a very considerable extent the susceptibility of infants to digestive disturbances and meningitis. The weight of the brain is doubled in the first year of life (from 400 to 800 grams).[1] Like consideration would seem to explain the susceptibility of infants to digestive disturbance and of children to acute infections, the tissues being more vulnerable when first exposed to the toxic influence of fermented food, and to the influences of sundry specific microbes. There are, however, certain features in connection with the age incidence of infectious diseases which must be pointed out. Both in animals and in man we observe that the newly born and the young are little affected by—in fact, are immune to—certain diseases which cause a high mortality in those of older years. Babies under three months old scarcely ever suffer from diphtheria, and this not because they are not exposed. The same is true with regard to young children and typhoid. While this is somewhat more common among the young than is usually supposed, it is almost unknown among infants, and in such young children as it attacks it causes in general a mild disease, compared with what we find in young adults. Many similar examples may be called to mind.

A priori, the more immature, the more unprepared the cells, the more vulnerable we should expect the tissues to be, but clearly this is not

[1] F. W. Beneke, Die Altersdisposition, Marburg, 1879.

always so. That certain tissues, liable especially to primary infection by the diseases in question, are more active and reactive in early life, while later they become exhausted and more susceptible, would not appear to afford a complete explanation, though that this may be a partial factor cannot be neglected. There is yet another possibility indicated by the essential nature of toxicity and infection. For a substance to be toxic and injurious to a cell, it is necessary that, entering that cell, it sets up such a molecular disturbance as either to arrest or to stimulate excessively the metabolic processes of that cell, or otherwise it must enter into chemical relationship with the biophores. It is well within the bounds of possibility that, as suggested by Abbott, a diffusible substance which sets up excessive molecular and destructive disturbances in the fully developed cell may have but little effect upon the more inert protoplasm of the immature cell, and that if certain bacteria gain entrance into the tissues, the cell may digest and otherwise destroy them, their toxins not combining with the biophores, and, as a consequence, not arresting the cell functions.

3. **Habit of Life at Different Life Periods.** - During infancy and early childhood the digestive organs are relatively most active, and in order to bring about the absorption of food necessary for rapid growth, they are peculiarly liable to strain. The lack of power of locomotion prevents much mingling with others and the extensive exposure to "contagion" and the zymotic diseases which supervene with active locomotion and mingling with other children. With adolescence and the forsaking of an outdoor and active, for a more sedentary and confined existence in workshops and other places, where large bodies of men are collected and ventilation often defective, tuberculosis is liable to supervene. With increasing corpulence and inability to take exercise in middle age, constipation, gallstone formation, etc., tend to be favored. Other environmental influences, such as those of climate, clothing, and social influences, come under the same category.

4. **Previous Infection.**—While many diseases, more particularly the acute exanthemata, are followed by immunity, there are others in which this immunity is but short-lived; others, again, like erysipelas, furunculosis, acute rheumatism, and, we may add, influenza or la grippe, in which one attack actually predisposes to a second. Whether, in these cases, the germs of the disease are not all destroyed, but some linger in the system and exhibit themselves actively if anything lowers the vitality, or whether a new infection occurs, is not precisely determined. It may be that either occurs.

What is even more noticeable is that an attack of one infectious disorder is frequently followed by an infection of a different nature. The tissues are weakened by the one disease, and in this condition are more susceptible. Thus, the acute exanthemata may follow one another and tuberculosis supervene upon any of them, or upon typhoid.

5. **Malnutrition.**—The terrible mortality from infectious diseases—typhus, relapsing fever, typhoid, septicemia—which has followed in the wake of famine in Russia, India, Ireland, during the last century, is an

adequate example of the effects of malnutrition in predisposing to disease. Here may be included local malnutrition, such as that brought about by lessened functional activity, due to impaired nerve supply. Paresis and paralysis, with imperfect function, imperfect metabolism, and weakening of the tissues predisposes to local infections and suppurative disturbances. Impaired blood supply has similar effects. To these we shall refer more fully in a subsequent paragraph. The effects of overstrain in predisposing to disease have been discussed in the previous chapter.

Tissue Susceptibility.—Just as the general susceptibility of the organism as a whole is noted to be increased by the means just indicated, so we can increase the local susceptibility of the different tissues and favor the growth of microbes within them, or the development of functional disorders, by injury, by malnutrition (impaired blood supply or nerve supply), and by lessened functional activity. To these, indeed, we have already referred in passing. But apart from this, which we may term acquired tissue susceptibility, we have also to recognize an inherent susceptibility to disease on the part of various tissues.

It is a matter, the significance of which is too little recognized, that very many pathogenic organisms show a predisposition to grow in special tissues; or, more correctly, that certain tissues exhibit a particular predisposition to permit these to grow within them. As regards the primary focus of infection, we see that the channel of entrance in general affords a partial explanation why this should become the seat of growth, that inhaled germs should especially affect the respiratory system, ingested germs the digestive tract. But even here it has to be noted that the diplococcus pneumoniæ, for example, has little effect upon the pharyngeal mucous membrane, growing there as a harmless saprophyte, whereas the diphtheria bacillus causes intense disturbance.

When we pass beyond, to the secondary foci, this tissue predisposition is still more marked. The tubercle bacillus flourishes in the lung, upon serous surfaces, in the different glandular organs, but rarely in muscle; infrequently in the brain substance, as compared with the pia-arachnoid; infrequently in the stomach wall, as compared with the small intestines; in the epiphyseal ends of bones, and in the joints of the young, but not commonly in the same regions in those of mature years. If the colon bacillus be injected into the blood stream, it sets up more especially a condition of acute enteritis. In like manner, passing in review each separate infectious disease, this specific tissue susceptibility can more or less definitely be pointed out.

This specific tissue susceptibility, then, is well marked; different pathogenic agents find in different tissues circumstances specially favoring their growth; the cells of these tissues react less perfectly against these specific bacteria. In certain individual cases explanations may be suggested for this predisposition. In tuberculosis, for instance, the acid production of the muscle, stomach walls, and brain substance has been suggested as explaining why the bacillus in general does not thrive in these organs—although Ficker's observations, that of all media the acid brain matter furnishes that upon which the tubercle

bacillus flourishes most rapidly and abundantly, may well make us doubt this. In other cases, the nature of the circulation through the tissues implicated has been invoked. But that does not satisfy the fact that particular microbes may multiply in these particular tissues. In short, it is not possible to find one common basis of explanation for this selective action beyond this, that in each tissue there is a varying environment, and certain environments are specially favorable for the growth of special bacteria.

It is the corollary to this condition of tissue susceptibility that deserves more recognition. If the typhoid bacillus is found growing in the spleen, liver, skin, and kidneys, and is difficult to isolate from other organs, it is obvious that to reach these particular organs it must have travelled through the blood stream, and have been equally liable to enter the others. So, also, if in young children the ends of the bones become tuberculous, obviously the tubercle bacilli must have entered the blood stream and have been carried through the system generally before reaching these remote regions. We are thus bound to conclude either: (1) that infectious microbes circulate passively through the various organs, in which they show no growth, causing no reaction until they reach a susceptible tissue, or (2) that, circulating thus, they tend to be destroyed in every other tissue of the body save those that are susceptible. The first alternation is not only eminently unlikely, but is negatived by experiments, which show that the vascular endothelium of organs like the liver, which later may exhibit no special foci of disease (*i. e.*, are not susceptible), actively takes up and destroys pathogenic bacteria. The second, thus, is the only adequate deduction from the facts at our disposal; and this leads us, further, to a very important conclusion, that *in infection the body is never involved as a whole. Coincidently with the growth of the specific germs in individual organs, there tends to be a reaction to, and destruction of, the same in other parts.* The bearing of this upon the recovery from infection we shall point out later.

We may now sum up the various forms of predisposition; they are:

1. *Inherited*:
   - (1) Specific, characterizing the species.
   - (2) Racial.
   - (3) Familial.
   - (4) Individual, as regards
     - (*a*) sexual incidence;
     - (*b*) age incidence;
     - (*c*) tissue incidence.
2. *Acquired*, as a consequence of
   - (1) Social and environmental conditions.
   - (2) Injury.
   - (3) Malnutrition.
   - (4) Previous attacks of
     - (*a*) the same disease;
     - (*b*) other infectious disease.
   - (5) Exhaustion.

Idiosyncrasy.—This term is applied to the exhibition of extreme susceptibility on the part of the individual to the influence of substances which not only have no disturbing action upon the normal individual, but often are to him the source of distinct pleasure or benefit. It is an extreme form of susceptibility, and that manifested in unusual directions. Thus, some individuals are unable to eat sundry not unusual articles of diet (strawberries, porridge, certain shellfish, mackerel, or other fish) without a train of symptoms showing themselves, which seem to indicate a distinct grade of intoxication, manifested by urticaria and abnormal skin eruptions, headache, running at the eyes, abdominal disturbance, etc. One well-known London physician of our acquaintance dare not take the pudding or cream at dinner away from home, for fear it be flavored with ginger, the least trace of which gives him acute misery for the better part of the next twenty-four hours. Similarly, there are drug idiosyncrasies, often accompanied by skin eruptions—from quinine, potassium iodide, opium, iodoform, and so on. Some of the most remarkable are in relation to animals, most commonly with cats; the presence of a cat in the room, even if unknown to and unsuspected by anyone, and hidden from sight, being sufficient to cause intense discomfort, and even a state of nervous terror, that is painful to the individual and all around. This, as Weir Mitchell[1] has recently pointed out, can only be due to the action of some emanation from the animal upon the sensitive olfactory mechanism, even though, in most cases, the affected persons state that they perceive no special odor. It thus becomes allied to that other more common idiosyncrasy, hay fever, in which, again, no odor is necessarily perceived, but in which we have practical experience that the fine, floating pollen of flowering plants and grasses is the irritative agent, the intense coryza and discomfort making its appearance at the period when plants are in flower, and disappearing if the individual take a sea voyage or by any other means escapes to where little pollen is likely to be.

[1] Trans. Assoc. Amer. Phys., 20: 1905: 1.

SECTION III.

THE MORBID AND REACTIVE PROCESSES.

INTRODUCTORY.

HAVING in the previous section discussed the causes of disease, we pass now to discuss how these causes act, and, doing so, observe that we can, from the point of view of general pathology, approach our subject from two directions; we can, that is, studying disease generally, recognize, underlying its various manifestations, certain common series of events or morbid processes—processes which, it is true, vary in their details in individual cases; nevertheless, the broad features of groups of cases are alike, and once we establish that morbid conditions constituting a particular group are allied and have a common basis, we can proceed to inquire what it is in any particular case that leads to what we may term divergence from type; or, on the other hand, rather than inquiring into the course of the different processes, we can make the tissues and the changes they undergo the main object of our inquiry, and classify thus the morbid changes affecting these tissues, rather than the morbid processes proper. It may well be urged that in the latter case we are dealing with the results of disease. All depends upon how we approach the treatment of the subject. If we seek purely to describe the histological alterations in the cells brought about by disease, then these conditions should not be dealt with in this section. If, on the other hand, we study the succession of changes leading ultimately to the different morbid states seen in the cells and tissues, then our study is that of processes. Further, it may be propounded that, broadly speaking, the changes in an individual cell do not constitute disease (as generally accepted); that depends upon the cumulative effect of the combined cell disturbances, and more than that, upon the disturbances set up by the perverted activities of these cells upon other cells and organs not primarily involved. Seen in this light, morbid cell changes are factors in the production of particular results. It is, however, a minor matter under which heading we consider these conditions, provided their nature be recognized. In dealing with them we shall have to discuss the changes leading to the production of each individual form of cell disturbance, and at the same time to describe the resultant effect of these changes upon the individual cell; conformably with

usage, we class them with the morbid processes. We take up the discussion of the same between that of the morbid processes proper and that of the results of disease upon the tissues and the organism as a whole.

In the heading to this section we refer to the morbid and reactive processes. It will be seen that, with the exception of conditions of arrest of cell activity and cell death, and the possible exception of neoplasia, or of some neoplastic conditions, all morbid processes are at the same time reactive; they are the expression of the reaction on the part of the tissues to noxæ of various orders.

Thus to repeat in the first part of this section the morbid and reactive processes proper will be discussed, in the second the morbid cell changes.

PART I.

THE MORBID AND REACTIVE PROCESSES PROPER.

CHAPTER I.

THE LOCAL REACTION TO INJURY: INFLAMMATION.

For the development of the sound pathologist, a full knowledge of the factors concerned in the inflammatory process and a right appreciation of the doctrine of inflammation is as essential as to the orthodox theologian is a right attitude in respect to the doctrine of the Trinity. As regards the one, there have been bitter fights and wide divergences of opinion; so with regard to the other—and these divergences in both continue to exist, and with them a wide tolerance. Nevertheless, the leaders of the pathological world, though they may differ in non-essentials, are at the present time in substantial agreement regarding the subject of inflammation. There is an orthodox doctrine, and that doctrine we shall proceed to expound.

Definition.—The condition of local "flaming"—inflammation—has of necessity been recognized from the very beginning of medical studies; but so long as little was known concerning the causes of disease and less regarding the processes, all that could be accomplished was to regard this as a *state* characterized by certain particular symptoms, and the first attempt at a definition, that of Celsus, so regarded it. Inflammation, he laid down, was a condition characterized by "rubor, tumor, calor, dolor"—redness, swelling, heat, and pain—to which definition later writers added a fifth cardinal symptom, that of "functio laesa," disturbed function. The great English pathologist of the eighteenth century, John Hunter, said that it was something more, that it was a process rather than a condition—a process set up by injury, and tending toward counteraction of the same. But he was before his time. Three-quarters of a century elapsed before Cohnheim, employing a microscope to study the changes ensuing in an injured area—the transparent web of the frog's foot—saw and first described with accuracy the changes that occur in the vessels of the injured part—the dilatation of those vessels—the eventual slowing of the current, and, it might be, *stasis*, or complete arrest—the exudation of fluid and immigration from them of leukocytes; saw in these the full explanation of all the cardinal symptoms, and concluded that the vascular changes were the essential feature of the inflammatory process. And, undoubtedly, in tissues well

supplied with vessels, these are the most striking feature, the feature dominating the whole field following upon injury, whether mechanical or chemical (by caustics or bacterial poisoning) above a certain grade. But with a lower grade of injury by, it may be, identical noxæ, these vascular changes are little noticeable, and are replaced by connective-tissue overgrowth; there is still injury, but the results differ, or rather correspond to those seen in the later stages of the process that follows injury of a severe grade; and secondly, a like order of end results is attained in tissues that are unprovided with vessels. It was these circumstances that led Burdon Sanderson, in the "seventies," to advance a broader definition, namely, that "inflammation is the succession of changes occurring in a part, as a result of injury, provided that that injury be not so excessive as to destroy the vitality of the part," or, briefly, and better, that it is "the (local) reaction to injury" (for some of the changes that occur in an injured part, hemorrhages, etc., are not reactive, and play no direct part in the inflammatory process).

From this date onward there has been an increasing recognition of the fact that the various processes which together make up the picture of inflammation are not merely the passive and deleterious outcome of local injury, but, on the contrary, are factors which tend to counteract the local effects of that injury; an increasing conviction that the distinction so much insisted upon by the older writers between inflammation and repair is non-existent, and several writers of this generation—Leber,[1] Neumann,[2] Councilman,[3] and others—have advanced definitions containing a clause to the effect that the tendency of all those processes is in the direction of repair of the injury. We ourselves have elsewhere stated[4] that inflammation "is the series of changes constituting the local manifestation of the attempt at repair of actual or referred injury to a part;" or, briefly, is "the local attempt at repair of actual or referred injury." Grawitz expresses the like idea in his definition of inflammation as *the reaction of irritated and damaged tissues which still retain vitality.*

To Metchnikoff,[5] through his most remarkable and long-continued studies upon the functions of the leukocytes in disease, and upon phagocytosis, both by leukocytes and the fixed cells of the organism, we owe, more than to any other single individual, the recognition of these counteracting forces. Just as Cohnheim, studying the vascular changes, saw in them the essential factors in the inflammatory process, so Metchnikoff, studying the leukocytes, would elevate them to an exclusive position in his definition, and would lay down that phagocytosis is

[1] Ueber die Entstehung der Entzündung, Leipzig, 1891.

[2] Ziegler's Beitr., 5; 1889; 345.

[3] Article "Inflammation," Dennis' System of Surgery. See also, in a similar sense, tt. Buchner, Fortschritte d. Med., 10; 1892; 363; Marchand, Wundheilung, Leipzig, 1900; Chantemesse and Podwyssotsky, Les processus généraux, 1905; Bier, Die Stauung als Heilmittel, 1904.

[4] Article "Inflammation," Allbutt's System of Medicine, 1; 1896.

[5] La pathologie comparée de l'inflammation, Paris, 1892. A work of the highest value, to which we shall frequently refer. It has been translated into English

inflammation. This involves too wholesale a neglect of other factors to be acceptable. "In studying the reactions of the organism to injury, we must be impressed by the multifariousness of natural processes; the end may be attained, not in one way only, but in many. It is not by cells of one order alone—by phagocytes—or by leukocytes in general, and only leukocytes, or merely by the reaction on the part of the fixed cells of the tissues, or by vascular changes alone, or by altered temperature, or solely by the chemical and mechanical action of the exudate, that repair is effected. All means are employed to antagonize the irritant and to effect healing"—now the one, now the other more particularly.

Such processes must not, we would insist, be regarded as primarily purposeful; they are adaptive. What we understand by adaptation we have already laid down on p. 101.[1] And considering them as adaptations, we arrive at a further simplification of our definition, namely, that inflammation is the succession of changes which constitute the local effort at adaptation to the changes initiated by actual or referred injury to a part; or, in short, *the local adaptive changes resulting from actual or referred injury.*

More recently there has been a tendency to widen still farther the scope of the inflammatory concept. It is seen that with local injury there are set up not merely local changes, but that tissues at a distance are also involved, and contribute toward counteracting the irritant and its effects; that, for example, there may be fever, the lymph glands may become enlarged, the bone-marrow stimulated to activity, with resulting increase in the number of circulating leukocytes and in the amount of antitoxin and protective substances in the blood serum. Thus, Ribbert[2] lays down that inflammation is "a vital manifestation on the part of the whole body, if primarily of the local tissues that have undergone injury, and is the sum of all the exalted vital processes," and Aschoff, we find, teaches similarly. While we admit, and that most fully, that as a result of injury there may be this participation by the rest of the organism, we feel strongly that to introduce these further processes into our conception of inflammation brings about an immediate confusion between the phenomena of inflammation and those of the general reaction to injury, and infection. As will be seen later, general reaction on the part of the organism as a whole, with or without marked primary local disturbances, is the distinguishing feature of "infection." We would thus emphasize that, to prevent confusion, it is advisable to restrict, as in the past, our conception of the inflammatory processes to those which are of local origin and occurrence.

THE COMPARATIVE PATHOLOGY OF INFLAMMATION.

We cannot better gain a grasp of the main features of the reaction to injury than by studying first the simplest cases, and gradually following

[1] For the distinction between adaptation and purpose see Adami, Inflammation, Macmillan, 1906: 221.

[2] Die Bedeutung der Entzundung, Bonn, 1905: 14 and 45.

up the processes seen in more and more advanced conditions. In other words, it is best to begin with the simple individual cell, with the unicellular organism, and trace the reactions that occur as we advance from the unicellular to the simpler metazoan, or multicellular forms; from these to the higher metazoan forms, and man himself. This we shall do rapidly, not taking up division after division, but noting merely those forms of life in which progressive evolution has led to the introduction of new factors in the reactive process.

Taking first the protozoa, we note that destruction of a portion of the cytoplasm—provided this does not include the nucleus—is followed by the closing together of the uninjured parts. In other words, provided the nucleus be uninjured, the cell recovers; provided also, we may note, that not too large a portion of the cytoplasm be destroyed or removed (p. 38). We note also other properties closely bearing upon the properties of the cells of higher forms of life, including man, namely: (1) the property of *chemiotaxis*—of being attracted toward certain substances, of being repelled from others; (2) the property of *adaptation*, whereby a negative may be changed into a positive chemiotaxis. It is found that by the gradual and careful addition to the fluid in which it lives a protozoan can be gradually accustomed to substances from which at first it was repelled, until eventually it will move actively toward stronger solutions of these substances;[1] and (3) the property of *phagocytosis*, that, namely, of ingesting solid particles—of eating them (φαγειν, to eat). This, at least, is the primary meaning of the term. It is inevitable, although unfortunate, that, with the development of Metchnikoff's studies and the evolution of his "phagocytic theory" into its present form, several other protective properties beyond that of ingestion and digestion have become attached to the conception of phagocytosis. Here we employ the term in its primary sense, and observe that one of three events may follow the ingestion of foreign particles by such a form as the amœba: (1) the particle may prove assimilable, in which case, as shown by Miss Greenwood and La Dantec, it becomes surrounded by a vacuole containing digestive fluid, and undergoes solution, portions proving indigestible being subsequently cast out from some region of the surface of the organism; (2) it may prove unassimilable, in which case, after a short sojourn within the cytoplasm, it is similarly discharged; or (3) if a living organism, in some cases a *symbiosis*, or living together, is set up; the protozoan host is not irritated by the parasite, and does not discharge it, and, on its part, the parasite, living upon the material assimilated by the host, may multiply until its progeny so fill the cytoplasm of its host, that they exhaust the foodstuffs, and lead to death of the host, when they become liberated into the surrounding medium. All these events, as we shall see, may likewise occur in the leukocytes and other cells of the multicellular organism.

Passing next to the lowest metazoan forms, we immediately observe a division of labor among the cells, the outer layer being more especially

[1] Stahl, Flora, 76: 1892: 247.

protective, the invaginated inner layer more particularly digestive. Between the epiderm and endoderm there develops a thin set of cells, the mesoderm, derived from the other two, which, as we advance, rapidly assumes great importance, forming the connective-tissue layer

FIG. 136 FIG. 137

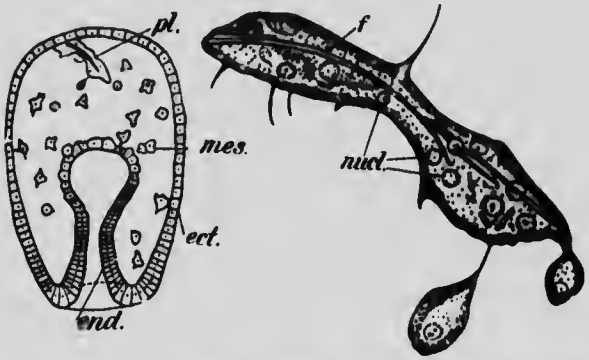


FIG. 136.—Larva of one of the simplest metazoan forms (Astropecten) to show *ect.*, ectoderm; *end.*, endoderm; *mes.*, wandering mesodermal cells which at *pl.* have attached themselves to a foreign body and formed a plasmodium around it.

FIG. 137.—The plasmodium of fused mesodermal cells seen in the previous figure, higher magnification; *nucl.*, nuclei of individual cells. (After Metchnikoff.)

of all the tissues, the internal skeleton, the muscles, the heart, and, subsequently, the closed vascular system. Here, in the lowliest stages, it is represented by relatively few cells, with long, fine processes, which

FIG. 138

Foreign-body giant cells from man; at *a* the leukocytes form multinucleated plasmodia around foreign fibers (silk), at *b* the giant cells have broken away containing debris of the fibers. (Ribbert.)

can be retracted so that the cells are capable of floating about freely in the body cavity. These are, in fact, the earliest representatives of the wandering cells, white corpuscles, or leukocytes of the higher animals. And already in these lowest forms we find them possessing protective

functions, though at the same time it must be noted that they are not the only class of cells that react. If any of the living cells be destroyed, those in the immediate neighborhood spread out by amœboid movement to fill the gap temporarily, and subsequently multiply, there bringing about *regeneration* (and the regenerative process of these lowest metazoan forms is nothing short of marvellous; a few cells may regenerate the whole animal). But if, as Metchnikoff has pointed out, foreign particles gain entry into the body cavity, it is the wandering cells that deal with them. If small, they may ingest them; if large, attaching themselves to and surrounding the objects, they fuse into a *plasmodium*, or multinucleated mass, thereby fixing it in position; if it be capable of digestion, forming a common stomach, as it were, and bringing about its dissolution; if inert and not digestible, then cutting it off from the body cavity. The power of forming a plasmodium around foreign bodies is possessed by leukocytes, from the lowest multicellular form up to man; one class of giant cells, those, for example, we see in tuberculosis, and those that form around foreign bodies introduced into the tissues are plasmodia of this nature.

Throughout the invertebrata we observe these two processes of regeneration and leukocytic activity, with little material addition; we note, indeed, that there gradually appears—in the crustacea, for example—more than one order of wandering cells, with different properties; some are phagocytic; others, as, for instance, those that pass out on to the surfaces of certain invertebrates, are explosive, and apparently with their disintegration liberate digestive and (it may be) bactericidal substances, whereby foreign organisms adhering to the carapace become destroyed and the surface cleansed (Hardy and Alcock). But though there is a heart, with rare exception there is no closed system of bloodvessels. The large vessels open into the body cavity, and the heart but serves to keep the body fluid circulating. Thus, not until we reach the vertebrata, does a fully developed vascular system enter as a prominent factor into the reaction to injury. At most, as in the arthropoda, the body fluid has extensive powers of clotting,[1] so that when injury is such as to cause communication between the body cavity and the external medium, the wound may gain a temporary closure through the agency of the coagulated fluid.

Nevertheless, the different classes of invertebrata afford some most remarkable examples both of regeneration[2] and of leukocytic activity. Of the latter, quite one of the most striking is that afforded by a parasitic disease of the Daphnia, or water flea, a minute crustacean, translucent, and just visible to the naked eye, and common in some fresh-water ponds and ditches. Metchnikoff, observing that the daphnias in his aquarium were becoming opaque and evidently dying off, found that the disease was produced by a blastomycete, or yeast, growing in the affected aquarium. This was an elongated form, termed by him

[1] See Leo Loeb, Jour. of Med. Research, N. S., 2; 1902; 145.

[2] For examples see the chapter on Regeneration.

Monospora, and characterized by producing long, sharp-pointed spores. These spores, taken in by the daphnia when they passed along the intestine, were apt to penetrate the delicate wall, and so gain entrance into the surrounding body cavity. If those so entering were few in number, the leukocytes attached themselves to them, often several together, forming a plasmodium, and eroded and destroyed them.

If, on the other hand, too many penetrated into the body cavity, the number of leukocytes was inadequate to deal with all, and some not attacked germinated. Whereas the wandering cells freely attached themselves to the spores, they were seen to leave the germinated torulæ severely alone, with the result that the body became filled with the yeast, became opaque in consequence, and death ensued.

With the vertebrate we find a fully developed and closed vascular system, distinct from the body cavity (lymphatic) system, though the latter receives its fluid from the blood, and yields its fluid back to it, so that there still exists a body cavity circulation, but that secondary to the main vascular system. And with this we find: (1) that the vessels of an injured part become directly concerned in the inflammatory process; (2) that here, in consequence, we have "flaming" as the result of injury, the vessels of the part undergoing dilatation, with its attendant results; (3) that the reaction shows itself more rapidly to the naked eye, and, indeed, has a more rapid course; and (4) that instead of the tardy and haphazard accumulation of leukocytes from the surrounding tissues and from the slowly circulating body cavity fluid, with the more rapid flow of blood through the injured area, leukocytes are constantly being carried into the area, and once there, provided the irritant has not too virulent properties, their chemiotactic properties lead them to make their way through the walls of the vessels toward the foreign body.

Undoubtedly, then, in the higher animals the vessels are a most important factor in the reaction to injury; they add greatly to the power of the individual in responding fully and promptly to local injury. It has, however, to be noted that the difference they introduce is one of degree rather than of kind; we find the same underlying local processes at work in the invertebrate as in the vertebrate; we find them proceeding in non-vascular areas in the vertebrates just as in the vascular. There is, thus, no essential difference introduced by the participation of the vessels in the reaction to injury; and that being so, to draw a sharp line of demarcation between the two sets of cases, to say that in the one set of cases we have inflammation, in another we have not, is to make a distinction where no fundamental difference exists. While all the vertebrates possess this closed vascular system, it is deserving of note that in the lowest forms the development is not nearly so perfect as in the higher—the capillaries are not so abundant, nor is the vasomotor apparatus nearly so complete, whether nervous, controlled from the central nervous system, or idiomuscular, depending upon direct stimulation for the dilatation and contraction of individual vessels. Among the urodela, or tailed amphibians, it is very evident that the

response to injury is slower, the diapedesis less, the part taken by the wandering cells already in the lymph spaces more noticeable, than it is in the mammalia.

THE CAUSES OF INFLAMMATION.

It follows from what we have said that anything which causes local injury to the tissues is a cause of inflammation, be it a mechanical trauma, a physical insult, as by heat, cold, or electricity, a disturbance brought about by altered metabolism and abnormal internal secretions, or bacterial or microbic invasion and growth. This last is the commonest cause of acute reaction, and differs from the physical and mechanical causes (though not from metabolic disturbances) in that, as a cause, it is not of momentary duration, but of continued. It is not the mere physical entry of microbes into the tissues that induces inflammation, but the liberation by them of their products in growth or disintegration. And so long as those products are being liberated, for so long is the cause in action. It differs from the metabolic causes in that the latter induce tissue irritation of a milder grade, and so do not induce acute, but rather chronic, reactions. But to say, as some surgeon-pathologists insist, that because bacteria induce the acute inflammation most commonly encountered and that which most frequently demands treatment, therefore inflammation is always the result of bacterial activity, and anything not caused by bacteria is not inflammation, convicts one, to put it in moderate language, of a certain lack of breadth of vision.[1]

We distinguish two grades—not forms—of inflammation, the *acute* and the *chronic*. Of each, it is true, we recognize subgrades, and the one order of cases passes imperceptibly into the other, but for practical purposes the division is useful. In the former we have a frank reaction of rapid development and course; in the latter, a reaction characterized by little evidence of the cardinal symptoms, and slow, progressive course. In the one, the condition unfolds itself in the course of hours or days; in the other, of weeks and months; and thus the salient features in typical cases show marked differences, even though, as we say, the study of intermediate stages convinces us that essentially the two are grades of one and the same process. We shall take up the subject of chronic inflammation later. Here we shall, for the time, confine ourselves to the consideration of the acute type; and first, in order to have a mental picture of the sequence of events, it will be well to describe with some little detail what can be seen when we produce experimentally such an acute inflammation, and follow the successive steps under the microscope.

[1] I have discussed the heresy (which, unfortunately, is taught in more than one school on this continent) in the Medical Record, March, 1896; Middleton-Goldsmith lectures, and the article "Inflammation," in Keen's System of Surgery

THE STAGES OF ACUTE INFLAMMATION EXPERIMENTALLY PRODUCED.

In affording the more typical picture, it is best to consider first what happens in a part well supplied with vessels. And two methods are open to us: either to choose some region that is transparent, and, injuring one spot in that region, to follow under the microscope the unfolding of the resulting disturbances. This was first done systematically by Cohnheim, and there are several such regions which may be selected—the delicate web of the frog's foot, the frog's tongue, which is attached in front only, and normally is directed backward; it can

FIG. 130

Inflamed mesentery of frog: *a*, margination of leukocytes in the dilated capillaries; *b*, migration of leukocytes; *c*, escape of red corpuscles; *d*, accumulation of leukocytes outside the capillaries. (Ribbert.)

easily be pulled forward and out; or, selecting animals higher in the scale, the mesentery of the cat or one of the animals of the laboratory is admirably delicate and so sensitive to injury that exposure to the air alone suffices to set up pronounced disturbance. Or, on the other hand, we can cause injury, bacterial or otherwise, to some internal vascular tissue, and, removing and studying the injured area from a series of animals at successive periods, can in this way trace the successive steps. The advantages and disadvantages of the methods are obvious.

The first is particularly useful for following the earliest stages, the changes in the caliber of the vessels and the rate of blood flow; even the relative position and movement of certain cells can be well observed; but the intervening skin or endothelium, along with the

absence of nuclear staining, renders a study of the finer cell changes impossible. The animal has to be immobilized by some drug, or by "pithing," which may well lower the excitability of the tissues, and prolonged examination is virtually impossible. The second gives permanent preparations, which can be studied at leisure, and permits a very thorough study of individual cell forms, but often leaves us in doubt as to whence the cells come; to be carried out thoroughly requires the sacrifice of a large number of animals, and even then leaves us in doubt whether some important stage may not have been passed over; while, owing to the mode of preparation, the vascular relationships and the blood contents of the part fail to be retained exactly as in life. The two combined afford us a very full picture.

FIG. 140

1, adhesion of leukocytes to the walls of a capillary in an inflamed area; 2, mode of migration of a polynuclear leukocyte. (Lavdowsky.)

Combining the results gained by these two methods, we gain the following picture:

The first result of local injury is temporary *contraction of the arteries* of the part, leading to a brief period of lessened blood supply.

This is succeeded slowly by progressive *arterial dilatation*, so slow that it cannot be of reflex nervous origin; indeed, it shows itself where the nerves to the part have been severed, and, as a result, within an hour or so (in the frog's web, injured by the application of a caustic) there is a *greatly increased blood flow* through the part, the *capillaries become distended*, and many, previously empty and unrecognizable, are now visible with the blood corpuscles hurrying through them.

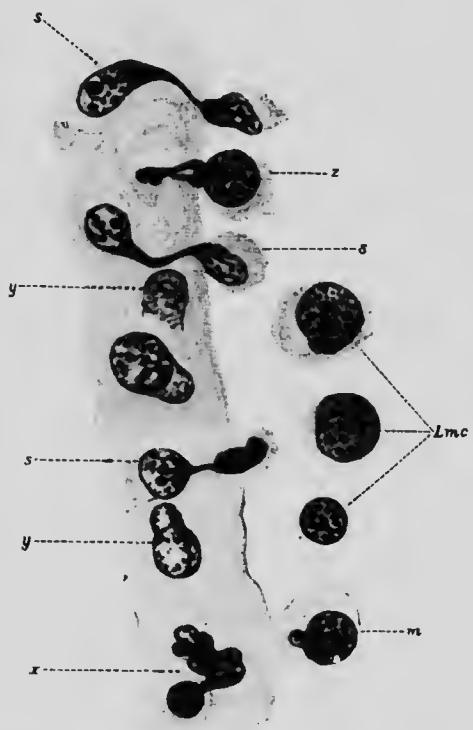
Gradually—in the course of the next hour (in the frog)—the *blood stream becomes slower*. Whereas, at first, the individual corpuscles in a capillary were unrecognizable, all that was visible being a darker central band, or current, with clearer fluid (blood plasma) on either side, now the band becomes broader, the side currents narrower and narrower, and with this, as the slowing continues, *individual blood corpuscles can be distinguished*. And, what is more, the two forms can be made out (this especially in the frog, in which the red corpuscles are relatively much larger). And it is seen that the white corpuscles more particularly are carried along the outer part of the stream.

At this stage there is already manifest increased swelling of the part, and, as determined by placing a cannula in the main lymphatic of the

leg of a dog whose foot has been inflamed by placing it in hot water, there is, at what corresponds to this period, a greatly increased *outflow of lymph*. The swelling, that is, is due to increased *exudation from the dilated vessels*.

If, now, the white corpuscles be studied, it is seen that they lag along, now adhering momentarily and becoming elongated and pear-shaped, now becoming free. What is more, while the red corpuscles

FIG. 141



Migration of lymphocytes through wall of capillary. *z*, *y*, *s*, nuclei of vessel wall cells; *Lmc*, lymphocytes; *x*, irregular shape of nucleus of lymphocyte in process of passage. (Maximow.)

progress onward, the white corpuscles lag behind, in consequence of these temporary adhesions, until it is noted that, proportionally, there can be a remarkable number of white blood cells in the inflamed area. As the current becomes greatly slowed, there may be *oscillation of the current*, and the leukocytes move to and fro with it, until, finally, they become firmly adherent. This is the stage of *margination* of the leukocytes.

Eventually—but by no means necessarily in every case—the slowing

of the current in some of the vessels may give place to complete standstill, or *stasis*.

Next, it is to be observed that certain of the leukocytes are appearing at the outer side of the capillary wall, and, if in a favorable specimen the process be followed carefully, it is seen that it is brought about by a process—pseudopodium—being extended or insinuated, which passes through the delicate wall, gradually gets larger on the outer side, and there often shows finer processes streaming away from the wall into the tissue or tissue spaces, until more of the cell is in the outer side than in the inner, and eventually the whole corpuscle comes to be external. To use an old illustration, the process closely resembles the trick of passing a bladder three-quarters full of water through a keyhole. Thus is accomplished the *diapedesis*,[1] or *migration of the leukocytes*.

As regards the particular orders of leukocytes that pass through, this is best studied by examination of specimens fixed rapidly, cut and stained, when leukocytes can be seen fixed in the process of passage. In an acute inflammation it is the *polymorphonuclears* that *especially migrate*, though it must be remembered that in special conditions the other forms—the eosinophiles and the lymphocytes—are capable of migration, the latter more particularly in subacute and chronic inflammation (Fig. 141). This has recently been amply proved by Schridde,[2] using his acetone method and differential stain.

This much for the earlier stages—the stages of development. Studying them we gain an explanation of the redness, the heat (increased determination of the blood to the part), and the swelling. Regarding the pain, we shall speak later.

These earlier stages are essentially the same in all cases of acute inflammation. The later stages can only be studied fully by the method of section, and what happens in an individual case depends upon the nature of the injury. Thus, it will be most satisfactory to consider now the different grades and varieties of injury, beginning with the simplest and advancing to the more severe, in each case discussing the process of events.

INFLAMMATION RESULTING IN HEALING BY "FIRST INTENTION."

The simplest case is that in which, without bacteria gaining entry into a wound, there is section of the tissues, with destruction of a certain number of cells and section of others not of necessity so serious as to

[1] Hamilton and some other authorities object to this use of the term diapedesis. They would confine it to the passive discharge of red corpuscles which may occur in very acute inflammation, or in greatly dilated capillaries that lack support, as in the lungs (hemorrhage "per diapedesin"). Nevertheless, the term diapedesis means primarily a "stepping through," not a "pushing through," and implies an acute process. Etymologically, the modern usage of the term is correct.

[2] Munch. med. Woch., 52; 1905: 1862.

destroy them, and in which either the wound is so small that the edges come together naturally, or, being larger, the edges are brought into apposition by one or other surgical means. Here, as a result of the first stages, there is an oozing or exudation of "serum" into the wound, along with some leukocytes and with an inconsiderable amount of blood from divided capillaries. Even if there be no blood, the interaction of the leukocytes, as sundry of them break down and liberate their fibrin ferment, of the destroyed cells similarly undergoing disintegration, and of the serum, lead to coagulation of the latter, and on the surface and between the apposed edges fibrin is laid down, and this acts as a *provisional cement substance*. Even within the first twenty-four hours, and without mitosis, the tissue cells bordering upon the wound enlarge and send out processes and undergo division; epithelial cells of the deeper layers may even, according to Leo Loeb, exhibit a certain grade of amœboid movement, with alteration in relative position, coming thus into immediate apposition with those on the opposite side. In this way there is a bridging over and interlacing of the cells of the two sides of the wound. Next, as we are now convinced, largely through the agency of the leukocytes, the debris of dead cells is carried away—eaten and removed—absorbed. The same is the case with the fibrin; this, too, undergoes absorption. In three days or so sections show occasional mitoses in the cells on either side of the wound; the capillaries in the two sides are seen to throw out bud-like processes, which unite across this gap, and repair is practically complete. For a few days longer there may continue some redness and slight tenderness along the wound, but this disappears, and the parts are practically in *statu quo*.

It is, or used to be, taught that every wound must leave its scar. That this is not the case everyone knows who shaves. Of late we performed an autopsy on a case in which laparotomy had been performed within three months, in which close examination externally failed to detect the operation wound, while internally it was only indicated by omental adhesions and the absence of important pelvic viscera.

Essentially, a similar course follows *contusions*, whether subcutaneous or affecting deeper viscera. There are the same preliminary stages, with redness, swelling, heat, and pain, though the condition is complicated generally by more extensive rupture of capillaries and greater escape of blood into the part. The fluid of such blood drains away by the lymphatics, as may, also, some of the corpuscles. The mass of the corpuscles, being out of place, degenerate, their hemoglobin dissolves out and undergoes a series of reactive processes, characterized by the color changes familiar in the "black eye." Eventually the leukocytes carry away the debris, and the parts, provided the tissue destruction has not been severe (as in laceration), return absolutely to the normal.

INFLAMMATION LEADING DIRECTLY TO THE FORMATION OF GRANULATION TISSUE.

If there has been loss of tissue, whether in communication with the exterior or through some cause leading to local necrosis or tissue death in an internal organ, provided bacteria do not grow in the wound, we have the same preliminary stages, only here, the injury being more severe and extensive, there is a greater reaction. More fluid is apt to be exuded, and, attracted by the dead cells and the products of their disintegration, more leukocytes migrate into the area. As a result, in an open wound the exudation, mixed with leukocytes and escaped blood, coagulates and forms a scab, which, drying on the surface, is in itself protective against bacterial invasion; and, if the wound has been effected in a clean manner, and due precaution be taken, the wound may remain sterile. Bacteria, it is true, may gain entrance from the wounded skin—for this is never sterile, and cannot be rendered germ-free—but under favorable conditions the phagocytic activity of the exuded leukocytes and the bactericidal properties of the exudate may destroy them before they have time to multiply and gain the upper hand. In an internal organ or part the dead tissue cannot be immediately removed (*e. g.*, an infarct, or limited area of blocked blood supply in an organ, or the various structures in dry gangrene); the exudate infiltrates it, its cells in dying coagulate, and the infiltrate between those cells also coagulates (*coagulation necrosis*).

Following upon this stage, we find that the dead cell material becomes either eaten up (phagocytosis) or gradually dissolved; it disappears. As shown by Lieber, aseptic collections of leukocytes and the fluid from the same have distinct digestive powers, but, in addition, we have come to recognize of late years the autolytic properties of the cells (p. 337). Whichever process plays the greater part, already, in three days or so after such tissue destruction, more particularly at the edge between the dead and living cells, there is observable a marked relative diminution in the amount of debris, and with this the appearance of a clearer zone between the intact tissue and the scab or area of coagulation necrosis, with its more closely packed migrated leukocytes.

The next stage observable is that, into this clearer zone new capillary buds project from the surrounding capillaries. This is the first stage, or almost the first stage, of *organization*, and deserves close study. We say almost the first, because, even before this shows itself, changes have been noticeable in the tissue cells bordering on the wound. They are found markedly swollen, showing unusual processes directed toward the area of injury, may, as in the previous case, undergo direct division, and within twenty-four hours, according to some authorities, although usually the period is later, the more orderly form of indirect division may be exhibited.

There still remains doubt as to the structure of the finest capillaries—whether they possess anything of the nature of the limiting membrane

or whether they consist merely of a tube, or potential tube of endothelial cells in immediate communication with the surrounding tissue cells. The changes they undergo in this process of organization would seem to indicate that the latter is the case. It would seem natural that where a tube under pressure passes from a region where it is surrounded and supported by tissues to a region where it is superficial and unsupported, it should give way on the side toward that surface, and

FIG. 142

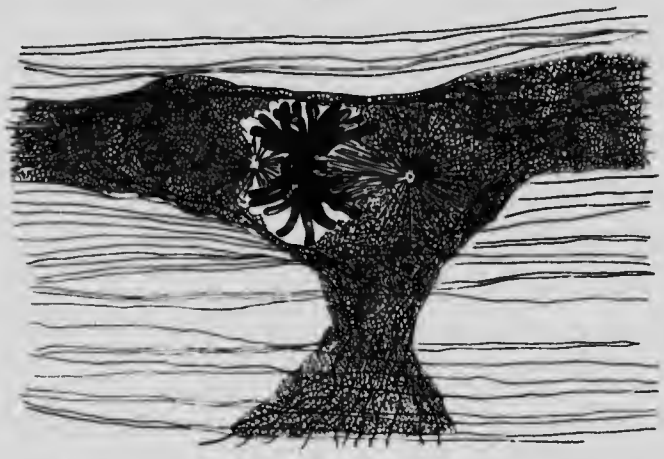
Formation of new vessels in granulation tissue: 1, from a Ziegler's chamber (formed of two coverslips) left in the peritoneal cavity of a rabbit for forty-eight days; portion of field bounded by two fully formed new capillaries; between them can be seen the solid buds and processes of developing new capillaries; 2, from a similar preparation to show formative cells, or fibroblasts, in direct connection with the endothelial processes. (Ziegler.)

that so, new capillaries should arise, as local "givings way," or projections on the free aspect of preëxisting capillaries, brought about by the internal blood pressure. But this is not seen to be the case. At the most, in an exposed wound the preëxisting capillaries tend to present general dilatation with curvature toward the wound surface. But, where a new capillary is to be formed, instead of a thinning of the wall, there is a thickening. The endothelial cell or cells at that point form a swelling, from which projects a primarily solid process. As this

grows it becomes hollowed out at its base and blood gains entrance into and distends it. Either before this occurs, or later, it is to be seen (in sections) that the thin filamentous end of the process has either come into contact with the wall or some other capillary, or has become connected with the delicate process of some fibroblast (growing connective-tissue cell), or with a similar process from some other capillary. In the latter case more particularly we encounter specimens showing that the process from either end becomes hollowed out, the "mother" endothelial cells of the buds multiply, and in this way is gained a new capillary identical in structure with the old.

It is in this way that *granulation tissue* is developed, by the formation of successive loops of new vessels. In this way the free surface of a wound becomes covered with a granular or velvety surface of reddened,

FIG. 142



Portion of a fibroblast, undergoing mitosis, greatly enlarged to show the intercellular and intracellular fibrils. (Lubarsch.)

minute projections, individual sets of these new loops surrounded by young fibroblasts, the products in the main of the multiplication of the preëxisting connective-tissue cells bordering on the wound, though of late the view has once more gained support that some, at least, of these fibroblasts are derived from one order of leukocytes, while very possibly the proliferating vascular endothelium may contribute some. The fact that new tissues never arise in isolated foci, but always in direct connection with preëxisting tissue, is strong evidence against cells that have wandered in from elsewhere playing a primary part in this process of new connective-tissue formation.

The identical process is to be met with in internal organs and in the organization of coagulated blood—thrombi—within the vessels, though here, there being no free surface, the orderly formation of loop on loop is not so obvious; there is first removal of the dead matter by the agency

PLATE XIII

Granulation Tissue. The Upper is Toward the Outer Surface. (Maximow.)

end., capillary endothelium; *new cap.*, endothelium of newly forming capillary; *fbl.*, fibroblasts; *l.*, polynuclear leukocytes; *x.*, the polyblasts of Maximow including plasma cells); *deb.*, debris of leukocytes; *deg.*, a degenerating "polyblast."

of leukocytes, autolysis, and absorption. Into the clear zone so formed the vascular loops project forward in an identical manner; these become clothed with fibroblasts, while farther forward there is simultaneously occurring the clearance of debris and the projection of new vascular processes.

Thus, in an orderly manner the dead tissue is removed and replaced and the free space filled in.

As the fibroblasts become mature, from being at first rounded or oval and fairly stout, with relatively large nucleus, they become elongated and spindle-shaped (spindle cells), or of elongate, stellate form; and not only do fine fibrillar processes project from their ends or sides, but with appropriate reagents they are to be made out traversing the body of the cell (Fig. 143), and these increase in number, replacing the cell substance proper, until the cell is represented by a meagre, attenuated nucleus, with but a trace of cytoplasm, lying surrounded by a bundle of fibrils—*white connective tissue.*

Whether the white connective-tissue fibrils are formed wholly out of the cell substance has been a matter of some debate; the weight of evidence indicates that the interstitial substance also contributes. Certainly the bundles of fibrils, and, indeed, the individual fibrils, extend through many cell areas. In this connection Leo Loeb's observations, made in our laboratory, are at least suggestive. He has pointed out that, if a little blood plasma containing leukocytes be expressed gently between two slides and then the one slide be pulled over the other, fibrin formation sets in, and upon examination all the fibrils are seen to lie in the line of traction, and, what is more, to traverse the bodies of the leukocytes. While the fibroblasts in granulation tissue are laid down with no trace of regularity, the bundles of white connective tissue are remarkably regular, in this resembling the bone lamellæ, in which, clearly, we have to deal with intercellular deposits.[1]

Such newly formed white connective tissue, as it grows older, undergoes contraction and condensation. The area of the new tissue becomes markedly smaller, the abundant capillaries become in the main compressed and obliterated; from being very vascular, the new "scar" becomes distinctly avascular; the sides of the wound, infarct, or thrombus approximate, and we have the formation of the characteristic *cicatrix.*

According to the tissue involved, so may we find some variation in the process. Thus, the brain contains a relatively small amount of ordinary connective tissue, and its vessels, it would seem, do not easily form new capillaries. Thus if there be a hemorrhage or other local tissue destruction, while there is congestion round the area and abundant passage in of leukocytes, which load themselves up with debris (Glüge's corpuscles), the formation of granulation tissue is very meagre; a cyst wall only may be formed, and, with the carriage away and absorption

[1] We shall discuss in an Appendix at the end of this volume, rather than here, Martin Heidenhain's contention, which has appeared while this work is passing through the press, that the intercellular fibrils are living and undergo active growth; for such a view bears upon the cell theory in general.

of the dead matter, as the brain, from its relationships, cannot fall in, it becomes replaced by serous fluid, so that a cyst develops. Such cyst formation will be discussed in the chapter on Cysts.

ACUTE FIBRINOUS INFLAMMATION OF SEROUS SURFACES.

What is but a variant of the above process is seen in the fibrinous inflammation of serous surfaces. Simple acute *serous* inflammation is a variant of the previous grade, characterized by abundant exudate from the greatly ingested vessels of the serous surface and relatively slight migration of leukocytes. With its arrest, the parts undergo *restitutio ad integrum*. In the fibrinous form, and the same is true of the serofibrinous, there is abundant migration of the leukocytes out of the surface vessels. The irritant—bacterial in this case—leads to widespread necrosis and casting off of the outer endothelial layer, and, just as thrombosis in a vessel is induced by destruction of the vascular endothelium, the blood coagulating or coagulumming over the site of injury, so here, the leukocytic exudation breaking down, coagulates upon the injured surface, with the result that a deposit of fibrin occurs—the homologue of the scab over an external wound. If the deposit be but slight, it is absorbed by subsequent leukocytes, the areas of serous endothelium that have not been destroyed exhibit proliferation, and new cells cover the surface. If it be more extensive, complete return to the normal does not occur; we encounter replacement of the dead fibrinous matter by granulation tissue. New vessels pass in from the serous surface, organization occurs around these, and, where the fibrinous exudate completely fills a cavity, or is adherent to both aspects, then the new vessels coming from opposite sides anastomose, and we have complete obliteration of the serous cavity (*concretio*, or *synechia*), or the formation of bands and veil-like membranes of connective tissue passing from one side to the other (*organized adhesions*).

SUPPURATIVE INFLAMMATION.

The essential feature of this grade of inflammation is the profound attraction of leukocytes to the area of injury, followed by the death of a large proportion of the same, and this unaccompanied by the rapid disintegration and dissolution of the dead cells which characterized the preceding grades. There is thus found a thick, more or less creamy and opaque fluid at the site of inflammation, and, on microscopic examination, this is found to be a suspension of leukocytes—the polymorphonuclear form being in overwhelming majority in all acute cases. Some of them exhibit well-staining nuclei, some have intracellular foreign matter—bacteria in various stages of degeneration—fatty and other matters, the result of phagocytic activity. These are cells presumably still active at the time of the removal of the pus. Others, again, show badly staining, broken-up nuclei. These are, clearly, degen-

crated and dead cells. Occasionally, notably in peritoneal inflammations, cells of other type may be observed, along with abundant free bacteria. If the fluid in which the cells are suspended be filtered off, it is found to be thick and singularly rich in proteins, the results of tissue destruction and leukocytic disintegration.

Such is *pus*, and, experimentally, it can be produced by many means—by the local injection of oil of turpentine, the local action of certain metals, such as mercury and copper and their salts; by the products of growth of certain bacteria, or by the bacteria themselves. Experimentally, that is, as Leber, Councilman, and others showed many years ago, it is possible to produce aseptic pus. This, however, is not the case in ordinary clinical practice; in man, suppurative inflammation, in nine hundred and ninety-nine cases out of a thousand, means the presence of bacteria. The abscesses that may follow the mercurial intramuscular injections, which constitute one method of treatment of syphilis, may be aseptic, as also, it may be, that the suppuration following deep burns may not in all cases be wholly ascribable to microbic agencies; the destroyed cell matter, that is, tends to cause an active migration of leukocytes. But in these cases it is impossible to exclude the presence of surface bacteria, and so decision is difficult.

The course of such suppurative inflammation can easily be followed in the lower animals by means of subcutaneous injection of pus-producing bacteria, thereby causing abscess formation away from the surface, and excluding the possible action of other agencies. The variation from the processes hitherto described consists in: (1) the progressive growth of the pathogenic organisms at the site of inflammation; (2) the progressive destruction of the tissues; (3) the more pronounced migration of leukocytes to the area; and (4) the indication of interaction between those leukocytes and the bacteria, and of the existence of yet other reactive processes, whereby the growth of the bacteria becomes limited and arrested, and their destruction brought about. Experimentally, that is, just as in more natural conditions, there is a tendency for the abscess to come to a head, and following the successive stages, the most striking feature is that the bacteria grow freely and abundantly, and then the time comes when the indications of abundant growth are succeeded by those of arrest and disappearance.

There is, in short, a period of incubation, during which the bacteria multiply locally without setting up any very marked reaction. Soon there is such reaction: the cells of the part become swollen, the capillaries in the immediate neighborhood full of blood, but only after this does the migration of leukocytes become noticeable. In other words, some little time is necessary before the bacteria, growing, are able to discharge sufficient toxins, and for those toxins to diffuse in sufficient concentration to attract the leukocytes out of the surrounding capillaries. From this time on the migration is the prominent feature—is so extensive that the leukocytes at the foci of bacterial growth completely obliterate the tissue cells; they take up the bacteria actively, remain in the centre of attraction, and—whether by the toxins of the

ingested microbes, or by the toxins of the still abundant bacteria that have remained uningested—undergo destruction and dissolution. For some days, therefore, the organism is unable to restrain the bacterial growth. Despite the abundant leukocytes, the area involved increases; the tissues of this area are killed and disintegrated, their place being taken by the abundant leukocytes, which continue to pour in from an increasing ring of surrounding dilated capillaries. Bacteria are to be detected outside the limits of the area, having grown there along the tissue spaces or been carried by the currents of the exudate.

And then, at last—after three or four days—the organism gets the upper hand, and we see our fully developed *abscess*. There is what Ribbert describes as a dense wall of leukocytes (Wallbildung) around the area; immediately outside and merging into this is a zone of dilated capillaries, the *pyogenic zone*, or "*membrane;*" there are no longer any bacteria outside, and, while the outer zone of leukocytes stains well, the central mass of leukocytes stains poorly and shows signs of nuclear disintegration and of death. Bacteria are still present in the central pus, and still living, as may be determined by making a culture, but their number is diminishing.

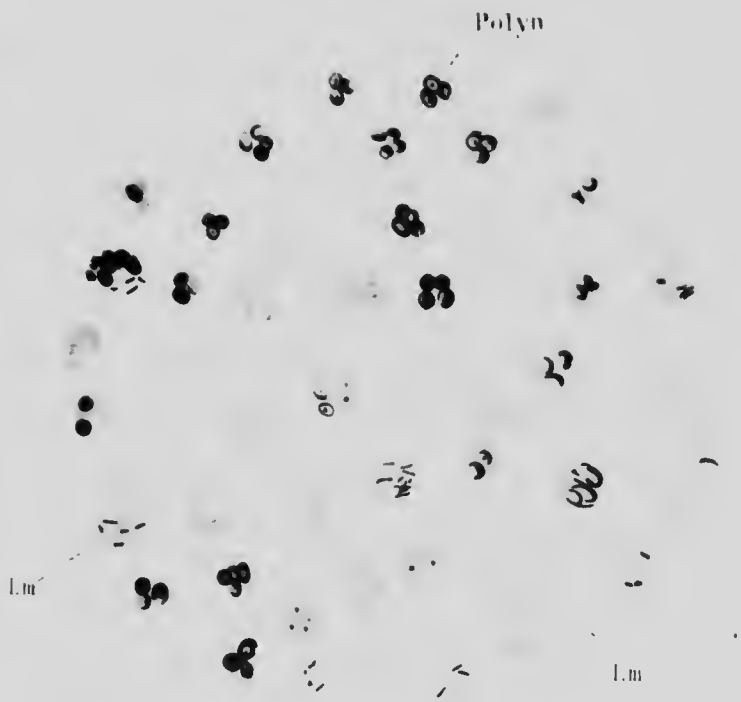
In the chapters upon general reaction and immunity (see particularly Chapter IX) we shall discuss more closely what has occurred to make the tissues more powerful.

Now follow the stages of resolution of the abscess: The micrococci or other microbes become fewer and fewer, and as the production of toxins diminishes, and the attractive force is lessened, the undestroyed leukocytes pass away from the area into the lymph and blood-vessels—there is absorption. If the abscess be of small extent, the area closes in; if larger, the destroyed tissue is replaced by granulation tissue and a cicatrix results.

The process here described as occurring in abscess formation holds also for inflammatory *ulceration*, with the difference that the latter process originates in close connection with an epidermal or mucous surface, and results in destruction of these surface layers, so that there is produced a loss of continuity of the tissues and exposure of the deeper layers—covered by pus—to the external medium. With resolution, there is healing by a like process of formation of granulation tissue. The like process obtains also in wounds, whether open or closed, that have become infected.

In *suppurative inflammations of serous surfaces*, another factor may be introduced. We have already seen that irritation of such highly vascular regions is liable to result in a fibrinous exudate. Where pyogenic bacteria gain entrance locally to a serous cavity—in appendicitis, for example—their toxins, before they become too concentrated, lead, first, to a fibrinous exudate, whereby the viscera in the immediate neighborhood become cemented together; and, while at the region of entrance the bacteria may multiply and induce pus formation, the surrounding fibrinous adhesions prevent the escape of these bacteria into the serous cavity in general, and, in virtue of the fibrinous adhesion,

PLATE XIV



Film Made from Peritoneal Fluid in Case of Peritonitis set up by Inoculating B. Coli Twenty-four Hours Previously into the Abdominal Cavity of a Rabbit. (Beattie.

polyn., polynuclear leukocytes, many containing bacilli; *l.m.*, large hyaline mononuclear cells, many acting as phagocytes for polynuclear cells, red corpuscles, etc.

dense, and permitting very slow diffusion of toxins, with arrest of bacterial passage, a localized abscess results in place of widespread suppuration—an abscess whose circumference, in part, is formed of inert matter, and not of living tissue. The products of bacterial growth, it is true, can dissolve this fibrin; thus, such an abscess tends to increase in size, but as it grows, so in favorable cases the outer zone of irritation, through the diffused toxins, leads to more fibrin being laid down, and if with active reaction on the part of the tissues and quiescence of the viscera, such fibrin formation can be adequately procured, the inflammation remains local. Indeed, with the increase in size, the visceral layers forming the walls of such an abscess may become eroded and the abscess discharge into the lumen of the intestines (for example) before the fibrinous adhesions give way; we thus may have *exogenous ulceration* of viscera.[1] Where, on the other hand, the fibrin formation is inadequate from one or other cause, from lack of reactive powers or from amount and intensity of action of the entering bacteria, there the bacteria become spread through the serous cavity, and general or diffuse suppurative inflammation occurs.

It is, perhaps, serviceable to banish the term *general*, as applied to peritonitis, as being too vague, and to distinguish between *universal* and *diffuse*. When, for example, there is perforation or rupture of the bowel, there may be immediate infection of a considerable neighborhood, and a purulent condition set up too diffused and indefinite in its boundaries to be spoken of as a local abscess; nevertheless, all around the outer limits fibrin formation is seen to have occurred. In this way the whole pelvis or one segment of the abdominal cavity may be involved, the rest being free. On the other hand, there may be no fibrin formation, and suppuration everywhere throughout the cavity—universal peritonitis.

A similar spreading suppurative condition may show itself in the solid tissues, where the "wall building" by the leukocytes is incomplete, and the bacteria, as a consequence, proliferate and spread in the tissue spaces and along the lymph channels. In this way we have set up a *cellulocutaneous inflammation*, with diffuse suppuration of a limb or subcutaneous tissues. Where the toxic properties of the bacteria are still more pronounced, the extensive tissue destruction which follows their spread becoming the most marked feature, and we have a *phlegmonous* or *gangrenous* inflammation.

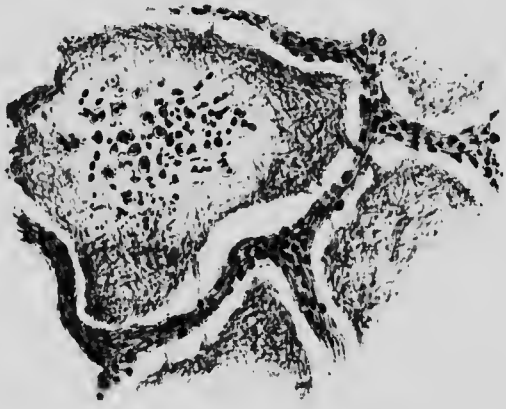
In all these latter cases in which the bacteria are not successfully retained in the locality of their primary manifestation, gaining entrance into the lymph and blood stream, they may be carried to a distance, and there, being deposited and finding conditions favorable for growth, may set up similar reactions, causing *metastatic* or secondary abscesses. More particularly in acute bacterial inflammations, stasis is apt to occur in surrounding vessels. By this means they become plugged, and, as an abscess extends, it is noteworthy that despite erosion of the tissues

[1] See Adami, Montreal Med. Jour., 32: 1903: 401.

hemorrhage is not liable to occur. Such plugs of coagulation may extend up a vein for some distance (thrombophlebitis), and as an abscess extends, causative bacteria gaining entrance into them may grow along them, and so into the vessels. Growing, they soften the clot, and from it infect the vessel walls (*pylephlebitis*); portions of the disintegrated clot may become loosened, dislodged into the main vein beyond the point of arrested circulation, and carried by the blood to the lungs, liver, or other organ, and there become arrested in some smaller vessels, thus causing an *embolus*, or plug, and setting up an *embolic abscess*.

We have not as yet exhausted the varieties of acute inflammatory manifestations. In this progressive description of the different orders we have purposely left out some which were not of the direct line. These we may now note.

FIG. 144



Fibrinous exudates in lung alveoli; case of acute lobar pneumonia; to show fibrinous network. (After Ribbert.)

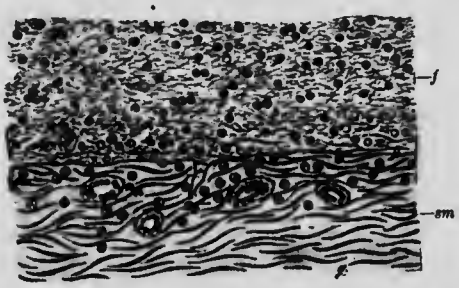
Hemorrhagic Inflammation.—The exudate may contain not merely leukocytes, but also red blood corpuscles, under two conditions: (1) where the causative agent is very toxic, setting up a greater dilatation and thinning of the capillary walls, along with, it may well be, a direct degeneration of the capillary endothelium, and (2) where the abundant capillaries are unsupported, so that their dilatation is not limited by the pressure of surrounding tissues. In both these cases erythrocytes may be forced through spaces in the capillary walls and escape with the exudate. In some cases of intense inflammation the number of leukocytes in the exudate may, from negative chemiotaxis, be very few, and, *per contra*, in inflammation of moderate grade, a stray erythrocyte may be found outside the vessels which, possibly, has passed out through the channel made by the actively migrating white cell (Fig. 139). In those other cases it has to be recognized that lack of continuity of the capillary wall is not necessarily produced by this means.

Such hemorrhagic inflammation often shows itself in connection

with serous surfaces. The commonest site, however, is the lung substance, where the hemorrhagic exudate into the delicate walled alveoli is the distinguishing feature of acute pneumonia. Here once more we note that, so soon as the blood (for the exudate in these cases is blood to all intents and purposes) escapes from the vessels, it tends to coagulate. In this way is produced *acute fibrinous inflammation.*

Membranous Inflammation.—Similar acute fibrinous inflammation may also affect mucous membranes, as of the throat and upper respiratory channels, but a distinction must be made between it and the *membranous* or *diphtheritic* inflammation. In this latter form an irritant acting from without or from the surface brings about necrosis of the surface layers—there is profound engorgement of the superficial vessels with exudation—and the same process happens as we noted in connection with infarcts, namely, the exudate and the dead cells undergo a common coagulation, and surface exudate and surface cell layers together form a (false) membrane which, in the earlier stages, is so intimately connected with the underlying living tissue that it cannot

FIG. 145



Schematic representation of a diphtheritic inflammation of a mucous surface. Complete loss of epithelial layer, the necrosis extending into the subepithelial layer; *f*, fibrinous layer; *sm*, submucosa.

be detached, herein differing from the slighter fibrinous exudate. Such diphtheritic false membrane may occur not only in the throat, but in the intestines, bladder, and other mucous surfaces, and even on exposed wounds.

Later, the accumulation of leukocytes between the false membrane and the sounder tissues below leads to a digestion of the fibrinous connections and loosening of the membrane.

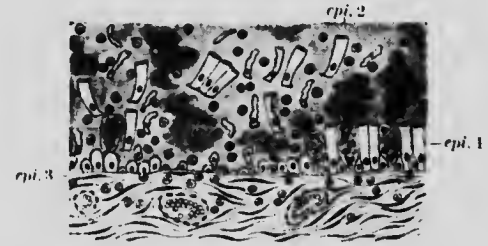
It is worthy of note in this connection that where there exists a well-formed basement membrane the diffusion inward of toxins is arrested to a considerable degree, only the surface epithelial layer undergoing necrosis and being cast off. This, at least, would seem to be the anatomical explanation of the firmly adherent false membrane in the pharynx in diphtheria, the looser, detachable membrane in the trachea and bronchi.

The terminology here is misleading and unfortunate; it dates from a time when the real nature of diphtheria was unknown and two condi-

tions were recognized—croup and diphtheria, the former affording a detachable fibrinous membrane, the latter a more adherent membrane. Needless to say that nowadays we know no "fibrinous croup," but, as regards false membranes, we observe that a diphtheritic membrane is by no means always due to the diphtheria bacillus. Our own custom is to employ the term *diphtheritic* for all false membranes; the term *diphtherial*, when we wish to indicate that this is associated the specific disease, diphtheria.

Catarrhal Inflammation.—A slighter grade of change, affecting mucous membranes, results in the *catarrhal inflammation*. Here although we note that many of the epithelial cells are cast off, and can be recognized in the abundant exudate, the dominant feature is irritation rather than necrosis. With the surface irritation there is pronounced congestion of the underlying vessels, abundant exudation of serum, and some leukocytes, but most marked of all, the columnar, epithelial cells are stimulated to excrete abundant mucus, and the copious mucus forms a layer over the inflamed surface, containing, also, leukocytes and cast-off epithelial cells. This discharge is regarded

FIG. 146



Schematic representation of a catarrhal inflammation: *epi.* 1, columnar epithelium still *in situ* but with increased number of goblet cells discharging mucus; *epi.* 2, epithelial cells liberated into exudate; *epi.* 3, remaining vegetative epithelial cells.

as, to a considerable extent, protective; not only are bacteria detained in it, but it is claimed to have a certain amount of bactericidal activity, and acids and other irritants diffuse through it with difficulty.

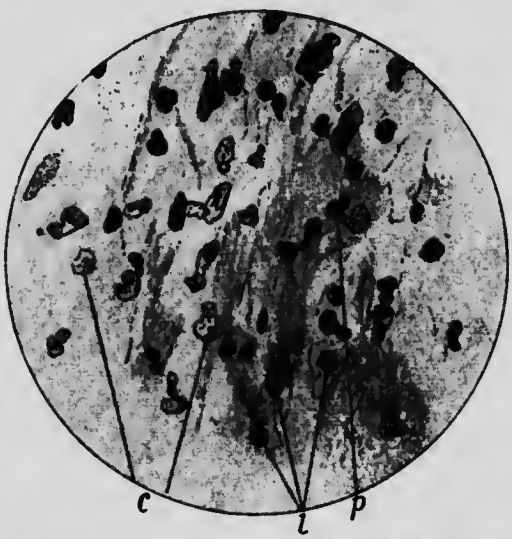
Inflammation in Non-vascular Areas.—There are several such non-vascular areas in the body: cartilage, the outer third (at least) of the cusps of the heart valves, the lens, and cornea. This last, more particularly, affords a favorable field for the study of the effects of local injury.

Here, as in vascular tissues, we may have various grades. The very slightest destruction of surface cells is followed merely by swelling and overgrowth of the surrounding cells and replacement by these new cells. A little more severe injury is followed by attraction of leukocytes from the surrounding tissue spaces of the cornea and from the lacrimal fluid bathing the surface of the eye (this always contains a few leukocytes). These first fill the wound, then, as the surrounding corneal

corpuscles multiply, they pass away and with them the debris of the dead cells is found to have gone also, and the part returns to the normal.

More severe injury is inflicted by injecting suppurative microbes, such as the *pyococcus aureus*, into the corneal tissue. As in the case of the experimental abscess, we recognize a period of growth of the bacteria, with swelling, degeneration, and destruction of the cells at the focus of growth; some extension of the bacteria along the surrounding tissue spaces, the more peripheral corneal corpuscles becoming swollen, in their turn, and their processes more prominent. Only after many hours—it may be next day—do we see evidence that the toxins have diffused through the corneal lymph spaces and affected the circular

FIG. 147



Mild grade of inflammation of cornea in man (keratitis e lagophthalmo), characterized by enlargement and direct division of the nuclei of the corneal corpuscles *c*, with but slight invasion of polynuclear leukocytes *p*, and lymphocytes *l*. (Tooke.)

marginal vein. This now becomes dilated and prominent, and microscopic examination at this stage shows margination of leukocytes and migration of the same *toward* the site of injury. Leber performed an admirable experiment to demonstrate that this migration is active, and that the mass of leukocytes is derived from the bloodvessels. He injected cocci into the cornea at three different points around the centre, and found that there was no leukocytic accumulation toward the central aspect of these foci, but on the peripheral aspect each showed a more or less wedge-shaped radial accumulation.

From now on the process closely resembles that which we have described in connection with the abscess—or, more exactly, what happens in the ulcer: progressive tissue destruction, with—in cases that

end in healing—even more marked accumulation of leukocytes. And, to complete the similarity, the vessels become definitely involved. We mentioned in connection with granulation tissue that the formation of the buds or processes which become new vessels was difficult to explain, save as due to chemiotactic influences. It is impossible to resist a like conclusion here. From the marginal vein processes are given off at several points, directed toward the ulcer. If the ulcer be not central, it is particularly on the side closest to the ulcer that these show themselves. They are not developed on the side of the vein away from the cornea. And as these processes enlarge, they become canalized, become new vessels in the previously non-vascular cornea, passing to the region of ulceration. Once formed, they may be observed, in man, for years afterward, the indication of old corneal inflammation. Similar new vessels are formed in the inflamed heart valves, and make their way into inflamed cartilage.

Whether, now, in the stages of healing definite granulation tissue is formed at the site of the ulcer, or merely absorption takes place, with proliferation of the corneal corpuscles and filling in of the wound, depends upon the extent of the ulceration and the duration of the process. In all cases, however, the new tissue is imperfect, the cells more irregularly disposed than normal corneal tissue, the cicatrix fibrous, white, and opaque. Where the process is not duly arrested, the whole thickness of the cornea becomes eroded, the aqueous humor escapes, and the inflammation may become general, affecting the whole eye.

In the *heart valves* the like process is complicated by the fact that the ulcerated surface is exposed to the blood stream, and on it fibrin becomes deposited, forming "*vegetations*." The causative organism may grow into these vegetations, and lead them to soften and become detached into the blood stream; if small, they may be completely absorbed by the agency of leukocytes; if not absorbed, the vascularization of the ulcerated cusp extends into them, their fibrin becomes replaced by granulation tissue; they become organized and fibroid.

CHAPTER II.

INFLAMMATION—(Continued).

CHRONIC INFLAMMATION.

There is another group of cases in which (*a*), there is a long-continued process (*b*), accompanied by few or none of the cardinal symptoms (*c*), in which the proliferative changes and formation of cicatricial fibrous tissue are more prominent than the vascular disturbances (*d*), more prominent also than are the evidences of leukocytic migration. And yet, studying these chronic conditions, we are convinced that they represent but another grade of the one process of inflammation. In the first place, they follow upon definite insult or injury to the tissue affected. Here, too, we have a series of intermediate cases passing imperceptibly from the most acute to the most chronic conditions, with no sharp line of distinction at any point; and, further, we recognize cases in which the beginning is of the acute type; others in which there are recurrent outbreaks of more acute disturbance, the changes progressing slowly but steadily in between these.

The word chronic is apt to be used very loosely. It is customary, for example, to speak of indications of previous acute inflammation as chronic—of old pleural, pericardial, or peritoneal adhesions as *chronic* pleurisy, pericarditis, or peritonitis. This is both wrong and misleading, and only permissible when—as often happens in chronic endocarditis—the altered condition of the parts in itself leads to further progressive changes. We should make the distinction between *old* pleurisy, or pleuritic adhesion, and *chronic* pleurisy, using the latter term only where we recognize slowly progressive changes, due to the continuance of irritation.

Like the acute conditions, the chronic changes may be set up either by bacterial or by non-bacterial irritation; in the latter case we may have to deal either with the effects of repeated slight mechanical injuries, or, more often, with the effects of perverted metabolism and continued slight intoxications affecting particularly certain tissues.

The Infectious Granuloma.—It is more instructive to begin with the study of cases which may verge on the subacute; for this purpose, the so-called *infectious granulomata* afford the best examples.

The term "infectious granuloma" is applied to the localized effects of the growth within the organism of a class of microbes which, while in particular weakly or very susceptible individuals they may induce a rapidly fatal disease, in general set up chronic disturbances, which induce no intense immediate reaction, but at the same time are not

easily antagonized once they gain a foothold in the tissues. The process of the arrest of their activities is a slow one, and often incomplete, the microbes being cut off from the surrounding tissues, but not of necessity killed. Often this process of arrest fails, and there is progressive extension of the condition. Each localized growth of the microbes in question sets up a localized reaction, resulting not in the formation of an abscess, but of a nodular tissue overgrowth and cell destruction—a tubercle. Such microbes are those of tuberculosis, leprosy, syphilis, and actinomycosis, to mention the more important. Relatively inert foreign particles and the ova of certain larger parasites set up similar changes. The tubercle proper, caused by the tubercle bacillus, affords us the best example; its mode of formation has been studied more especially by Baumgarten and Borrel.

When the tubercle bacillus, or a collection of tubercle bacilli, injected into the circulation, comes to rest within a capillary, they are apt to be taken up by the endothelial cells of that capillary within a few minutes; or, if too many are to be taken up, it is found that they become surrounded by large cells, which now we recognize are swollen and proliferated endothelial cells. The earliest reaction, thus, is on the part of the tissues, and is not a cell destruction, but cell growth. Along with these large so-called *epithelioid* cells a certain but relatively not large number of leukocytes also collect. At first polynuclear, later lymphocytic.

FIG. 148

Schematic representation of a tubercle: *a*, giant cell with necrotic centre and multiple nuclei more peripherally arranged; *b*, epithelioid cells; *c*, lymphocytes.

Through this endothelial swelling and proliferation the capillary first involved becomes closed up, and later, the outer capillaries in the neighborhood become similarly closed, so that the tubercle becomes strictly an *extra vascular* formation. During the first stages, then, cell growth around the bacilli continues to be the most marked feature. The large endothelial cells immediately surrounding the bacilli may fuse together, forming a *giant cell*, having the mass of bacilli in the centre. This is not always seen, but, when present, is very characteristic. Nor would it seem that the numerous nuclei of the giant cell are purely due to cell fusion; as shown in the accompanying figures from Dr. Duval's[1] studies upon chronic glanders, the multiplication is in part by amitosis. As the bacilli multiply[2]—and also, it may be, as some of them are destroyed

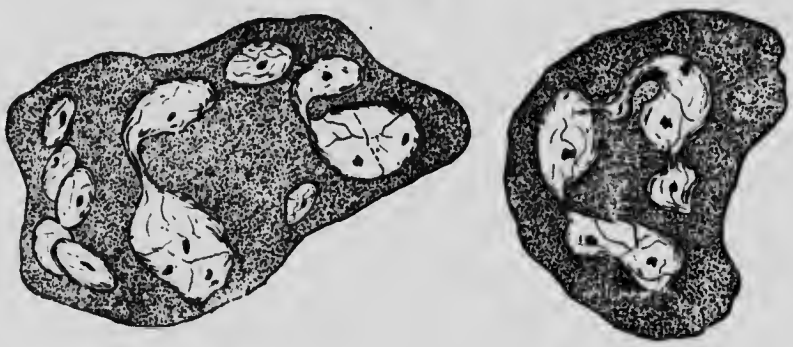
[1] Duval and White, Jour. of Exp. Medicine, 9: 1907: 352.

[2] Prudden and Hodenpyl have shown that the injection of dead tubercle bacilli will lead to these earlier stages, in which case the gradual diffusion out of the intracellular toxins can be the only explanation of the succession of changes induced.

and their intracellular toxins liberated—from acting in the less concentrated form as stimulants to cell proliferation, in the more concentrated form they act as intoxicants, and lead to the death of the cells in the immediate neighborhood. Thus, the typical giant cell comes to exhibit a central, badly staining, necrosed area, around which—often more on one side than the other—other endothelial cells have fused, whereby it comes to pass that the typical tuberculous giant cell exhibits on section a peripheral circle, or crescent, of nuclei surrounding a more or less hyaline necrosed mass, the tubercle bacilli being found more particularly at the edge of the necrosed area, although indications of broken-down bacilli may, with care, be detected throughout the central area.

The complete early tubercle shows, thus, a central giant cell surrounded by a collection of larger, more hyaline, epithelial cells, and a certain number of interspersed lymphocytes—the typical "small round cells" of subacute and chronic inflammation—or, less frequently, of polymorphonuclear leukocytes. Outside this there may be some dilatation of the surrounding capillaries, but it is not very marked.

FIG. 149



A *B*

Giant cells from experimentally induced chronic glanders. In *A* two of the nuclei show amitosis; in *B* the multiplication is completely amitotic. (Duval and White.)

As the bacilli continue to propagate, the areas of cells destroyed increases, and we gain a larger and larger central area of necrosis of that type known as *caseation*. The affected cells completely lose their power of staining, the cell bodies undergo fatty granular disintegration and lose their outlines—an opaque granular cheesy mass fills the centre. Now, around this there may be found several newly formed giant cells, and as the central area increases so does the peripheral ring of active cells increase in circumference, until the mass may be clearly visible to the naked eye. After this stage it may be noted that the bacilli are not merely within the giant cells, but interstitial also, lying between the cells in the central area.

Some, indeed, escape—grow, or are carried by leukocytes—outside

the bounds of the tubercle, and, coming to rest in the lymph spaces, there may form foci for the development of new young tubercles, whereby, in place of one, there may be a conglomeration of several small tubercles around a central necrotic area. These give origin to yet other tubercles, so that eventually a gross conglomerate mass of tubercles, with large central area of cnsention, becomes developed. Such a mass, in its continued growth, may come to involve a surface, or the wall of a large vessel, or a bronchus, and, causing the destruction of the superficial layers, may rupture and discharge the cheesy matter with its bacillary contents, causing thus a *tuberculous ulcer*, and favoring thus the spread of the bacilli to other regions. In this case we have developed a progressive tuberculosis. On the other hand, as the tissues become accustomed and adapted to the toxins (we shall discuss the means later), and as the development of the tubercle thus proceeds at a less rapid rate, time is given for the fixed connective-tissue cells at the periphery of the tubercle to develop from fibroblasts into definite connective-tissue cells. And we may obtain thus the formation of a well-marked connective-tissue capsule surrounding the growth. With this there is arrested activity on the part of the bacilli—indeed, if the tubercles are small, they may undergo complete absorption; if, through fusion, larger caseous masses have been formed, there may be consolidation of the same, with calcification, and hence calcareous nodules, surrounded by a dense fibrous capsule (often seen at the apex of the lungs), come to represent the old tubercle. In such caseous and caseocalcareous nodules the bacilli may, it would seem, persist for years, for the matter is found capable of infecting guinea-pigs. If the health of the individual be greatly lessened, the indications at postmortem are that they may form foci for renewed growth of the bacilli, and, it may be, rapidly progressive extension of the disease.

There is now no doubt that tubercles may undergo complete absorption. This has been demonstrated in dogs having experimental peritoneal tuberculosis, and there are surgical records to the same effect. We have ourselves seen in the postmortem-room only a few larger caseous masses left in the abdominal cavity of a woman on whom operation had been attempted some months before, and given up as hopeless on account of the universal tuberculosis. The patient, after the attempted operation, had been treated with Röntgen rays for some months, as a last resort, and died, not of tuberculosis, but of obstruction of the bowel.

With variation, rather in detail than in principle, the description applies to the other infective granulomata. In syphilis, the giant cells are not so frequent, and the necrosed centre matter becomes "gummy" rather than caseous; in actinomycosis the tendency is for the necrosis to be of a more suppurative type—leukocytes making their way into the dead area and causing dissolution. Still more marked liquefaction is seen in chronic glanders.

Around foreign particles, while there may be extensive giant-cell formation, there is little necrosis—purely fibroblastic accumulation,

passing on to fibrosis, with subsequent hyaline degeneration, which must be regarded as a necrobiosis rather than a necrosis. The same is true regarding the eggs and larvæ of parasitic worms and the inflammation around them.

Chronic Diffuse Inflammation.—But tuberculosis and syphilis may also set up not these localized granulomata, but diffuse fibroid changes in organs. Such may be the after-results of multiple miliary granulomas. We have seen the transition from the one to the other well marked in the heart of a child with congenital syphilis. More often it would seem to be caused by the actions of the toxins apart from the bacteria. Such fibrosis—cirrhosis—is common in the syphilitic liver, both of the congenital and the acquired disease. French writers have called attention to its existence in the liver in tuberculosis. The fibroid changes of recurrent rheumatism, seen more particularly in the heart valves, are also, it would seem, primarily of bacterial origin.

There exists, further, a widespread group of conditions that we class as chronic—"itis" (the term "itis" attached to the name of an organ should always denote a state of inflammation)—chronic nephritis, hepatitis, thyroiditis, and so on, in which, although in some cases the irritant may be of bacterial origin, faulty metabolism and imperfect nutrition appear to be the main causes. In these, so far as we can see, excessive or disturbed secreting activity leads to degeneration and atrophy of the specific secreting cells of the organism, and either with the reduction in the nobler elements, the less noble connective tissue undergoes proliferation, to replace the lost tissue—a process similar to what we see takes place in the formation of a cicatrix—or substances which act as irritants to more delicate and highly organized cells act as stimulants to the more lowly connective-tissue elements, and so, destroying the former, lead to the proliferation of the latter. It may be that both factors are at work. In all such cases we are apt to see proliferation accompanied by little vascular dilatation, and if leukocytes be present in any number, they are of the lymphocytic origin, and not polymuclear, and are most abundant around the larger vessels.

Other examples of injury leading almost entirely to proliferation of the connective elements we have already noted, namely, the fibroid capsular formation around relatively inert foreign bodies.

How far injury may lead to proliferation of the higher tissues we shall discuss in connection with neoplasia.

THE MAIN DATA REGARDING INFLAMMATION.

In another place[1] we have analyzed in some detail the various factors concerned in the process of inflammation. Apart from unwillingness to repeat ourselves unduly, we cannot here devote the same space to such analysis. It is, however, necessary that we should call attention

[1] Inflammation, an Introduction to the Study of Pathology, Macmillan, 1907.

to the conclusions that are to be deduced from the study of the different grades of the process, for certain facts stand out very prominently, and must be made the basis for our judgment regarding the essential nature of inflammation, and in so doing we can call attention to matters which could not easily be introduced in a straightforward description of the stages and different varieties of inflammatory manifestation.

1. **The Cause of Inflammation.**—First, then, all the grades we have described have followed upon injury of one or other nature, and even where the injury has been continued, in all we have evidence of reaction.

2. **The Two Prominent Factors in the Process of Inflammation.**—This reaction shows itself in many ways. Whether vessels be present or not, we observe two predominant factors coming into play: (*a*) Sooner or later, proliferation of the cells immediately around the injured area; (*b*) attraction of the wandering cells to the area of injury.

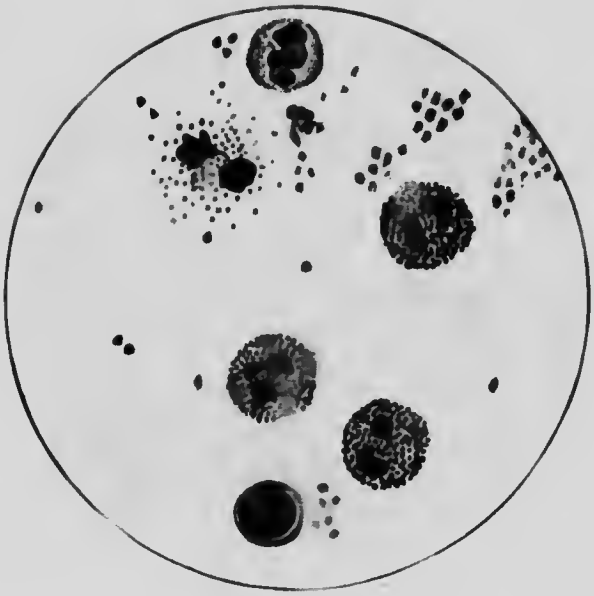
3. **Secondary Role of Vessels.**—The presence of vessels adds no new features to the process; it does but reinforce processes already in action where vessels were absent, rendering the reaction more rapid and more complete. More particularly is this the case in respect to the migration of leukocytes and the conveyance of increased fluid (exudation) to the part.

4. **Tissue Proliferation.**—In the slightest grades, and again in microbic inflammation, where the toxins are not too concentrated, cell proliferation may show itself as the very beginning of the reaction. In severer grades it is only with resolution that it becomes marked. In intermediate grades cell destruction may be proceeding at the centre, while at the periphery, where the irritant is less intense, proliferation may be in evidence. It has been customary to draw a sharp line of distinction between inflammation and repair; this is irrational.

5. **Capacity for Proliferation of Different Tissues.**—As regards the individual tissues, we note that it is the lowest, the most undifferentiated of all, namely, connective tissue, that is most apt to undergo proliferation. And here we may note, although we shall have to consider the matter further when considering regeneration, that the more highly differentiated a tissue, the less is its capacity to proliferate and exhibit reparative processes. As, also, that where a tissue under favorable conditions can manifest proliferation and new-growth, that same tissue under conditions of acute or chronic inflammation may exhibit little tendency to reproduce itself. Where two tissues are proliferating together, the one actively and rapidly, the other at a slower rate, the former tends to hinder and arrest the growth of the other. Thus in general in inflammation it is the connective tissue that tends to replace or supplant all other tissues, and on surfaces the simplest forms of epithelium or mucous membrane, and not the more elaborate glands, hair follicles, etc.

6. **Leukocytes in Inflammation.**—Turning now to the leukocytes, a word must first be said regarding the varieties of the same. We now recognize three groups:

PLATE XV



[illegible] Trachoma

[illegible]

(*a*) That which we may term the "bone-marrow group," because, although there are indications that these may also be produced elsewhere, it is in the bone-marrow more particularly that in the adult we encounter the mother cells from which these develop. The members of this group are more especially the polymorphonuclear (finely granular oxyphile), the commonest form present in the blood, and the eosinophiles.

(*b*) The lymph-follicle group consists of the lymphocytes and the plasma cells; Schridde[1] has recently confirmed the conclusions reached by Ribbert, Saxer, Marschalko, and Marchand, by demonstrating by a special method that both these cells possess identical granules.

(*c*) The endothelial and tissue-cell group, of which the large "hyaline" cells (Metchnikoff's macrophages) are the representatives (see Plate XV). Each of these varieties may be encountered in one or other grade of the inflammatory process. In acute inflammation, it is the polynuclears that dominate the scene. It is these that are seen actively migrating and actively phagocytic for bacteria.

In acute inflammation, also, we observe that the eosinophiles are involved. Those that happen to be in the tissue are among the first to be found at the site of injury; in the very earliest stages several observers have found them relatively abundant. They are not, or scarcely at all, phagocytic. The part they play is in debate. In inflammation of the peritoneum, MacCallum, of Baltimore, has found them massed in the capillaries of the mesentery and omentum.

In the infectious granulomas the hyaline and endothelial cells play a prominent part, as again in inflammation of moderate intensity of the peritoneum and serous surfaces. These large, clear cells, with relatively pale-staining nuclei, are actively phagocytic for other cells and cell debris—as are all the tissue-cell group; as also for bacteria of medium grade of virulence (of the type of the tubercle and glanders bacilli), not so actively phagocytic for the microbes of suppuration.

It is in chronic inflammation also that we encounter the lymphocytes and plasma cells as prominent features, both more particularly clustered around the vessels. They are not markedly phagocytic.

7. **Leukocytic Migration.**—There is a definite object in this accumulation of leukocytes at the site of injury and irritation. We have noted that they are attracted by dead-cell matter, and that they remove the debris. (Experimentally, if a fine glass tube containing tissue extract be inserted in one of the large veins, the leukocytes from the circulating blood are found to accumulate in it.) We have seen, also, that they actively ingest pathogenic microbes, if these be not too virulent, and, when ingested, may digest and destroy them. And it is found that even where either the ingested bacteria are too virulent, and lead to the death of the leukocytes, or where the cells are destroyed by the bacterial toxins diffused in the medium, they still may be of service, for in their disintegration and dissolution they liberate antibacterial

[1] Die Kornelungen der Plasmazellen, Wiesbaden, Bergman, 1905.

and antitoxic substances. It has been found, for instance, that if an acute aseptic inflammation be set up in the pleural cavity, by powdered glass, aleurone, etc., an exudate is given off containing abundant leukocytes. If these leukocytes be filtered off, the filtrate is much more bactericidal than is the lymph or blood serum of the same animal, and this is traced to the breaking down and dissolution of many of the migrated leukocytes. How far, also, it is due to an active excretion from the living leukocytes is still a matter of debate. Hardy and Kartheck described very definitely the active discharge of the granules from eosinophilous leukocytes, comparing them with the discharge of secreting cells; but others have failed to confirm. Undoubtedly, however, the exudate comes to contain more bactericidal and antitoxic substances than the circulating blood plasma.

8. **Fate of Leukocytes.**—As to the fate of the leukocytes, it is various. Many, we have noted, undergo dissolution *in situ;* this, indeed, seems to be the fate of the majority; some become ingested by other leukocytes and by the proliferated tissue cells of the part; some pass back out of the area of inflammation into the lymph stream, or actually break into the capillaries.

The members of the bone-marrow and lymph-follicle groups never form tissue. It had been thought by Maximow and others that the plasma cells have this power. Schridde, by his method of granule staining, has shown that, though plasma cells may come to be retained in connective tissue, and even to take on a spindle-cell shape, lying between the fibers, they retain their particular granulation; in other words, never become typical fibroblasts. Of the tissue-cell group, some, at least, have the power of tissue formation—as might, indeed, be expected.

9. **Fluid Exudate.**—Beyond favoring materially the carriage and migration of leukocytes into the inflamed area, the vessels, through their dilatation, are the direct cause of the increased exudation of fluid into the injured area. Possibly, this is not the correct way of stating the relationship. We know that there is a close interaction between the tissues and the blood; that when, for example, blood is drained from the body, the tissues rapidly give up fluid into the vessels. It may, thus, well be—nay, probably is—that physical changes in the tissues, due to cell irritation in the first place, act on the vessels, and call for increased flow of fluid from the vessels into the tissue spaces; that the dilatation of the vessels is the direct result of the tissue disturbances, and not primarily brought about by nervous influences. That this is so we have already indicated. But once the vessels have dilated, as indicated by the increased lymph flow from the parts, the exudation is in excess of the immediate needs of the tissues. We have developed, in short, a flushing process, serviceable so far as it dilutes the irritant, harmful so far as it carries the irritant out of the primary focus: serviceable in bacterial inflammations in that it brings a constant supply of antibacterial serum to the part, harmful in the same in that, also, it brings more foodstuffs for those bacteria; serviceable, lastly, as pointed

out by Hilton,[1] by acting as fluid splint, securing immobility, and harmful if too long continued, because it favors the formation of adhesions, rendering the part rigid.

10. **Repair.**—Indeed, while we cannot but see throughout the whole study of inflammation that the tendency is toward an arrest and repair of the injury, at the same time it is constantly being impressed upon us that the reaction is not directly proportioned to the injury inflicted; it may, in some respects, be inadequate; in others excessive.

Of this, instances will occur to the reader. The leukocytes may be repelled instead of attracted; may take up bacteria that they cannot destroy; may carry them away to other parts, and so originate new foci of inflammation. The tissue proliferation may be wanting, or may be superabundant, leading to exuberant granulations, keloid, etc. The fibrinous deposit on serous surfaces may be greatly lacking (as often happens in typhoidal perforations), so that there is no limitation of the inflammatory process, or excessive, so that full absorption is impossible; the organization of the same may lead to constriction and kinking of the gut, or to the formation of bands, causing strangulation.

Inflammation is not repair; it is, as we have elsewhere expressed it, the attempt thereat. It is an adaptation on the part of the organism to unusual conditions, and as such, being outside the normal range of tissue reactions, it is almost inevitably less perfect than is the normal reaction to normal stimuli. As we have pointed out (p. 109), adaptation is not an immediate process; while the cells can accomplish more than is normally demanded of them, it takes time for them to respond appropriately to stimuli that are beyond the normal, and in inflammation, before the cells have, as it were, learnt their lesson, such changes may have been produced that return to the normal is impossible—nay, more, before it has educated itself the organism may be overcome.

11. **Participation of the Organism in Inflammation.**—This leads us to consider the further point: How is it that in microbic inflammations that are recovered from, the bacteria at first thrive, and then later are arrested in their growth? Is it purely due to local accustomance and adaptation of the leukocytes and tissue cells to the changed conditions, so that, becoming used at first (those that are not immediately destroyed) to small doses of the toxins, they eventually become able to neutralize much larger doses; or is there assistance from the rest of the organism? We must assume that both are in action (p. 377). Here attention must again be called to the fact that, whereas inflammation is, we hold, essentially a local process, it may be, and generally is, accompanied by general disturbances—by a certain amount of fever and malaise, even by general leukocytosis. Clearly, the products of cell destruction in any extensive injury, and, again, the toxins of bacteria, diffuse out, or are flushed out, of the local area into the lymph and blood, and so may tell upon the organism in general. It is not, let us repeat, only bacteria

[1] Rest and Pain, 1863:89 (a work that should be a "companion book" of every medical student).

that cause fever and malaise; the development of an infarct or an internal hemorrhage is followed by a distinct rise of temperature and general discomfort. As Hildebrandt and others have shown years ago, the injection of enzymes into the circulation, or of tissue extracts, leads to the febrile state—and when tissues break down such enzymes and dissociation products become liberated. Where there is leukocytosis—increased number of leukocytes in the blood—it is a clear indication that the inflammatory products circulating in the blood and carried to the bone-marrow have there attracted the leukocytes from the tissue spaces into the vessels, if they have not directly stimulated the mother cells to increased proliferative activity. Such leukocytosis is clearly a means whereby the rest of the body may aid in arresting the inflammatory process.

12. **The Nervous System in Inflammation.**—There is another and important means of relationship between the injured area and the organism in general, which now we must take into consideration, having thus far wholly neglected it, its mode of action not being observable by histological observations. We refer to the *nervous system*. Pain, in the first place, is one of the cardinal symptoms of the condition. It has been usual until within the last few years to explain this as due in the main to pressure of the exudate upon the delicate nerve-endings, to point out that where a tissue is loose and can accommodate itself to greater increase in size, there is no pain accompanying inflammation; where it is dense, and the exudate cannot escape, there pain is severe. We now see that this explanation is invalid when, as by Schleich's and other methods, the injection of fluids into a part is found to induce local anesthesia. We can, thus, only conclude that pain is the expression of irritation of the nerve-endings by the diffused toxins (using this term in its widest sense), and recognize that the slighter pain in loose tissues is due to the greater affusion of fluid and dilution of those toxins. In more severe cases the actual exposure of the nerves and destruction of their endings affords an adequate explanation. While, ordinarily, the early stages of the inflammatory process are the result of local influences and independent of stimuli or direction from the central nervous system, undoubtedly the higher centres can, and do, play a part at a later period—nay, they may actually initiate a process indistinguishable from true inflammation. As proving the capacity of the central nervous system to intervene, it will be best to consider these cases first. There is ample evidence that imagined injury to a part may be followed, and that rapidly, by all the essential symptoms of inflammation, save, it may be, the migration of leukocytes. As we can have grave inflammatory changes unaccompanied by this migration, the exception is not sufficient to warrant us in declaring that, therefore, these conditions must not be regarded as inflammation. Such nervous mimicry doubtless explains the spontaneous and apparently causeless inflammatory manifestations which may show themselves in hysterical subjects; explains also to a large extent localized, or sometimes widespread cutaneous and other acute congestions and inflammatory disturbances seen in cases of

idiosyncrasy (p. 372). Its existence is best demonstrated in certain hypnotized subjects, in whom the suggestion of burning or other local injury may lead to the sensation of acute pain in the part, followed within a very short time by local vascular congestion, heat, swelling, and pronounced exudation. As an indication of the central origin, it has frequently been noted that these manifestations tend to be bilateral and symmetrical, although the supposed injury has been unilateral. The condition of *herpes zoster*, with its pronounced inflammatory manifestations and serous exudation along the course of distribution of certain cutaneous nerves, appears to come in this category, the observations, more particularly of Head and Campbell,[1] demonstrating that the primary lesion in these cases is in connection with the posterior ganglia of spinal nerves. It is from these considerations that we have been forced to include in our definition the clause to the effect that the process may follow referred injury.

Now, clearly this referred injury and its results are frequent factors in inflammatory manifestations. It is by this that we have to explain the swollen and reddened cheek, and the earache, and, it may be, discharge from the ear in cases of abscess of the root of a tooth, the extensive involvement and swelling of the surrounding tissues in cases of joint injury. The areas of the face, above noted, have a common innervation; the same is true of the individual joints and the cutaneous and other tissues surrounding them; or, more exactly, these parts are supplied from the same level of the spinal cord. Irritation of the nerve-endings in the injured area induce excessive stimulation of the nerve cells of the posterior horns, with irradiation of the stimuli not alone along the reflex area particularly involved, but to other associated cells in the immediate neighborhood, with, as a result, not only referred pain, but reflex vasomotor changes initiated in the areas controlled by these nerve cells.

That the vasomotor nerves play a part in modifying the inflammatory process is well demonstrated in regions such as the rabbit's ear, in which the course of the vasoconstrictors has been differentiated from that of the vasodilators. Where the former nerves are divided and the latter alone in action, the vascular dilatation and exudation are more pronounced, and the process of inflammation has a more rapid course, than in the reverse condition — uncontrolled action of vasoconstriction.

13. **Temperature Changes.**—Here, too, a word must be said regarding the *increased heat of inflamed areas*. In plants, by the use of delicate electrothermometric methods, it has been demonstrated that injury is followed by distinct, if small, local rise of temperature. There is here no circulation, and such rise can only be the expression of the increased metabolic activity of the surrounding cells. If such a rise occurs in animals, it is too small to be appreciated, and is wholly masked by the vascular changes, to which—to the increased pouring in

[1] Brain, 23: 1900: 353.

of arterial blood—must be ascribed the increased local heat. Just as it is a general law that within certain limits increased temperature leads to increased metabolism, so have we evidence that the increased local temperature leads to a more rapid and complete evolution on the inflammatory process.

14. **Adequacy of the Inflammatory Reaction.**—For long years it has been the custom to regard inflammation as a harmful process. The above considerations show, as the great old surgeon, John Hunter, recognized long ago, that nothing could be farther from the truth. What is true is that, where it shows itself, it indicates that harm has been, or is being, done to the organism, and that the system is reacting and tending to counteract that harm. It is, thus, a danger signal, and if the surgeon can assist matters by removing the cause of the harm, such assistance is clearly indicated.

It is further evident that the reaction on the part of the tissues may be (*a*) inadequate, (*b*) adequate, or (*c*) excessive. The natural tendency, observing the grave local disturbances, is to regard the third of these as most usual, and to seek to mitigate the symptoms. This, again, is seen to be an error; most often the reaction is inadequate, and modern surgeons, like the late von Mikuliez, are increasing the leukocytosis prior to operation; or, like Bier, are favoring and increasing the hyperemia and exudation, and this with excellent results when the process is carried to the proper limits.[1]

FIBROSIS AND ITS RELATIONSHIP TO INFLAMMATION.

In considering chronic inflammation we have called attention to the constant, or almost constant, development of increased fibrous tissue—of fibrosis—as a consequence of the process. Here it becomes necessary to inquire whether fibrosis, which is so widespread a condition, is always of inflammatory origin.

The answer to this question must be in the negative; there are conditions of fibrosis which, by no process of reasoning, we can include among the results of inflammation—conditions in which we can recognize no preceding local injury as the primary cause. We have to acknowledge, that is, that stimulation within physiological limits, as well as grades of pathological irritation, may lead to the overgrowth of fibrous connective, as of other tissues. We have to recognize physiological strain as a cause of growth. We see this in the case of muscle in the increased growths dependent upon exercise, in bone in the greater size of the processes and ridges of insertion of muscles in those of active muscular, compared with those of poor muscular, development. We must admit the same for the connective tissues. What we regard as the best illustration is one to which we called attention in this connection some years

[1] We have discussed more fully the rationale of these methods in the article "Inflammation," in Keen's System of Surgery.

ago,[1] namely, the development of the most usual type of arteriosclerosis, in which we find a pronounced fibrous overgrowth in patches affecting the intima of the aorta. The cause of this form is becoming increasingly admitted. Thoma was the first to emphasize it, namely, a localized giving way of the media, resulting in a localized bulging outward of the artery. This is apt to occur at points where the wall is weakened by the passage through of arterial branches. We see the process thus very commonly along the lines of origin of the intercostal arteries. As noted by Torolst, the injury may be due to degeneration of the media, and Klotz, working in our laboratory at the Royal Victoria Hospital, has demonstrated that this is of the nature of a fatty degeneration, and that slight grades of the degeneration are almost physiological with the onset of middle life.[2] Thus, the overgrowth of fibrous tissue in the intima is of compensatory nature; and how perfect it may be was demonstrated by Thoma, by filling arteriosclerotic aortas with melted wax, when, on cooling, and removing the aorta, the cast was found almost perfectly cylindrical.[3] The appearance of the projecting patches in the intima may be only apparent, or, more correctly, only shows itself after the aorta has been cut open.

How, then, is this overgrowth of the intima brought about? In the early cases we see no trace of new vessels in the thickened areas, no leukocytic infiltration, no evidences of an inflammatory process. Only in more advanced cases may we at times encounter vessels passing into the areas of intimal degeneration and observe a replacement of areas of necrosed matter by granulation tissue. The normal arterial intima is, in fact, avascular, nourished from the blood stream passing over it, its deeper layers also, by diffusion from the vessels of the media; nor are vessels evident in the innermost layer of the media. There are two zones of growth in the intima, an innermost, immediately beneath the endothelial lining; an outermost, the so-called musculo-elastic layer (Jores), immediately within the internal elastic lamina. Both of these may show signs of proliferation in these cases, while, as layer after layer of dense connective tissue is laid down between them, the more central parts of the new-growth are apt to become badly nourished, and degenerate. And the only explanation to be deduced from this new-growth is, that when through internal pressure the weakened media gives way, the intima lining the area of distention is put on the stretch—undergoes strain, and, being at the same time well nourished, proceeds to proliferate, and only ceases to grow when the new cells formed by it completely fill in the area of distension.

Here the intima, as such, has not undergone primary injury; the degeneration and giving-way have been in a different cell layer; the

[1] On the relationship between inflammation and sundry forms of fibrosis, New York Medical Record, 1896; i: 505.

[2] Jour. of Exp. Med., 7: 1905; 633.

[3] Klotz, repeating this experiment of Thoma's, finds, however, that this is not always the case.

change is not in any sense an endarteritis; it is vicarious, due to stimulation, not injury, of the cells involved.[1]

We observe a similar, though less marked, change in the walls of the veins in cases of prolonged, though not extreme, passive congestion. (In extreme cases the venous condition of the blood, and consequent lack of adequate nourishment, leads to dilatation pure and simple.) We ourselves and several other observers have called attention to its existence in some cases of passive congestion of the liver (nutmeg liver.) And in lymphatic territories the same may occur. Mere obstruction to the main lymphatic trunks from a part does not lead to complete stagnation of the lymph; on the contrary, there is a continual interchange between it and the blood in the capillaries. Nevertheless, there may be set up continuous and prolonged distension of the parts, and this, similarly, is followed by fibrosis—diffuse in this case. Such appears to be the explanation of the commonest form of *elephantiasis*, the fibrosis of macroglossia, and other cases of lymphatic obstruction, whether congenital or acquired.

FIG. 150

Section of the aorta from a case of nodose arteriosclerosis, to show the bulging and thinning of the media, prepared by Dr. Mathewson. × 8 diameters. The section shows also the hyaline degeneration of the deeper layers of the overgrown intima, and the persistence of a fine layer of less altered intima tissue immediately beneath the media. The media in this case showed evidences of calcareous degeneration in patches with some hyaline change.

Another condition of fibrosis, that of *fibromatosis*, or development of multiple fibroid growths, showing itself more particularly in connection with the sheaths of nerves, would seem, from the specimens we have examined, to originate in a congenital fault of the lymph vessels of the affected parts. The condition differs from fibroma formation proper in that the overgrowths are not encapsulated, but pass imperceptibly into the related normal connective tissue; early specimens show a well-marked lymphangiectasis, or obstructive dilatation of the lymph vessels and channels.

The *fibromas* proper, or neoplasms, formed of fibrous tissue, must also be separated from the inflammatory fibrosis. As to their causation, we are still uncertain.

[1] This, it may be noted, is not the only form of arteriosclerosis, but is a common one: the subject will be discussed more fully in the second volume of this work.

We thus are able to classify the fibroses as follows:

I. Of inflammatory origin.

1. *Replacement fibroses*, in which the fibrous tissue takes the place of other tissue that has been destroyed (cicatricial fibrous tissue, including that of infarcts). The "scleroses" of the central nervous system come under this heading, although in them neuroglia in the main, and not ordinary fibrous tissue, is usually concerned. Here, also, is perhaps to to be included the fibrosis of chronic interstitial nephritis and hepatitis.

2. *Proliferative Fibroses.* Here more particularly we have: (*a*) the capsular fibroses of the infective granulomas, around inert bodies, etc., and (*b*) postinflammatory fibroses, in which the connective tissue continues to grow, as in *keloid*, after the irritant has ceased to act.

3. *Postfibrinous fibroses*, if we may so term them. The new connective-tissue formations which replace (*a*) thrombosed blood within the vessels, and (*b*) fibrinous exudates on serous surfaces, adhesions, etc., occupy an intermediate position between the two; they are replacement-fibroses to the extent that they replace the fibrinous coagulation, proliferative in that they are tissue where previously no tissue proper existed.

II. Of non-inflammatory origin.

1. *Due to strain:* (*a*) arterial, (*b*) venous, and (*c*) lymphogenous fibroses, as above indicated.

2. *Neoplastic.*

CHAPTER III.

THE SYSTEMIC REACTION TO MICROBIC INJURY, THE PROCESS OF INFECTION.

From this consideration of the local reaction to injury we must now pass on to that of general systemic reaction, and, continuing in due sequence, before considering any one particular order of reaction, should first analyze the various noxæ causing general bodily disturbance, whether physical or chemical, endeavoring to recognize sundry broad groups, each of which sets up disturbance of a particular order. Attempting this, we could distinguish certain conditions set up in which blood changes are primary or predominant; others, nervous disturbances; others, in which certain glands are picked out to bear the brunt of the reaction, and should have to consider, in turn, the effects of disorders involving one or other system, upon the rest of the organism. This systematic survey of processes affecting the several systems and their results we shall take up at a later date. To enter into it now would lead us to consider in series the progressive and regressive changes which may affect individual systems and organs before gaining an insight into progressive and regressive disturbances in general, and would thus lead to extensive repetition. It will be more serviceable to select for consideration the more common general processes, and that in the order of their frequency rather than of their relationship to one or other system. And, doing this, undoubtedly the first general process to be considered is the systemic reaction to microbic injury, or *infection*.

Definition.—Attention must be called to the double meaning of this term, as employed by the hygienist and the pathologist. For the hygienist, water, air, and other media may be infected, *i. e.*, infection consists in the mere presence of potentially harmful microbes, and the mere act of their coming into contact with the animal organism. Thus, the hygienist distinguishes between: (1) sporadic infections, isolated cases; (2) *endemic*, where a notable proportion of cases of a given microbic disease is met with year after year affecting the inhabitants of a given region; and (3) *epidemic*, where a disease, of a sudden, affects a large number of inhabitants, the number of cases rapidly increasing and later decreasing. Diseases of animals may, similarly, be *sporadic*, *enzootic*, or *epizootic* (ἐπί, upon; ζῷον, animal). For the pathologist, infection is a process; for him the mere presence of pathogenic bacteria in the mouth or the skin, in the digestive tract, does not constitute infection; that is brought about by the growth of those bacteria, the diffusion of their products, and the reaction they induce in the organism in the essence of the process. For the patholo-

gist, therefore, the process of infection is *the succession of changes induced in the organism generally by the growth within it of microbes;* or, in other words, it is *the interaction between the organism and the microorganism*. This interaction may, in the main, be local, and then the processes, recurring locally, constitute infective inflammation; the general disturbances which follow such local growth, or which are brought about by widespread proliferation of the microbes, constitute "general infection," or, briefly, "infection."

Causation.—We have already considered the mode of entrance of pathogenic organisms into the organism, as also, to some extent, the circumstances favoring their growth, and have considered also the subject of *susceptibility*, of imperfect reactive powers, so that there is inadequate destruction of microbes coming in contact with, or gaining entrance by any means into, the tissue. There is, however, another aspect of the subject. Bacteria may grow in the tissues, not because the tissues are weaker than normal, but because those bacteria possess a virulence over and above the power of the cells to counteract. We thus, to recapitulate, may make the following table of circumstances leading to the growth of bacteria with the organism.

I.—Imperfect reactive powers (*susceptibility*).

(*A*) *Individual* susceptibility.

1. Inherited.
   - Specific.
   - Racial.
   - Familial.
   - Individual.
2. Acquired.
   - As the result of previous attacks of disease set up by (*a*) the same, or (*b*) another species of microbe.
   - As the result of injury.
   - As the result of malnutrition.
   - As the result of exhaustion.

(*B*) *Tissue* susceptibility.

1. Inherent, the special susceptibility of certain tissues to become the seat of growth of certain microorganisms.
2. Acquired through
   - Injury.
   - Local malnutrition.
   - Impairment of nerve supply.
   - Local exhaustion.
   - Local disease.

II.—Pathogenicity of microbes (virulence) due to simultaneous entrance of

1. A small number of highly virulent microbes.
2. A large number of lowly virulent microbes.

It is the interaction of I and II which determines the development of infection; microbes of low virulence are capable of infecting susceptible individuals, and are without effect on those of normal resisting

powers when introduced in equal numbers in the two cases; microbes of high virulence, if they induce disease in those relatively refractory, do not induce so grave a disease as in those relatively susceptible.

THE COURSE OF INFECTION.

We have now to consider the results of bacterial growth, and how these results are brought about—the *process of infection*.

It will be well, in the first place, to sketch the course and features of some typical uncomplicated case of infectious disease; for such a purpose a case of typhoid fever affords a good example.

The patient has upon a given date taken, it may be, some milk coming from a farm where the hygienic arrangements have been imperfect, and where recently there have occurred one or more cases of the disease. For several days no ill effects are experienced, but then symptoms of malaise show themselves—slight but persistent headache, lassitude, some abdominal discomfort, with constipation, or, it may be, diarrhœa, pains in the back, and so on. These disturbances at first are so slight as to be regarded as transient, and do not prevent the patient continuing his daily duties, but they continue, and grow steadily worse, until, eight days or so after the contaminated milk had been drunk, the patient feels so weak and feverish that work is impossible, and he has to take to bed and call in a medical man.

We note, that is, a stage of *incubation*, during the latter part of which *prodromal* or *premonitory* symptoms show themselves, this incubative stage continuing until the onset of a definite *febrile state*. As a rule, for clinical purposes we date the illness from the first day of recognized fever.

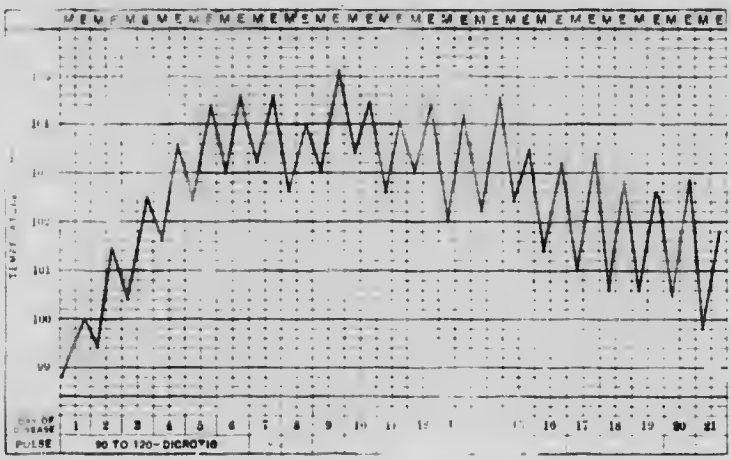
Not to dwell upon unessentials, the medical man, when called in, finds the following condition: heightened bodily temperature, general muscular weakness, alterations in (*a*) the nervous system, manifested either by irritability and excitement or by lassitude and dulness; (*b*) or the circulatory system, shown by a rapid, full pulse, with evidences of vasomotor disturbance (flushings, dilatation of superficial vessels, etc.); (*c*) respiratory system—increased rapidity of respiration; (*d*) digestive system—dryness of the mouth (diminished salivary excretion), distaste for food (anorexia), obscure abdominal discomfort or pain, with constipation, giving place to looseness of the bowels and foul motions (or these may be present from the first).

Day by day, for a week or so, the temperature rises, until it may attain to 103° to 104° F., and, with this, all the other symptoms—mental, nervous, muscular, circulatory, respiratory, and abdominal—become more pronounced; and, in addition, disturbances of the urinary system show themselves, in the shape of diminutions of the salts of the urine, notably of the chlorides, and of increase of other constituents, notably the urates; while a characteristic cutaneous eruption begins to show itself toward the end of the first week, in the shape of scattered

"rose spots." Examination of the blood shows that this, also, is modified, for, while typhoid differs from the majority of infections, in there being little or no increase in the number of circulating leukocytes, in common with most, there is a definite diminution in the number of red corpuscles per cubic millimeter, and, as shown by the Grünbaum-Widal test, the serum gains new properties, being able to cause the typhoid bacilli to become motionless and adhere together, or agglutinate, even when it is diluted fifty times.

This is the stage of *fervescence*, or pyretogenic stage. Following upon it, for a fortnight or so, is the *fastigium*, or stage of high fever, a period in which the febrile temperature is maintained at first at a constant high level; later, toward the end of the period, while toward the night it may reach the previous high level, it tends during the daytime to

FIG. 151



Course of typhoid fever. (... ... from Musser.)

descend two or more degrees. Accompanying this febrile temperature, the other disturbances continue, and, as a consequence, the patient becomes increasingly weak and emaciated. In an uncomplicated case, however, toward the end of the third week an improvement manifests itself. The temperature shows a distinct tendency to fall, and each twenty-four hours the maximum may be a degree or more lower than the maximum of the previous day, there is refreshing sleep, the mind becomes clearer, appetite and craving for food manifest themselves, pulse and respirations become more normal, the motions less foul. We reach, in short, the stage of *defervescence*, and in four to six days the normal temperature is again attained. Now follows the stage of *convalescence*. The great emaciation and exhaustion of the tissues leaves the patient very weak, and attempts to move actively easily tell upon the circulation, etc., while any but the most easily digestible food tells

upon the digestive system, and may easily favor a *relapse*. Gradually the patient returns to the *status quo ante*. I need not here dwell upon *sequelæ* (morbid conditions which *follow* a disease, and are due to the action of the same original cause, *e. g.*, in typhoid, the formation of abscesses in various parts, due to the B. typhosus; inflammation of the gall-bladder, set up by the same, etc.); or *complications* (morbid conditions of other causation, which may accompany the primary disease, *e. g.*, in typhoid, the development of acute pneumonia, due to the diplococcus pneumoniæ, and inflammatory disturbances, brought about by B. coli infection)—all that we wish here is to give a fair picture of a typical infection resulting in recovery, so as to have a basis for the presentation of our subject.

The Period of Incubation.—Once bacteria or other microbes begin to grow in the tissues, from that moment we have the beginning of the infective process. But, although it begins thus, we are not able to recognize it. If the entrance of the germs be local, there is, inevitably, a preliminary period of local growth, with absence of general disturbance. Strictly, this, and only this, should be regarded as the period of incubation; in practice we cannot carry out this idea. We have to determine upon some one easily recognizable symptom, from the onset of which we can date the onset of active disease, and the supervention of *fever* affords us this useful starting point. Whence it follows that the period of incubation, in the clinical acceptation of the term, is made up of two stages—that of purely local growth of the microorganisms and local disturbance, and that of *prodromal* symptoms, in which the bacterial products, or even, in some cases, the bacteria themselves have become to some extent generalized, and have originated disturbances in the system at large, but have not as yet caused a febrile reaction with other pronounced systemic disturbances. This period of incubation varies greatly in the different infections and in different individual cases. Certain bacteria are so virulent toward certain of the smaller animals of the laboratory that they cause death within four to six hours. In such cases there is not much time for the manifestation of an incubation period, but, even here, in cases in which to produce the most rapidly fatal results the infective germs are injected directly into the vessels, it has been shown by Lemaire[1] that if we take that blood and make cultures from it at intervals of half an hour there is to be noted a preliminary period in which the number of circulating bacteria is greatly reduced—a period of reaction—of destruction of the bacteria and removal of them from the circulation; then, apparently, the cells of the body become exhausted, and there follows a second period of rapid proliferation and increase in the number of the circulatory bacteria. At the other extreme, the incubation period may last for weeks or months. The longest period has been noted in rabies. Ordinarily in this disease the period of incubation varies from a fortnight to a month; but there are certain well-authenticated cases.

[1] Buxton has recently confirmed and amplified these observations.

though these are exceptional, in which as much as six months have intervened between the entrance of the virus into the system and the development of symptoms.

The relationship between purely local growth and the diffusion of the bacterial products during the prodromal period is most variable, so that only in a certain class of cases is it possible to recognize this period of incubation with any definiteness; add to this that in certain diseases (*e. g.*, cholera) actual fever may be largely wanting, and thus we have to accept other symptoms as indicating the commencement of the active stage of infection.

The infective microbes also vary greatly in the extent to which they proliferate before they, through their products, induce general disturbances. Thus, to give a few examples of the variations met with:

1. There may be a minute boil or furuncle on the face, due to the local growth of a streptococcus. Although this growth is so local, there nevertheless is rapidly induced a slight febrile condition, with general malaise. The germ remains local, and the infection is singularly local; nevertheless, the general disturbances set up by diffusion of the bacterial products is relatively profound—out of all proportion to the extent of local disturbances. The development of the febrile state here is not coincident with any diffusion of the bacteria themselves. It even precedes the period of maturation of the boil.

2. In tetanus there is a similar strictly local growth of the bacteria, and the same is the case in diphtheria. In both these cases there is a well-marked period of incubation, in both the supervention of the febrile state indicates only that the diffusion of the bacterial products has reached a point at which the amount of concentration of those products is sufficient to induce severe disturbances in certain tissues away from the period of local growth.

3. On the other hand, in smallpox the development of the febrile state coincides with the earliest appearance of the cutaneous papules. The presence of these papules undoubtedly indicates that the virus has entered the blood from the focus of primary local infection, and has been carried through the system, and so to the vessels of the skin, during the period of incubation. Here, also, it may be noted, the site of primary entrance and primary local growth remains still to be discovered.

4. Lastly, in disease like tuberculosis there is primary local growth, but that localized growth develops so gradually, the tumors are so gradually diffused, that it is difficult, if not impossible, to recognize any one period at which incubation develops into general infection. We can, at most, speak of a pretuberculous stage, during which the tuberculin reaction affords an indication of the presence of the tubercle bacilli within the tissues.

From these instances it is clear that *what determines the development of symptoms of general infection is not the presence of the specific bacteria circulating throughout the body, or even the extent of the local inflammatory disturbances set up by them, but is the toxicity of their products and*

the relative amount of the same. And the length of the incubation period in any given case is determined by several factors:

1. The toxicity of the products of a specific microbe.

2. The amount of toxic substances developed in a given time (this depending upon the number of germs gaining entrance, and the virulence of those germs).

3. The neutralizing powers of the organism (whereby, in the same disease, the incubation period in different individuals is found to vary, often to the extent of several days).

4. A fourth factor is indicated by the researches of Roux and Yersin, and Sidney Martin, already noted (p. 286), namely, the time taken by the enzymes primarily excreted by the pathogenic organisms to act upon certain constituents of the fluids or tissues of the body and convert them into toxic albumoses, the direct agents in setting up the symptoms of generalized disturbance.

Thus, to sum up: *The period of incubation, as generally understood, consists of at least two stages, the first, of varying length, that of purely local growth and local disturbance, the second in which there are prodromal symptoms—general disturbances of a relatively mild type, due, not to the bacteria themselves, but essentially to the diffusion of their products of growth into the general circulation. These products of growth may not, in all cases, be themselves toxic, but may by enzyme action convert certain of the body proteins into toxic bodies (albumoses).*

Grades and Types of Infection.—As noted upon page 421, we can classify to some extent the pathogenic microorganisms according as to whether, in the main, their growth in the system is *local* or whether it is diffuse, setting up a *bacteriemia*. This distinction, useful otherwise, is for the present purposes largely useless. In the first place, there are many intermediate grades, the typhoid bacillus, for instance, has mainly local growth, but to be present in and produce the rose spots, must circulate in the blood; the sequelæ of pneumonia convince us more and more that the pneumococcus, while it has its seat of election in the lungs, passes readily into the blood. Secondly, one and the same organism, like the pyococcus aureus and the streptococcus, may in one individual have a purely local growth; in another, set up extensive septicemia; and in the two cases the symptoms vary in degree rather in kind. While thirdly, in both orders the symptoms are brought about by one common cause, namely, the diffusible toxins. It is the nature and toxicity of those products that are the prime factors in the development of infections; they cause the characteristic disturbances of metabolism. According as to how these products tell upon the organism, and how the organism is capable of neutralizing or destroying them, so can we recognize the following types of infection:

1. Fulminating or malignant.
2. Acute.
3. Chronic (persisting, subacute).
4. Subinfection.

Fulminating or Malignant Infection.—Occasionally we find in man, or in the lower animals, that an infection is from the first so rapid in its development that we are hopeless of obtaining a favorable issue; the organism appears to be incapable of adequate reaction. Some reaction there is in each case, but it is wholly ineffectual, and becomes less and less marked. The symptoms are those of a rapid intoxication, with depression of the functions. The heart beat and pulse become more and more rapid and feeble, with great lowering of the blood pressure; the respirations very rapid and shallow; there is pronounced "typhoid state," with coma and depression of the higher mental centres, and no excitement; the temperature may from the first rapidly sink, until it is far below the normal; if the disease be one characterized under ordinary conditions by well-marked leukocytosis, there is found pronounced and progressive leukopenia (or lack of leukocytes), and a condition of coma quickly gives place to death. All this may take place within a few hours. Experimentally, by "passage," we can so exalt the virulence of certain bacteria that we can kill the animals of the laboratory within six hours, and that with minimal injections. But not with all bacteria; no amount of passage will reduce the period of experimental tuberculosis to less than ten days. Difference has to be acknowledged. In man, both exaltation of virulence and entrance of excessive numbers of bacteria at a time would seem to play a part. Such fulminant cases are more particularly seen in tropical countries—in cases of cholera, yellow fever, the plague. Here both the general bodily health is lowered by the surroundings, and pathogenic organisms at the higher external temperature can proliferate and multiply outside the body and at the same time retain their virulence. But such cases are far from being unknown in temperate climates. We have ourselves obtained autopsies and gained pure cultures from a case of Streptococcus peritonitis fatal within twelve hours from the onset of the first symptoms, and of epidemic cerebrospinal meningitis, fatal within six hours; malignant hemorrhagic cases of smallpox, scarlet fever, typhoid, fatal within twelve hours, are far from being unknown. These hemorrhagic conditions are indications that the circulatory toxins are sufficiently concentrated to act upon and cause degeneration of the epithelium of the capillaries, with weakening of the wall and subsequent rupture. With this often there is rapid destruction of the corpuscles and diffusion out of their hemoglobin. We can, to some extent, reproduce this hemorrhagic state by injection of the sterile fluids of growth of virulent organisms into the vessels of lower animals.

In all these cases the slight, or absent, febrile reaction is especially noticeable. Indeed, it may be laid down as a general rule that if, in a case of infection, the temperature becomes rapidly subnormal, and the condition of the patient, with the lowering of the temperature, instead of improving, becomes worse, death may be expected in the course of a few hours. The cells of the body, instead of being stimulated, are paralyzed by the toxic substances, metabolism, and in consequence

heat production is arrested, and the fall of the temperature is an indication of intense intoxication.

2. **Acute Infection.**—This is the ordinary "type" infection already described, that, characterized by a definite incubation period and a febrile stage or fastigium, which, according to the intensity of the process and the resisting powers of the system, either terminates in death or in defervescence and convalescence. The process of recovery may be interrupted by the recurrence of one or more *relapses* or *remissions* (repetitions of the symptoms and disturbances characteristic of the primary disease), or by *sequelæ* or by *complications*. In most cases defervescence is gradual, a matter of some days; we speak then of recovery by *lysis*. In other cases (as often in acute lobar pneumonia) the temperature may fall to the neighborhood of the normal within twenty-four hours; we speak then of recovery by *crisis*.

In accordance with custom, and, we must admit, there is a certain convenience in so doing, we shall devote a separate chapter to the febrile state and fever, *i. e.*, to a consideration of the processes occurring in actual infection; and in that connection, also, it will be best to discuss the process of resolution and the cause of relapse, these being all allied subjects.

3. **Chronic Infections.**—Another well-marked class of infections is characterized by insidious development, long continuance, with termination either in death after the disease had lasted for months, or it may be years, or gradual recovery. The whole process is prolonged, and may lack any sharp definition into successive stages. Examples of this class are to be seen in tuberculosis, syphilis, glanders, and actinomycosis.

In syphilis, a division into successive stages is more a matter of clinical convenience than of absolute fact—at least as between the secondary and tertiary stages, for so-called tertiary lesions may exist with secondary, and, as between primary and secondary, the transition is variable, and may be very insidious.

In all of these it would appear that there exists a focus of primary infection; in some, as in syphilis, it is very obvious. For weeks, as in syphilis, or months, as in actinomycosis, or permanently, as in mycetoma pedis (a disease closely allied to actinomycosis, but in general only affecting at lower extremity), we only had but to deal with the local growth of the microorganism originating local disturbances, with more or less pronounced general disturbances of a febrile nature. Of the nature of this local growth we have already spoken (p. 402).

A second subgroup is the *chronic remittent*, best represented by the rheumatic group of disorders, in the causation of which the indications at this present time are that more than one form of organism is concerned. Here we have to deal with conditions which may begin insidiously, but often acutely. In either case the progressive nature of the disorders set up indicates that there is not with defervescence complete recovery or total destruction of the pathogenic organism, and, while the progress continues slowly to act upon the joints or

the heart valves, from time to time the condition lights up again into an acute form.[1]

In all these cases it would seem that we have to deal with microbes which, while developing their toxins at a relatively slow rate, are themselves distinctly resistant to the action of the tissues and bodily humors. On the other hand, growing and producing their toxins slowly, there is neither the same extent of intoxication nor the same well-marked reaction on the part of the system which we see in acute infections. There is, nevertheless, fever, though this tends to be of a more remittent type than is seen in the majority of the acute infections, and there is progressive emaciation and weakness as the disease advances.

Subinfection.—The appreciation of the fact that from the alimentary and respiratory tracts bacteria are constantly being taken into the system (p. 290), leads us to recognize the existence of yet another condition—that in which those bacteria, pathogenetic and non-pathogenetic instead of proliferating, are destroyed in the various tissues and organs to which they may be carried by the lymph and blood streams, a condition for which we have suggested the name *subinfection*.[2] Normally, as we have indicated, the taking in of bacteria is relatively slight, and the exercise of what are strictly the physiological functions of the cells in bringing about the destruction of the same leads, we may be assured, to no disturbance, either local or general. There are, however, conditions of congestion and chronic slight inflammation of the intestinal mucosa in which there is an accompanying great increase in the passage of leukocytes into the submucosa, and thence between the epithelial cells into the lumen of the bowel; and as a consequence both of the increased passage out of the leukocytes and of the increased proliferation of intestinal bacteria, which accompanies, if it does not cause, the inflammation in question, there is increased taking in of these bacteria.

We obtain evidence of this increase by examination of the mesenteric glands and liver cells. In cases of chronic intestinal irritation we find in them abundant minute granules, which, at first, one is liable to regard as pigment granules. Indeed, we acknowledge that it takes long study before one can rid oneself of the conviction that this is not the case. But thorough study and careful focussing of their sections under a very high power—a one-eighteenth inch immersion, for example—has convinced us that these granules are some of the final stages of bacterial destruction. They may be single; most often they

[1] The more recent work upon this etiology of acute rheumatism, in connection with Poynton and Paine's organism (Lancet, November 11, 1905: 860 and 932) and the Streptococcus pyogenes, is given by Beattie, Journal of Medical Research, 14: 1906: 399. We fail to see that any etiological distinction can be drawn between acute and chronic remittent type; indeed, in our laboratory at the Royal Victoria Hospital, from the disorganized hip-joint of a man who has suffered from such remittent rheumatism for twenty years, and was wholly crippled thereby, we gained abundant diplococci, which, cultivated by Dr. G. A. Charlton, exhibited all the characters of Poynton and Paine's organism.

[2] Journal of the American Medical Association, 33 : 1899 1506 and 1572.

are in pairs, resembling diplococci; rarely in sets of three, or rows of four, and often a distinct halo, as of a digestive vacuole, can be seen around them. Some hours after intravenous injection of B. coli intravenously into the lower animals, identical appearances are to be seen in the liver cells, and we have noted that the first stage in the taking up of the bacilli by the endothelial cells of the hepatic capillaries is the conversion of those bacilli into similar though somewhat larger diplococcoid bodies and sets of three or four granules. Then these bodies disappear from the endothelium, and, we hold, are represented by those more reduced bodies in the liver cells and, it may be added, in the bile.

The effects of such continued passage of considerable numbers of bacteria into the system must be equivalent to the growth of the same within the tissues, and the destruction of the same, if long continued and excessive, should bring on cell exhaustion. The frequency with which, in cases of cirrhosis of the liver, we have been able to gain cultures of intestinal bacteria from the liver, as also from the ascitic fluid during life, has led us to suggest that these are at least one factor in the production of that condition, and Weaver and Hektoen have isolated a form allied to the B. coli, with which they have set up cirrhosis in guinea-pigs.

FIG. 152

Swollen endothelial cell of capillary of rabbit's liver containing Bacillus coli in various stages of degeneration, within thirty minutes of injection of the bacilli into the blood stream. Part only of the nucleus is shown in the section.

We do not pretend that these are a constant factor in all cases of cirrhosis, even of Laennec's type, or that in any one case they are the only factor. There must first be intestinal irritation, whether by alcohol, by acid fermentation, or otherwise. But we believe that they play an important role in the etiology of a large proportion of cases.

The almost constant evidence of old gastritis, the known hemolytic powers of members of the coli group, the existence in abundance of similar diplococcoid bodies in the liver cells, leads us to believe that in pernicious anemia some member of this group, or some other species of bacteria possessing strong hemolytic powers, is likewise involved. In support of this view, Charlton,[1] working in our laboratory, has been able to produce not, it is true, a typical pernicious anemia, but a singularly grave anemia, accompanied by poikilocytosis and the presence of normoblasts, by successive inoculations of a B. coli of low virulence into rabbits, the original strain having been obtained from the intestines of a healthy normal rabbit.

Nicholls,[2] also, has demonstrated the existence of similar minute

[1] Journal of Medical Research, N. S., 3 : 1902 : 344.
[2] Montreal Medical Journal, 28 : 1899 : 161.

diplococcoid bodies in the cells of the tubuli contorti and elsewhere in the kidneys, and concludes that they are a factor in some cases of chronic interstitial nephritis.

It is but right to warn the reader that these observations and views have not as yet gained general acceptance. We mention them because we are firmly convinced of their correctness, and because we believe that they throw light upon certain very obscure forms of disease.

Exogenous Bacterial Intoxication.—From such conditions we pass next to what, in our classification of intoxications, we speak of as exogenous intoxications of saprophytic origin. There is, it will be seen, but a slight step from the introduction of bacteria into the tissues, destruction of them forthwith, and liberation of their toxins, to the absorption of the toxins liberated by bacterial growth in the intestinal canal, the bacteria themselves not being to any extent taken into the system. Such conditions do not come within our definition of the process of infection. It is well, however, to call attention to the same in this place, the more so because Hunter[1] and others have ascribed pernicious anemia and allied conditions to such absorption of toxins. In diphtheria and cholera we have two pronounced infections which only just come within the terms of our definition, for the bacteria here only grow upon the surface of the mucous membranes and scarce enter the tissues. It is true that they destroy the surface layers, and this destruction doubtless aids very materially the absorption of the toxins. But even when the surface layers are not destroyed, it may well be that extensive absorption occurs of bacterial toxins. Where fermented feces are retained we know that malaise and an actual febrile state may ensue. But in such cases it is impossible to analyze and distinguish between the absorption of bacterial toxins and that of the products of fecal disintegration, and, we may add, the entrance of bacteria into the tissues. At most, we can, it seems to us, admit the existence of this order of condition.

The various orders of infection proper pass the one into the other (save that a malignant case does not become less acute), and there may be various intermediate stages. An acute infection may suddenly assume the malignant type, or may from the first tend toward malignancy. We have noted how an acute or subacute may recur and be associated with chronic disturbance. A microorganism which ordinarily induces chronic infection may set up a disturbance that is distinctly acute, either by gaining entrance into the blood stream and consequent wide distribution and multiple foci of growth, or by attacking an individual of greatly lowered vitality, and, lastly, a study of "terminal infections" would indicate that eventually subinfection is liable to give place to acute infection—germs of low virulence, ordinarily destroyed by the cells coming to grow actively in the tissues when the resisting powers become lowered beyond a certain minimum. The study of such terminal infections supports the dictum of Osler, that "persons rarely die of the disease with which they suffer."

[1] Pernicious Anæmia, London, Griffin, 1901.

CHAPTER IV.

THE SYSTEMIC REACTION—(CONTINUED).

THE FEBRILE STATE.

THUS study of the different types of infection prepares us to consider the nature of the reaction between the organism as a whole and the microorganism, of that chain of disturbances which, collectively, we speak of as *fever;* or, if it be objected that this term should be only employed to indicate heightened temperature, as *the febrile state.*

Here, once again, we confront a difficulty, due to the prevailing laxity in the employment of terms. The oldest definition, that of Galen, describes fever as *calor præter naturam*, and, if influenced by tradition alone, as such and such only should we consider the condition. But two very distinct orders of events, at least, bring about such *calor præter naturam*, namely, the diffusive microbic products and certain other substances, and traumatic and other disturbances of the nervous system, regarding both of which, it is needless to say, Galen was in supreme ignorance. To retain the old definition demands that we persist in grouping together phenomena of unlike origin, in opposition to all right principles of classification. The more modern acceptation of the term is thus to be commended—that which regards fever as a particular train of symptoms and changes in the organism associated with heightened bodily temperature constituting the infective reaction. We would even say that the phrase "associated with heightened temperature" is inserted in accordance with usage and clinical demands, and this because the same train of disturbances may present itself without materially heightened temperature. We must consider all these cases together, and thus, for convenience, lay down that:

1. The reaction to infection may be with or without rise of temperature (may be "febrile" or "afebrile").

2. That throughout, mere heightened bodily temperature, however produced, will be referred to as *pyrexia.*

This course is not absolutely logical, but it is the only one practical under the circumstances. The causation of pyrexia and the subject of thermogenesis in general will be discussed in a separate chapter.

In the febrile state, then, we observe increased bodily temperature, along with that series of disturbances of the circulatory, nervous, respiratory, and digestive systems and the excretory organs which we have noted in our description of acute infection. Passing, now, to describe and analyze more fully these various changes in the different systems

and organs, we shall be in a position to recognize more surely the nature of the fever.

The Febrile Temperature Changes.—The Stages of Fever.—As already noted, we can, in most acute infections, distinguish three stages:

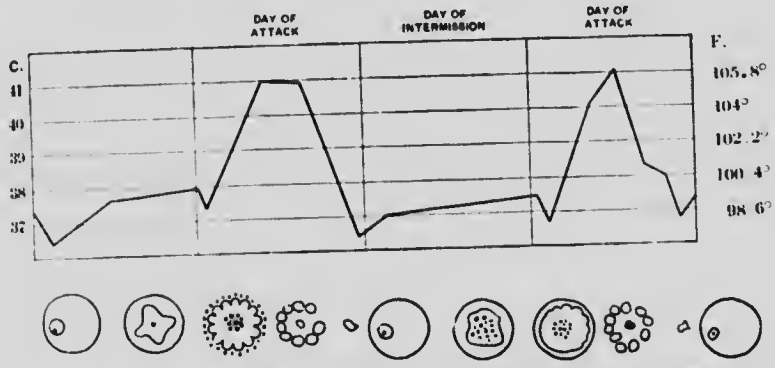
1. *The Pyrogenetic.*—This may be short, with rapid rise in the course of an hour or two, as in ague, or, as in typhoid, may extend over several days.

2. *The Fastigial.*—This, again, according to the nature of the process, may be brief, or may extend over several days.

3. *The Defervescent.*—This may be brief, the temperature diminishing rapidly by *crisis*, or gradual and prolonged—*lysis*.

In some fevers, as in typhoid, toward the conclusion of the fastigium, but before defervescence occurs, the temperature, from having previously shown but slight daily oscillation, may present a daily variation of several degrees. It is then termed *amphibolous*.

FIG. 153



Intermittent fever. Tertian ague. Diagram of temperature chart, to show relationship of the intermission to the stage of growth and maturation of the hematozoon.

The Varieties of Fever.—According to the temperature changes, we can distinguish:

1. **Continued Fever.**—In these, during the fastigium, the daily temperature changes, *though occurring at a higher level*, are little if at all greater than those seen in health (typhoid, pneumonia, etc.).

2. **Remittent Fever.**—Here the daily temperature changes may extend over several degrees and the temperature curve, while continuing above the normal, is very variable (pyemia, suppurative changes, tuberculosis, accompanied by secondary infection).

3. **Intermittent and Recurrent Fevers.**—In intermittent fever there is a succession of febrile attacks, each characterized by pyrogenetic, fastigial, and defervescent stages, and separated by intervals of twenty hours or more, the temperature during the interval being normal (malarial fever). A variety of the form, in which the interval is of several days' duration, is sometimes spoken of as *recurrent* (relapsing fever proper, Malta or Mediterranean fever).

Stages of Pyrexia.—Here it will be useful to note the terms employed in describing and classifying the different grades of rise of body temperature occurring in febrile states. For in fevers we have every grade of rise of bodily temperature, and in the same infection different individuals react differently. In children, for example, a very slight disturbance is liable to cause a profound rise; in the aged, on the contrary, severe infection may be associated with relatively little increase. Wunderlich's divisions are usually followed:

Subfebrile, or high normal from . .	37.5° to 38° C., or below 100° F.
Low febrile	38.0° to 38.5° C., or 100° to 101° F.
Moderately febrile	38.5° to 39.5° C., or 101° to 103° F.
High febrile	39.5° to 40.5° C., or 103° to 105° F.
" " morning, above . . .	39.5° C.
" " evening, about . . .	40.5° C.
Hyperpyrexial	41.0° C. and over, or 105° F. and over.

Reversing the usual procedure, we shall not now discuss the causation of this increased temperature, but will now discuss the disturbances other than pyrexial that characterize the febrile state, believing that by this means it is possible to gain a more thorough grasp of the subject and to come more fully prepared to the discussion of pyretic phenomena.

THE ASSOCIATED FEBRILE DISTURBANCES.

Nervous Disturbances.—Chills.—During the pyrogenetic stage in very many fevers a marked feature is the supervention of one or a succession of *chills*. The patient feels cold, the teeth chatter, the sensations experienced are identical with those which follow exposure to cold with rapid cooling of the surface of the body. But now the hand, and the thermometer, often indicate that the surface is distinctly hotter than normal, although, at the same time, the thermometer in the rectum shows there a yet greater rise of temperature. We are dealing clearly with a nervous phenomenon, and one that is not the direct effect of cooling upon the cutaneous nerve-endings. It is true that the surface phenomena, save for this frequent increase in heat, are closely allied to what is seen in actual cooling; the extremities and the face may be pale and even livid; there is, obviously, localized arterial contraction. This view that we are dealing with a nervous phenomenon, incited from the central nervous system, is supported by the fact that in those of unstable nervous constitution identical chills may occur without exposure to cold and without infection. What the nervous change is, that is, at the root of these chills, it is difficult to say. Marey[1] has suggested that relative increase in the temperature of the central organs may produce the same results as relative decrease in surface temperature, and that relative temperature possibly plays a part is suggested

[1] La circulation du sang, Paris, 1881.

by Recklinghausen's[1] observation that when the chills have passed and high fever has developed, they may be brought on again by exposing an extremity. With relapse, also, in the course of a fever they may show themselves. Mere local anemia of the surface vessels, which is common both in cooling and in chills, would not seem to be a satisfactory explanation, for the same may occur under other conditions without chills being produced.

But, underlying these chills, we must see that the local anemia indicates that the blood is attracted to other organs, that there is a corresponding congestion elsewhere; as, also, that the relative cutaneous anemia indicates during this period a relative storage of heat in the system.

With the onset of the fastigium the surface vessels become congested, and now there is a sensation of general surface and body heat—of feverishness.

Other Febrile Nervous Disturbances.—These are but one of a series of nervous disturbances, which we may divide into two categories, namely, states of nervous irritation and of nervous depression. Among the former we must class headaches and mental irritability, photophobia, sleeplessness, hallucinations, and the graver conditions of active delirium, with confusion of intellect. This may pass on into the next state, that of exhaustion and depression. Other conditions of the second category are apathy, arrest of mental activity, prostration and involuntary passage of excreta, quiet muttering delirium, and complete coma.

While the different conditions are, to some extent, an index of the severity of the fever, mental and nervous exhaustion being matters of graver import than are irritability and active delirium, we have to recognize that in different forms of infection there is a wide variance in the extent of the nervous disturbance. While in some cases we have to deal with active meningitis and presence of the specific organisms directly affecting the surface of the brain, and in others, it may be, with alterations in the circulation of the brain rather than with direct stimulation, in the main these nervous disturbances have to be ascribed to the action of the diffusible toxins circulating in the blood. They correspond with the nervous disturbances set up by other toxic agents, and, while they vary so greatly, we can reproduce one or other group by the intravenous injection of the sterile culture fluids or products of growth of specific pathogenic microbes. The most striking demonstration of this direct action of toxins upon nerve tissues has been afforded by Meyer and Ransom,[2] in their studies of the course pursued by the tetanus toxin, in which they showed with absolute precision that this toxin has a direct affinity with, and selective action upon, the nervous tissues, and passes up the peripheral nerves. Dr Vester

[1] Hdbch. d. Allgem. Pathol. der Kreislaufs, Stuttgart, 1883: 451.

[2] Schmiedeberg's Arch., 49: 1903. An excellent *résumé* of this important subject is given by Archibald, Montreal Medical Journal, 34: 1905: 871

MICROCOPY RESOLUTION TEST CHART

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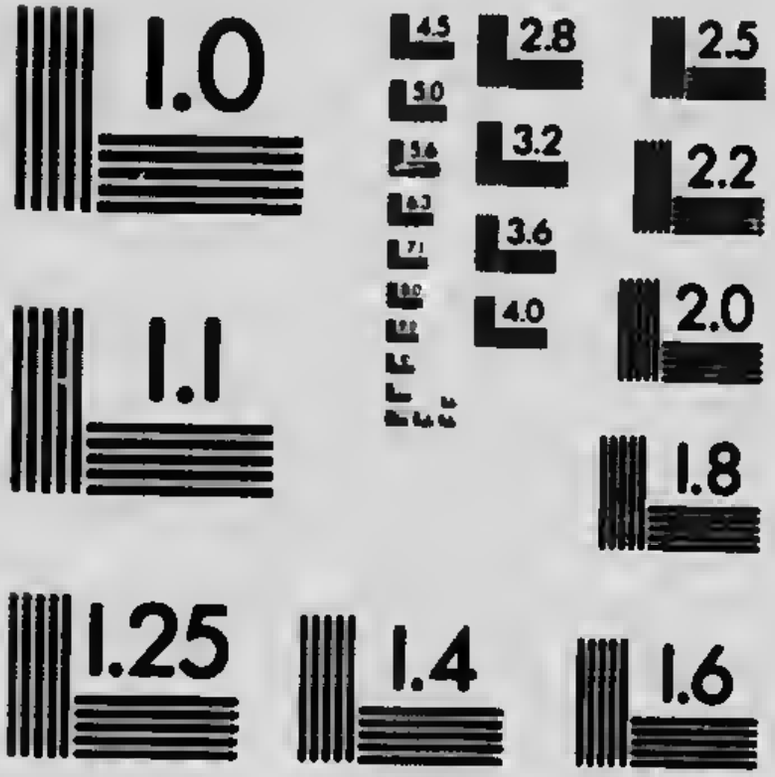

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and Zagari[1] had, some years previously, demonstrated the same remarkable passage in connection with rabies, but there it is still undetermined whether we deal with the passage of the toxin or of the infective agent.

In diphtheria, which likewise is characterized by definite nervous symptoms, Rainy[2] and others have shown that the toxins produce direct histological changes upon the motor cells of the cord in cases in which paresis was present during life. Sidney Martin had previously noted the destructive effects of those toxins upon the nerve fibers. Yet earlier, Charrin,[3] by injection of culture fluids of the B. pyocyaneus, had brought about in the rabbit the same spastic state of the hind limbs, with paralysis of the sphincters, etc., which are features of the blue pus disease in that animal, and, as Williams and Cameron,[4] of Montreal, were among the first to point out, are features of the disease in the human infant. The evidence, therefore, that bacterial toxins are capable of acting directly upon the nervous system is very definite, and such action affords the simplest and most direct explanation of those nervous disturbances in infections generally which are not obviously the result of exhaustion.

Muscular Disturbances.—Rigors.—Associated with chills are *rigors*—fine fibrillary contractions of the muscles of the face, trunk, and extremities, involuntary in nature. Like chills, they are common to exposure to cold and to the incipient stage of many fevers. They represent a reflex stimulation of the muscles whereby, through the frequent and rapid contraction of the individual fibers, no definite movements are induced; in fact, opposing muscles are synchronously affected. The most that is produced is what corresponds to an increased stiffening up of the muscles generally, well indicated by the term "rigor." Every whit as much as the flapping of the arms of the chilled coachman, these rapid individual contractions mean work, and muscular work means the giving off of heat. Rigors, in short, are a mechanism whereby there is produced reflexly increased heat production, and, occurring simultaneously with the febrile chill, suggest strongly that they, too, are a means of promoting increased heat of the organism.

Other Muscular Disturbances.—Atrophy.—It is apt to be forgotten that the normal muscle is not only working when it is undergoing active contraction, but works and produces heat in the apparently resting condition. The condition of tonus is a state of partial contraction, and it can be demonstrated by recording the finger or hand movements after active exercise, or, in cases of paralysis agitans, that the fine twitchings have a definite rate per second, the irregularity of the curves tending to be regular, and brought about by interference between the rates of stimuli passing to opposing groups of muscles. Increased contraction and tonus clearly play a part in the earliest stages of the

[1] Archiv, p. l. Scienze mediche, 9; 1887.

[2] Journal of Pathology, 6; 1900; 444 (with good bibliography).

[3] La maladie pyocyanique, Paris.

[4] Journal of Pathology, 3; 1895.

febrile state; later, it gives way to muscular relaxation and exhaustion, and the muscles of the body in general are noticed to diminish in size at a greater rate than is to be explained by the combined lack of exercise and diminished assimilation. This rapid "burning up" of the muscles is another indication of increased heat production.

Circulatory Disturbances.—In certain cases, the so-called *sthenic* fevers, and, in certain stages of acute infections in general, we find the pulse full and bounding; in others—the *asthenic* fevers—it is weak and easily compressible. In all cases it and the heart beat are markedly increased in rate. While it may be laid down as a valuable rule for prognosis that strengthening of the pulse and lowering of the rate in any individual case of fever is a favorable sign, we have to confess that we know sadly little concerning the meaning and the causation of the febrile pulse; the factors possibly concerned in any given case are too many to permit a sure analysis. What these factors are we will briefly indicate.

1. Whenever the bed of the blood stream is widened in any considerable area without corresponding contraction of the bed in other areas, there is lessened resistance to the inflow of the blood, the pressure sinks, and the heart rate increases. The general lack of bodily tone and the actual vascular dilatation observed during the fastigium indicate that this factor is at work.

2. Increased temperature of the blood and organism generally has an identical action. If the frog's—or the cat's—heart be removed from the body and kept beating by supplying it with blood, warming that blood leads to more rapid and less powerful heart action; as, again, warming the rabbit's ear leads to obvious vascular dilatation and increase in stream bed.

3. The direct action of bacterial toxins upon (*a*) the peripheral vessels has also to be considered. And this action varies in the different infections. With diphtheria, Sharp[1] found that the toxins applied direct to the heart muscles cause, first, a more powerful beat, followed by weakening, with less complete systole and more prolonged diastole, until complete arrest ensued in the diastolic state. Woodhead found that the same toxin leads directly to a condition of fatty degeneration. But, at the same time, we know that it has a specific action on the peripheral nerves, and disintegration of the vagus has been determined in some cases of sudden death, which vagus degeneration would seem the most satisfactory explanation of this terrible sequel of diphtheria. A similar action upon the vagus has been determined for influenza toxins (la grippe). Arloing and Courmont have found that the products of the Pyococcus aureus lead to capillary dilatation; those of the B. pyocyaneus, according to Charrin and Gley, lead to contraction of the arterioles, but these at the same time (Mora and Doyon) act directly on the vagus, arresting its inhibitory action and causing increased rapidity of beat. These examples, afforded one and all by

[1] Journal of Anatomy and Physiology, 31: 1897: 199.

capable observers, will serve to indicate the intricacy of the subject and the need to study the vascular changes in each infection separately.

4. Yet another factor in affections such as cholera, which are accompanied by profuse diarrhea, is actual diminution in the amount of the blood; this, again, leads to rapidity of heart action and weak pulse. The results, as far as the heart is concerned, are the same as diminution of resistance to onward passage.

It follows, naturally, that the different stages of a fever afford different types of pulse and pulse tracings; that in the stage of contraction of the peripheral vessels the pulse is small and firm; in the fastigium it is of a fuller, softer type. It further is particularly liable to exhibit dicrotism, an indication, as now generally accepted, of loss of tone of the walls of the larger arteries. On these, also, it would seem, toxins have a direct action. The accompanying tracings of the pulse

FIG. 154

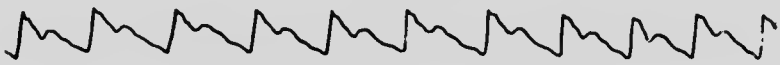


FIG. 155

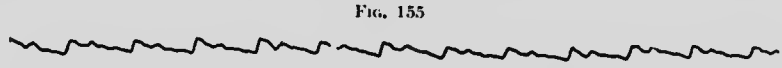
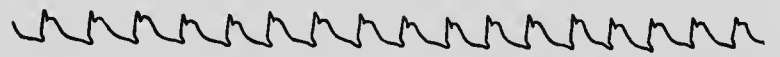


FIG. 156

FIG. 157



Tracings taken from successive stages of a paroxysm of ague (tertian malaria) Fig. 154, from the period before an attack. Fig. 155, beginning of the attack (stage of shivering). Fig. 156, in height of attack. Fig. 157, beginning of the stage of defervescence (sweating stage). (Mannaberg.)

in the apyretic period and the period of chills (pyretogenic), heat (fastigium), and perspiration (defervescence) of two malarial paroxysms on successive days exhibits well the changes in type and rate of the pulse in these different conditions.

Alterations in the Blood.—We shall not attempt to describe minutely the blood changes in the different infections; they are very various, and are detailed fully in the many excellent works on hematology. We can but note the main features.

Red Corpuscles.—It may be laid down that, save in those cases in which there is a severe drain of fluid from the organism, as in cholera, when, in consequence of the concentration of the formed elements, they appear to undergo a great increase, infection, even in mild grades, if continued for a few days, leads to diminution in the number of

the erythrocytes. Their destruction in the febrile state is greater than their reproduction. Certain microbes, streptococci, and many members of the B. coli group have, through their toxins, a distinct hemolytic action upon the corpuscles in the test-tube, and if a smear be made from the swollen spleen, in typhoid and other fevers, it is often possible to note that the large endothelial cells from the splenic sinuses contain more or less degenerated red corpuscles.

White Corpuscles.—Here a very considerable variation exists in the different infections both as regards the total number of leukocytes found in the blood and the relative proportion of the different forms. In most cases there is a distinct increase, in some, as in pyemic conditions, streptococcic infections, pneumonia, the general increase is very marked; in others, notably in typhoid, not only is there no leukocytosis, but the number may be below the normal. Where, in a disease characterized by absence of leukocytosis, a sharp rise in the number of leukocytes is observed, we have indications of a second infection. In typhoid, for example, such leukocytosis should suggest the possible development of perforation, but it must be kept in mind that a rapidly developing septic condition, particularly where the patient is already in a weak state may be accompanied by no leukocytosis. Where, in infection characterized by leukocytosis, the number of leukocytes steadily, or even rapidly, increases during the fastigium, this need occasion no great concern; it is, if anything, an indication of good reactive powers; while, when the fever is at its height, and when the number shows a pronounced fall, or, throughout, the leukocytosis is deficient, we have a condition of serious, not to say grave, import—an indication of deficient reaction and not improbable fatal ending. Where a moderate fall occurs in a case that has proceeded in a natural manner for some period, we may have indications of approaching resolution; indeed, Kanthack by this sign was able in a large number of cases to predict the oncoming crisis in pneumonia twenty-four hours before the temperature began to drop, or any other symptoms of the event had declared itself.

Regarding the different forms of leukocytes noticeable by their frequency in the different infections, it may be said that, in acute infections, the polynuclears are the predominating form; in mere chronic diseases, such as tuberculosis, the lymphocytes are relatively frequent, without the other forms showing great increase in number. In the febrile conditions accompanying the presence of intestinal worms, as already noted (p. 319), there is a liability for a striking increase in the number of eosinophiles, with or without pyrexia.

Respiratory Disturbances.—The increased rate of respiration is a cardinal symptom in the course of infection. Such increased rate is common to all conditions in which either the body is exposed to heightened external temperature, or the bodily temperature itself is raised. It is one of the means of discharging and reducing the heat of the body, for, not merely is heat lost in the process of warming the inspired air, and more heat lost by inhaling and exhaling a large quantity of air in a

given time, but also by internal evaporation, the moistening of the air in the lungs, further loss of heat occurs.

But even when, as in a vapor bath, the external air is already both saturated and heated, the same increased rate of breathing is to be noted, rendering it doubtful whether loss of bodily heat is the main function of the increased rate. We must pass beyond the mere act of increase in rate to its cause, and lay down that anything which leads to increased temperature of the blood bathing the respiratory centre is accompanied by increased rate of respiration; this is very largely an automatic process, primarily resulting, it is true, in lessening the bodily temperature, and so that of the blood passing to the cord, but still occurring when the end cannot be obtained, or when the increased temperature is beneficial to the rest of the organism.

There is another cause of increased rate, acting also, we believe, through the respiratory centre in the cord, which appears to have a more immediate bearing in the febrile state.[1] We would refer to this as oxygen-hunger, even though it acts through its results, namely, accumulation of carbonic acid gas in the blood. We know from abundant observations that increased temperature favors increased metabolism in the individual tissues, and heightened metabolism means increased using up of oxygen, and results in increased discharge of carbonic acid. Under ordinary physiological conditions, if the body be exposed to heat, we note a tendency to combat this heightened metabolism; the individual indulges in a minimum of exercise, and little food is taken. In fevers we have the striking phenomena that, despite the anorexia, the bedridden condition, and complete lack of muscular exercise, the amount of oxygen absorbed in a given time continues to be greatly increased, as also does the amount of carbonic acid given off. And the higher the body temperature, the greater the absorption of the one and the discharge of the other. As Haldane has shown (p. 349), it is the increased CO_2 tension in the circulating blood that is immediately concerned in acceleration of respiration. In one case of febrile chill, Liebermeister found that two and a half times the usual amount of CO was being given off. Leyden, from his observations, laid down that in general the increase is one and a half times the normal. Herein is the primary cause of increased respiratory rate, and here, also, we have a striking demonstration of what must be regarded as the prominent underlying feature of fever, namely, greatly increased metabolism, that metabolism leading to the increased temperature, to increased discharge of CO_2 into the blood, and to the increased rate of respiration. As with defervescence the temperature falls, the discharge of CO_2 returns to the normal.

Urinary Disturbances.—Here, in general, we find that: (1) the amount of urine passed *per diem* is diminished; (2) what is passed is

[1] The conflicting views of Hering, Breuer, and Head (whose studies on the vagus led them to conclude that respiration is largely a reflex act, determined by the condition in the alveoli of the lungs) are weighed and criticised by Pembrey in Recent Advances in Physiology and Biochemistry, 1906: 563.

concentrated and high-colored; (3) more urea and introgenous constituents (uric acid, kreatinin, etc.) are passed *per diem*; (4) more potash salts; (5) the chlorides are noticeably deficient, as, again, are the phosphates.

That the amount, *i. e.*, the water, is diminished, is explicable by: (1) the lowered blood pressure (and rate of flow); (2) the increased discharge of water by the lungs, the skin, and, in some cases, the feces. The increased pigmentation is another evidence of that destruction of the red corpuscles already referred to—and this explains, also, to a large extent, the increase in potassium salts (for the red corpuscles are relatively rich in potassium. Most characteristic is the increase in nitrogenous constituents. The urea in a continued fever is increased from 70 to 100 per cent.; sometimes threefold; the increase in uric acid and kreatinin is more irregular. While the increase is not in all cases nearly parallel to the temperature variations, it is, nevertheless, a very constant phenomenon; and while, again, the amount of nitrogen discharged *per diem* by a healthy person may, under certain circumstances, exceed that shown by the febrile patient, the amount of urea passed by the latter is much greater than would be passed by a healthy individual *on the same diet*.

Thus, the study of the urine affords one more convincing demonstration that the febrile state is characterized by increased metabolism, increased breaking down of proteins. And these proteins cannot be food and reserve materials; they must be derived from the tissues.

Regarding the diminution of the chlorides excreted, it cannot be said that as yet we possess a satisfactory explanation. That the diminished consumption of food is responsible for a large proportion of the decrease must be regarded as well established, but this is not everything.[1] Large quantities of sodium chloride may be given by the mouth and yet the excretion be deficient. Against this, it might be urged that absorption from the alimentary canal is greatly lessened, but such argument will not explain why, in fevers, the amount of the chlorides in the circulatory blood may not be found diminished. We are thus driven to conclude either that in fever there is an altered selective secretory activity on the part of the glomerular epithelium, or absorptive capacity on the part of the tubular epithelium (if the view be accepted that constituents of fluid filtered through the glomeruli undergo reabsorption), or lastly, with Forster and Sollman,[2] that excretion or non-excretion of the chlorides is dependent upon the relative amounts free in the plasma or combined there with colloid materials. But, accepting this last view, there is no explanation why, in fever, there should be this increased combination with colloids.

Yet another feature of febrile urine is worthy of note, namely, its toxicity. Although most observers in this field have failed to take into

[1] Hatcher and Sollman, Amer. Jour. Physiol., 8: 1903: 117.

[2] Sollman has contributed a valuable series of papers on this subject. Amer. Jour. Physiol., 8: 1903: 155, 9: 1903: 425 and 454, 13: 1905: 241, 291.

account the toxic actions of the increased potash contents, there can no longer be reasonable doubt that different toxic substances are discharged by the urine in different infections. The urine, in short, affords one means of removal of the toxins from the organism.

Lastly, in every febrile condition we are liable to find albumin in the urine, and, associated with this, we find cloudy swelling and a more or less well-marked grade of parenchymatous nephritis, set up, it would seem, in the main by the elimination of toxins and the deleterious products of tissue disintegration. The congestion of the kidneys set up by altered blood pressure would not, that is, appear to afford an adequate explanation for the pronounced parenchymatous nephritis frequently noted.

Digestive Disturbances.—Anorexia.—Distaste for food and loss of appetite is characteristic of all fevers in animals, as well as man. With this, as indicated by the mouth (for there is a marked sympathy between all parts of the intestinal canal), there is a marked diminution in the digestive secretion, and, as indicated by the frequent presence of masses of coagulated casein in the stomach in those on milk diet, who have died from typhoid and other high fevers, lessened absorption of substances which demand selective absorption. In the less severe, continued febrile states, as indicated by tuberculosis, the anorexia and lessened absorptive powers do not necessarily go together; there forced overfeeding leads certainly to increased absorption and positive benefit.

To attempt to explain the anorexia and arrest of intestinal activities is at present to indulge in little beyond pure theory, *i. e.*, to conclude from the frequent discharge of mucus all along the stomach and intestines that the cells are engaged mainly in exeretive processes, tending to discharge the toxins, and cannot, therefore, be equally active in absorptive processes; or, again, that it is a means whereby the cells of the tissues in general devote their energies to the elaboration of antitoxins instead of to commonplace assimilation of foodstuffs. Briefly, we know nothing adequate to explain it, and can only note that it is one of the striking features of fever. At most, there are certain indications that bodies of the nature of complements exist in greater amounts in the blood of moderately starved than in that of full-fed animals; but these observations require to be materially extended before they can safely be built upon. The more recent observations by Rankin and Martin in our laboratory upon opsonins in starvation point in the opposite direction.

Into the changes occurring in the liver and accessory digestive glands we would not here enter at length, beyond stating that these tend to exhibit the same cloudy swelling and parenchymatous inflammation noted as occurring in the kidneys. Like changes may be produced in experimental hyperpyrexia, or by subjecting small animals to greatly increased external warmth, but that the mere increase of temperature is not the essential cause is shown by the fact that pronounced disturbances of like nature may occur in diphtheria and in severe infections characterized by lack of pyrexia. Increased excretion of toxins and

products of cell disintegration and physical change in the cells brought about by this excretion must be regarded as the cause.

Cutaneous Disturbances.—Here, as in connection with the loss of bodily heat through the respiration, we note a want of evidence of accurate relationship between heat production and heat discharge. The rule of the organism under physiological conditions is, that increased bodily heat is accompanied by dilatation of the cutaneous vessels, favoring more rapid discharge of heat, and, in addition, by increased perspiration, which yet more materially, by the evaporation of the sweat, brings about loss of heat. As regards surface dilatation, while this is well marked in the fastigium, it is noticeably absent in the period of pyretogenesis. As regards perspiration, it is, to say the least, irregular. There is no constant relationship between it and the height of the fever. It is generally pronounced, not when the fever is rising, but when it is going down, in the stage of defervescence; it is most marked accompanying the rapid fall of temperature to the normal, and below (cold sweats), heralding the fatal event in malignant fevers; may occur locally, as in tuberculosis, or may be a feature throughout the disease, as in acute rheumatism. In short, like the respiratory changes, it is not primarily related to the temperature needs of the body; more extended observations than have as yet been made require to be undertaken to determine its relationship to the excretion of toxic matter from the system.

Of the exanthematous manifestations, some, like the pocks in smallpox and syphilis, and the roseolæ of typhoid, are directly infective, due to the presence and proliferation of the specific microbes in and around the cutaneous capillaries; some, particularly those of hemorrhagic type, are merely toxic, caused by circulating toxins. It is possible experimentally by the injection of sundry toxins to induce cutaneous petechiæ and hemorrhages, indication that those toxins directly affect the walls of the vessels.

Emaciation.—This further cardinal symptom of the continued febrile [illegible] be far more marked than can be explained by lessened intake [illegible]. Notably, there is a reduction of the fatty tissue—a burning [illegible] the fat—and, with this, also of the muscles. Of fat, it must be noted that in its combustion it is capable of giving off more calories of heat than any other constituent of the body. *There is in fever, to repeat, no mere retention of heat, but a most evident increased production.*

CHAPTER V.

THE SYSTEMIC REACTION—(CONTINUED).

THERMOGENESIS AND PYREXIA.

PASSING in review the data afforded in the last chapter, these conclusions stand out prominent: (1) The febrile state is characterized by an increased metabolism altogether out of proportion to the amount of food and energy producing material taken in, the breaking down processes being greater than the building up; and (2) that with the increased heat production there is not a corresponding discharge of heat, so that the body temperature tends to rise. To this a third may be added, that there is evident lack of coordination between heat production and heat discharge. More correctly, this may exist—as is indicated by the regularity of the temperature curve—during the fastigium, but at a higher level than the normal, or, in other words, the bodily heat becomes regulated to maintain a higher temperature.

From the respect mingled with awe with which from childhood upward he has seen the thermometer treated, and from the prominence given to the temperature chart in the wards, the student very naturally concludes that the temperature changes are the all-important factor in the febrile state. Let us here state emphatically that this is not the case. The temperature changes are but the expression and the outcome of other underlying conditions, and these it is that, so far as the organism is concerned, are all important. The temperature chart is important to the physician as indicating how these other conditions are telling upon the general state of the organism. While thus we would not dwell too long upon those temperature changes, there are other states besides infection in which there is rise of bodily temperature, and, in order to understand these and their relationship, it is necessary to recall what we know concerning thermogenesis and heat regulation. This knowledge should be familiar; we shall, therefore, state the main data as succinctly as possible.

Heat Production.—Heat is liberated in the organism under these conditions:

1. From the food, *i. e.*, from the recombination of dissociated foodstuffs (p. 85).

2. From tissue katabolism, *i. e.*, from the oxygenation of tissue products. All work performed by the cells leads to dissociation in the cell substances, and it is ultimately the union of these products of dissociation with oxygen that produces heat.

If, therefore, in febrile conditions there be increased production of

heat, despite lessened intake of foodstuffs, and despite a loss of heat that is not less than normal, that increase can only be due to tissue disintegration and oxidation. The same is true of other conditions in which there is increased heat production irrespective of food taken. If, also, through nervous influences increased heat production be brought about, it is not the nervous centres themselves that develop heat; it is the dissociative changes in the cells of sundry tissues set up by nervous stimulation that is the cause.

Heat Discharge.—There may be loss of heat from the body through:

1. Surface radiation and conduction.
2. Surface convection or evaporation—of sweat and in the lungs.
3. The passage from the body of excreta.

The discharge may be *increased* and the temperature of the body lowered:

1. By dilatation of the surface vessels.
2. By increased pouring out of sweat.
3. By increased respiration, whereby more air is warmed in passage over the respiratory surfaces and greater evaporation takes place in the lungs. (It is by this increased respiration (panting), in the main, that the dog, unable to perspire, cools himself down.)
4. By increased excretion (a very minor factor).

It may be *diminished* by the opposite conditions—contraction of surface vessels and arrest of perspiration, slower or shallower respiration

According to Vierordt if the total income of available energy is 2,500,000 calories (a calorie is the amount of heat necessary to raise 1 gm. of water 1° C. at the normal atmospheric pressure) then:

1.8 per cent. is lost in the urine and feces	27,500 calories.
3.5 per cent. is lost in the expired air	84,500 "
7.2 per cent. is lost in the evaporation of water from lungs	182,120 "
14.5 per cent. is lost in the evaporation of water from skin	364,120 "
73.0 per cent. is lost in the radiation and conduction from the skin	1,791,820 "

The lower the temperature of the external medium in immediate contact below that of the body, the greater, other things being equal, the loss of heat; the more nearly these approach equality the less the loss of heat, and if the external temperature exceed that of the body, and at the same time, by saturation with moisture, evaporation is prevented, there is an actual gain of heat.

Despite the fact that at different periods, through muscular exercise and the taking of food, the heat production undergoes great changes, and through alterations in the external medium the heat discharge is similarly liable to vary greatly, the temperature of the warm-blooded keeps remarkably constant, herein differing from the cold-blooded animal, in which the bodily temperature rises and falls with the external temperature. The infant is intermediate, and its temperature is modified

considerably by that of its surroundings.[1] But in the adult man, whether within the Arctic circle or in the Tropics, the mean temperature is maintained in the near vicinity of 38.2° C. (97.4° F.). Conditions of great heat, as already indicated, will raise it above this point; of great cold and exposure, if forced exercise and food be not taken, will lower it. In cases of sunstroke the rectal temperature has been found as high as 42.9° C. (109.2° F.), but such temperatures are fatal, and it may be laid down that 42° C. (107.5° F.) is the upper limit of temperature compatible with continued existence.[2]

Cases are on record in which, with a rectal temperature of 24° C., those who have been so exposed have recovered, but when the temperature falls below 20° C. death is inevitable. Men thus are not "frozen to death;" they die before reaching the frozen state.

In the conditions of health there is a daily variation of temperature, as might be expected, the minimum being during sleep when the muscles are relaxed and the respiratory change is lowest.[3]

Heat Regulating Mechanism.—The existence of a *heat regulating mechanism* is thus evident; of a mechanism which within very wide limits is marvellously exact and precise in action. As a matter of fact, we possess indications pointing definitely to the existence and site of [illegible] of such a mechanism, although there is still debate as to the number and mode of action of the same. The very existence of two sets of sensory nerves, one for the sensation of heat, the other for that of cold, in itself indicates the existence of a controlling mechanism. Both by clinical observation from the time of Brodie, in the beginning of last century, onward, and by direct experiment it has been noted that injury or stimulation of certain areas of the brain or medulla have been followed by marked rise of bodily temperature, of others by lowering of the same.[4]

It is not difficult to understand that laceration or section of the spinal cord, high up, by paralyzing the muscles, leads to lowering of the temperature, as also by paralysis of the vasomotor mechanism. It is this latter that mainly is effective by leading to dilatation of the cutaneous vessels, etc., for if in those cases the body be properly swathed the temperature rises to the normal. Cutting between the medulla and pons was found, by Horatio Wood,[5] to lead occasionally to a considerable rise, which was also noted at times by Heidenhain.

[1] The same, also, is true of warm-blooded animals in the state of hibernation.

[2] Much higher temperature than this has been recorded of axillary, anal, and rectal temperatures—even of 150° F. and over—and in those not seriously ill; but in so many of these careful det[illegible] work has shown the existence of some trick—placing the thermometer in the tea or hot water, pressing, etc.—that imposture must always be diagnosticated in these cases (see Professor Welch, discussion of Dr. A. Jacobi's paper on Hyperthermy, Trans. Assoc. Amer. Phys., 10: 1895: 189.

[3] Vide Pembrey, Jour. of Physiol., 15: 1894: 401.

[4] For clinical cases see more particularly Hale White, Guy's Hosp. Rep., 27: 1883-81: 48, and Jour. of Physiol., 1891.

[5] Fever, Smithsonian Contributions to Knowledge, Washington, No. 357, 1880.

These results have been opposed by others, but the reputation of both observers for careful, conscientious work is so great that the fact must be accepted. There is more abundant confirmation of the observation of Richet and of Aronsohn and Sachs, that puncture and electrical stimulation of an area in the corpus striatum leads to increased heat production and marked elevation of temperature.

It may be urged that we have no right to speak of these as heat-producing centres;[1] that there exist in the brain centres controlling tissues, such as the muscles and the liver, which, in activity, produce heat all must admit, and it is such visceral centres that are stimulated. To a certain extent, we agree with this objection. Heat can only be produced under these conditions by tissue metabolism. This, however, does not prevent us from regarding centres which thus may lead to a rise of heat as heat-producing centres. Similarly centres governing the sweat glands and cutaneous vasodilators become heat-discharging centres—and looking at the mechanism in this light we must, with MacAlister, predicate the existence of some central heat-controlling centre regulating the (various) heat-producing and heat-discharging apparatus—a centre which stimulates the former and inhibits the latter in order to raise the body temperature, and does the reverse in order to lower it. Without such it is difficult to see how regulation can occur. And we must regard this as being called into action (1) by reflex means; (2) by the temperature of the circulating blood telling directly upon its activity; and (3) by substances diffused in the circulating blood acting upon its constituent nerve cells. Here we trespass into a region of physiology that awaits fuller explanation. All that is sure is that *within the brain and spinal cord are nerve cells which on stimulation lead, some of them, to increased production of heat by the tissues, others to increased loss of heat from the body surfaces. The wonderful regulation of the bodily temperature under ordinary conditions is a strong indication that controlling the production and the loss is one pair or an intimately associated system of heat-regulating centres.*

In fever this heat regulating mechanism is gravely disturbed, and the facts we have brought forward are in themselves adequate to prove that the disturbance is in the direction of increased heat production rather than of lessened discharge.

Calorimetric Observations.—It must be emphasized that the thermometer can only afford information regarding the *balance* or resultant at a given moment between the heat production and income on the one hand, and the heat loss and expenditure on the other, of a particular part; it gives no information regarding the actual *amount* of heat that is being developed by the body, or the extent of heat *loss*. To determine these, observations of a totally different order have to be undertaken, namely, methods of indirect and direct calorimetry. We have,

[1] This is Mosso's view, Arch. ital. de Biol., 13: 1890: 459. Reichert attaches more importance to centres in the spinal cord (Univ. Med. Mag., Phila., 5: 1893: 406 and 6: 1894: 303).

that is, to compare the heat-producing capacity of the ingested food, and of the oxygen absorbed in respiration during a given period (after deducting the number of unused calories represented in the excreted and discharged matter from the organism during that period) with the contemporaneous amount of heat actually lost by the organism (from the skin, the lungs, and in the excreta), in order to assure ourselves either that there is a relative increase or a decrease of heat production and of heat loss. The methods for determining these data are very elaborate, and many sources of error have to be guarded against. So also it would seem that the ratio of heat production to heat loss varies, not only at different periods in the course of one and the same fever, but differs in fevers of different causation. It is not surprising, therefore, that there has been not a little divergence on the results obtained. Long and exact studies have been made by capable observers in many countries, by Liebermeister, Rosenthal, and Rubner in Germany, by Lavoisier and D'Arsonval in France, by Ott, Horatio Wood, Reichert, and Atwater in America. The pioneer observer was Crawford, of Edinburgh (1778). Some of the fullest and most exact calorimetric studies upon the febrile states are those of Wood.[1] It may in general be said that (1) during the initial period of fever there is increased production with some diminution of loss; (2) during the fastigium both heat production and heat loss are increased above the normal; (3) a daily temperature variation occurs parallel to that seen in health, but differing in being at a higher level; (4) heat inhibition is not paralyzed, but the individual is not so responsive to those stimuli which in the normal individual induce a lowered temperature; (5) in defervescence there is lowered heat production with definite increase in loss of heat.[2]

Lastly, before attempting to sum up, it will be well to classify the conditions in which we obtain the febrile state, *i. e.*, a condition of increased bodily temperature with allied increased metabolism. Up to this point we have purely considered the matter in relation to infection; evidently, from what has just been brought forward, the subject is a much wider one.

Causes of the Development of the Febrile Temperature. — 1. First and foremost, *infection*, the proliferation within the organism of pathogenic organisms, both bacterial and animal forms (as in malaria, smallpox (?), syphilis, etc.). Closely allied to these, and strictly belonging to the infective group of causes, must be included sundry disturbances set up by gross parasites, of which the trichina spiralis affords the best example.

[1] Fever, a study in Morbid and Normal Pathology, Philadelphia, 1880, and Smithsonian Contributions, *loc. cit.*

[2] For a general review of the subject of calorimetry and calorimetric methods the reader may be referred to Reichert's article in the American Text-book of Physiology, 1 : 1903 : 467, and that by Kemp in Buck's Reference Handbook; the latter gives the more important bibliographical references. An excellent treatise, although dealing in the main with the calorimetric values of foodstuffs, is Atwater's "Methods and Results of Investigations on the Chemistry and Economy of Food," United States Department of Agriculture, Bulletin 21, 1896.

2. The microbes act through their toxins; it is the diffusion of these toxins that produces the symptoms, as can be demonstrated experimentally by the injection of toxins apart from the microbes, when a like train of symptoms is set up. Absorption of toxins from the alimentary canal is, judging from the analogy of cholera and diphtheria, a probable cause of the subfebrile state which may accompany constipation.

The researches upon the bodies of the nature of toxins in their relationship to fever extend back over a space of fifty years. Billroth and O. Weber independently observed that the inoculation of putrefactive material, whether of animal or vegetable origin, led to the production of a febrile state, reaching its maximum in from two to twenty-eight hours with preliminary pyretogenic stage and a fastigium, simulating typical infection, but their material obviously was impure, containing infective agents. Panum, from putrefying solutions, extracted a body insoluble in alcohol, but soluble in water, of which 0.012 grain would kill a small dog, producing febrile disturbances and the symptoms of acute infection.

Hermann,[1] whose most thorough work and recognition of the importance of what we now term toxins is generally forgotten, concluded that the body he gained, having like properties to that described by Panum, was of proteid origin, that it worked as a ferment, and that there were specific differences in the essential toxins of the different infections.

In more recent years it has been noted not only that the products of growth of bacteria in various media induce febrile states simulating in their peculiar features the fevers produced by the individual pathogenic bacteria, but further extracts of the actual body substances. Proteins, as Buchner termed them, or, as is more usual at the present moment, *endotoxins*, are found to cause pyrexia and the febrile state. Roussy first showed this in connection with yeast, Buchner proved it in the case of bacteria. Koch's tuberculin R.—the juice expressed from the bodies of tubercle bacilli under high pressure—causes, when inoculated, a very definite fever, with an incubation period, *i. e.*, several hours elapse before any change is noted, then a sharp rise to a maximum, some twenty-four hours after inoculation, followed by a sharp fall.

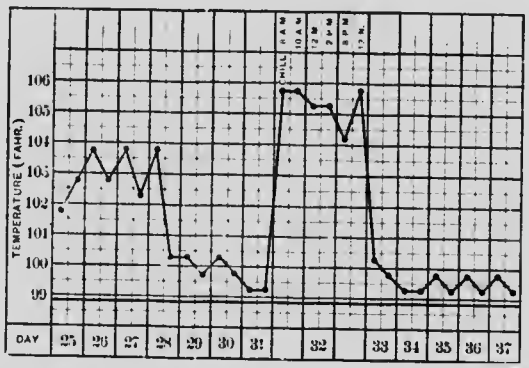
3. As Hildebrandt pointed out many years ago, all enzymes and ferment-like bodies, when inoculated, lead, after a short preliminary period of definite lowering of the temperature, to an even more marked rise of the same. It is to be noted that a like temporary depression is observable after injecting most toxins. With pyocyaneus toxins we have found it well marked, lasting for an hour or two, and followed by a rapid rise. Hildebrandt's observations have been denied by some who urge that where pure ferments are employed no rise occurs. But "pure" ferments in our experience are very largely inactive ferments.

4. *Hemorrhagic Products* (hemolysis). A large internal hemorrhage, after a like period of depression, is always followed by pyrexia, which

[1] Experimentelle Studien über die Wirkung faulender Stoffe auf den thierischen Organismus, 1866.

may last for some days, and this in the absence of any signs of sepsis. The subcutaneous injection or intravenous inoculation of the blood of another species when not immediately fatal has the same results, as has like inoculation of the blood of another individual of the same species. Something clearly is liberated in the process of coagulation and breaking down which leads to the rise. It has been shown that fibrin ferment will cause these results, from which it would seem that in all the group of cases the common cause is liberation of fibrin ferment. If this be so, then here we have but a special case of the preceding group of causes. This, however, is still under debate. Intimately allied, if not identical in causation, is the pyrexia following upon the intravenous inoculation of large quantities of water or of other substance causing recognizable destruction of the corpuscles.

FIG. 158



Pyrexia following thrombosis in the course of typhoid fever. (T. McCrae.)

5. The last case suggests strongly that fibrin ferment alone is not the cause of the pyrexia in these cases, the hemolysis mainly affecting the red corpuscles. As a matter of fact, the sterile *extracts or juices of tissues* in general produce rise of temperature. This rise is well seen in the administration of thyroid extract. Such diffusion out of tissue juices, or of the contained enzymes of the same of one or other nature, affords the most satisfactory explanation of the sharp rise of temperature in cases of infarct formation and of thrombosis, a rise so characteristic that we are justified in attributing sharp rises occurring in the course of cases of acute endocarditis to the supervention of infarcts and necrosis, in the spleen, kidney, or other organ. Comparing the temperature chart in such cases with the lesions found, we have, on several occasions, been able to convince ourselves of this relationship. Allied to this is the pyrexia which may follow simple fracture of the large bones. In von Volkmann's clinic, of fourteen cases of simple uncomplicated fracture of the femur without sign of septic infection, no less than eleven manifested a pronounced and persistent pyrexia; in

five the temperature remained for several days between 39° and 40° C. The local hemorrhage may be the main cause of this rise, or, again, the local tissue laceration and destruction.

6. *Certain drugs* also induce pyrexia. O. Weber first pointed this out in connection with sulphuretted hydrogen. Strychnine working in the muscles through the nerves may definitely raise the temperature. Hale White has shown that β-tetrahydronapthalamin has very pronounced pyretogenic properties.

7. Subjection to greatly increased external temperature. This produces not merely pyrexia, but if that pyrexia be considerable or continued, it is associated with tissue degeneration, cloudy swelling, and parenchymatous degeneration, disturbances closely simulating those which accompany infection; the increased internal temperature leads, that is, to increased metabolism and, it may be, perverted.

It is questionable, to say the least, whether the hyperpyrexia of *sunstroke* should be here included; its sudden onset, accompanied by pronounced nervous symptoms, indicates that here we deal more directly with a primary nervous origin, and the common prophylactic means employed in all countries, that of protecting the head and back of the neck against the sun's rays, would seem to indicate that either the local action of heat upon the medullary centres, or, it may be, the direct action of certain of the sun's rays through cutaneous and subcutaneous tissues upon those centres, is the effective cause. The etiology of this condition is still far from being firmly established, but, as already indicated, the pyrexia may be intense and progressively ascending.

A definite febrile state may follow burns and scalds if at all extensive. The more recent observations of Bardeen, T. McCrae, and others attribute this not to the actual exposure to heat, for it may become noticeable only some hours after the injury, nor, again, to nervous shock, but, judging from the accompanying evidence of selective toxic disturbances, more particularly in the lymph glands and the kidneys, to the absorbed products of cell destruction. This form, therefore, should be included under our fifth heading.

8. Lastly, we have those cases of pyrexia produced by *nervous influences* purely, by irritation, in some cases of the heat-producing mechanism, in others, it may be, by inhibition more especially of heat discharge. The absence of anything corresponding to an incubation stage distinguishes these cases from the infective group of cases, their rapid onset also from the cases due to the action of toxins and cell substances. Where, as in clinical cases, the irritation leading to the condition is continued, degenerative conditions of the tissues are observed. In sunstroke—if this should here be included—despite the short duration of fatal cases, these parenchymatous degenerations are often very striking.

Are we justified in classing all these different forms of pyrexia together? Certainly there are differences. In infection alone do we have the absolutely typical example of continued fever, incubation period, pyretogenic stage, fastigium, and defervescence, characterized by what we may express as universal metabolic disturbances. But

with the products of bacterial growth—toxins—with enzymes and tissue extracts, we approach very near to the typical condition, the only differences being the absence of that portion of the incubation period dependent upon the proliferation of the microbes until such time as they produce sufficient toxic matter to affect the organism generally, and those differences produced in the continuance of the fever by the continued development of toxins. Yet in cases of gradual diffusion of tissue products and enzymes (internal hemorrhages, burns, etc.), there may be similar continuance, and in all of them we note the existence of a distinct period between the introduction or formation of the disturbing causes and the development of pyrexia, a period the significance of which is indicated by the observations of Sidney Martin on diphtheritic toxin (p. 286) and of Preston Kyes[1] on snake-venom lecithin, to which we shall refer shortly (p. 494). Toxins as such, it would seem, gain full toxic powers only after forming certain combinations within the organism, and for this combination time is requisite. This period is wanting in the pyrexia induced by drugs and by nervous disturbances, and in these the pyretogenic period is greatly shortened. In these, also, the evidence of widespread metabolic disturbances are, it may be, of a somewhat different order, even if histologically we can determine no points of essential difference in the processes observed.

THE ESSENTIAL SIGNIFICANCE OF THE FEBRILE STATE.

Clearly the infective, enzyme, and tissue extract reactions form a well-defined group; they represent the development of a common process. Now it is noteworthy, as we shall point out in the succeeding chapters upon immunity, that *in all of these the reaction results in the production of antibodies*, of substances which neutralize the toxic causes. And recognizing this, we appear coincidently to gain insight into the essential nature of fever. Just as we saw that inflammation is the process of adaptation of the tissues to local injury, so is fever *the process of adaptation to such toxic agencies as can be neutralized by the development of antibodies.*

In further support of this view it is to be noted that if an excessive dose of a toxin be injected—one that is fatal within a few hours—instead of a rise of temperature there is a progressive fall, or, at most, a transient rise is followed by a rapid fall, which continues until a point far below the normal is reached, when death ensues. The tissues, in short, are poisoned, and there is no adequate general reaction. And the same is to be noted in malignant fever, and in the fatal termination of acute fevers; *the fatal event is heralded by arrest of the febrile reaction and falling temperature.* To this, it is true, there are exceptions. We note cases, both experimental and clinical, in which, on the contrary, death occurs in hyperpyrexia. But studying these, we observe that

[1] Berl. klin. Woch., 1903: 957 and 982.

they are instances in which the toxins have a markedly selective action—either on the nervous system, as in tetanus (there is a similar selective action on the nervous centres in sunstroke), or the lungs, as in pneumonia, or the heart, as in acute rheumatism—so that evidently in these cases death is due to some one of the vital trinity becoming inactive while the general reaction is proceeding vigorously.

It may be in some cases the very intensity of the reaction defeats itself, and that death is directly caused by the hyperpyrexia. We are, however, inclined to believe that such cases are primarily examples of selective action on the nerve centres; that, as indicated, in fever in general the heat regulating centres are still in action, although working at a higher level, and that in these particular cases of death in hyperpyrexia it is through the complete inhibition or intense stimulation—of the centres—that the hyperpyrexia is brought about.

Regarding the drug pyrexias, it will be interesting to determine—for such has not yet been done—whether as a body heemical substances which induce pyrexia lead, upon inoculation or absorption, to the development of a similar class of antibodies.[1]

THE RELATIONSHIP OF THE NERVOUS SYSTEM TO PYREXIA AND OTHER PROCESSES.

And finally, with nervous pyrexia and hyperpyrexia, here again we have the close parallelism with what we determined in connection with inflammation. Just as there we noted that without actual local injury the nerve centres could independently originate the succession of processes which ordinarily require to be initiated by actual injury, so here we have to acknowledge that without the presence of what we may broadly refer to as "toxins," the higher nervous centres can set going the series of general changes throughout the organism, which, with the nervous system in normal state, are only called into being by the presence of such toxins. Just as in neurotic inflammation we saw that the complete succession of manifestations was wanting, so here, while there is induced by the nervous centres increased metabolism and heat production with its associated pyrexia, there are of necessity wanting the tissue changes leading to antitoxin formation (although what these are we do not surely know) and the actual production of antibodies.

Dangerous, as from the essential unlikeness of distinct phenomena all similes must be, occasionally we encounter one that is of more use than many paragraphs, and that because it impresses forcibly some impor-

[1] In this connection it is at least interesting to note the marked tolerance that can be acquired to relatively enormous doses of strychnine. We would not suggest that the converse holds, namely, that where antibodies are found the febrile state is developed; we have, that is, the instance of diphtheria, in which pyrexia may be a relatively slight feature (though some there is always), and, nevertheless, pronounced development of antitoxins.

tant point, or basal relationship. There has been a long and sometimes angry debate regarding the relative importance and activity of the nervous system and the tissue cells, respectively, in the performance of function, whether under physiological or pathological conditions. Some would see every little act of every individual cell under normal conditions initiated and governed by impulses proceeding from the nervous centres. For them nervous matter is the fountain and origin of all bodily activities. Others see the cells as largely independent, stimulated in the main by alterations in their environment. For these the difficulty is to explain and harmonize cell activities undoubtedly set up by nervous stimulation; they would deny that processes of direct and nervous origin can in their sequence and results be identical. The parable of the coach, the coachman, and the horses places the inter-relationship in a right light. Those horses have been foaled, have learned to eat and to run and to perform the natural functions without any necessary supervision by the coachman, but when grown up he has had to train them to run together in harness and pull the coach. And, well trained, so accustomed have they become to the daily round that, without direction, they will fall into their appointed places, will go cautiously down the decline, or work harder, pulling the coach up hill. Undoubtedly, the constant tension of the reins upon the bit and the variations in the same, guide and direct them. So also the whip will suddenly stimulate them to increased exertion, and that without any necessary knowledge on their part of why such call has been made upon them. The coachman may be excited and flog them to a gallop downhill, where they have been trained to go cautiously, and they gallop; or may be drunk, and lead them off the road, and bound they are to go where he guides. But such is their training, that if, being on the road with the coach running behind, he becomes incapacitated or falls off, they will keep to the road, will even manage the curves, will strain up hill, and proceed with caution down; nay, even will draw up at the accustomed halting place. Only their pace may be uncertain, and if some unaccustomed obstacle presents itself before them, then, lacking guidance, they may come to a standstill; or, seized with panic and each acting for itself, may break the pole, and tangle the harness; or, dragging the coach hither and thither off the road, may bring it and themselves to destruction.

The application of this parable to these states of nervous hyperpyrexia and their relationship to fever proper is obvious. Kept in mind, it time and again is of help in harmonizing apparently antagonistic data bearing upon the functional activity of the different tissues in relationship to the nervous system.

CHAPTER VI.

IMMUNIZATION AND IMMUNITY.

We have laid it down in the preceding chapter that in the course of infectious fevers and those set up by certain organic substances there are developed within the system certain "antibodies," by means of which toxic bodies become neutralized, so that the system becomes protected, and, with this the febrile disturbance comes to an end. It is now in place to inquire more closely into these processes of *immunization*, and into the steps whereby these antibodies are formed and *immunity* is acquired. Already we have regarded the subject from one aspect. We have seen that continued existence means continued adaptation, that an environment suitable for individuals of one species may be fatal for those of another, and that, consequently, if all species are primarily of common origin, then during evolution the ancestors of the different existing species, subjected to different environments, have undergone adaptations in different directions, have become modified, and, indeed, immune to influences which, without such modification, would have brought about cessation of activity and death. Speaking broadly, the individual must be regarded as having gained through inheritance a relative immunity, within certain limits, in respect to the action of all the agencies, physical, chemical, and organized, which constitute his normal environment. This statement is, perhaps, too extreme; there are agencies to which living matter shows no interaction, in respect to which it is absolutely inert; it makes no combination with certain chemical substances, and is uninfluenced, for example, by alternating electric currents beyond a certain range of frequency; is not stimulated, likewise, by certain sound waves, or by light waves of more than a certain amplitude. As regards such agencies, we must recognize (1) an *absolute immunity*. For all the other agencies, however—and their number is practically infinite—which are capable of affecting the molecular arrangement of living matter, we must recognize (2) this *relative immunity*—that living matter has gained the capacity of withstanding the action of such up to a certain limit without being destroyed. We must recognize, further, as above implied, (3) that this relationship is *quantitative*, that there are limits beyond which the action of an agency becomes detrimental; and next, that as regards any particular agent, not only the different species, but the different individuals of the same species, whether through inheritance or acquirement, exhibit different grades of reaction. We must recognize, that is, (4) the existence of ex-specie and individual *susceptibility* or predisposition.

With reference to the mechanism whereby *inherited immunity* is brought about, little can here be said; nothing, in fact, beyond what was stated in our discussion of inheritance in general (p. 143), and, with regard to *acquired immunity*, many acquirements are so gradual that our study becomes limited. Experimentally, that is, we can but inquire into those cases in which the development of this relative immunity is rapid, occurring within a few days or weeks; or, to be correct, it is these cases alone that have so far been studied, and that form the basis of our knowledge. Thus, to all intents and purposes, we are confined to the processes of immunization with which is associated the development of fever, to a study of immunity produced through infection and toward toxins, enzymes, and tissue extracts.

Such has been the outburst of work during the last decennium upon this subject, so great the accumulation of data of a wholly new order, so diverse the views of individual workers, and so appalling the array of new terms introduced, that, when in addition the solution is still unsettled, the unessential matter not having yet undergone precipitation, there is no branch of pathology more difficult to teach or that offers greater difficulties to the student to master. We shall have to touch upon many problems yet unsolved, and to note data which are apparently contradictory, along with others that must be regarded as established and of the very highest importance.

Under these circumstances, the only satisfactory introduction to the subject is the historical, whereby, first and foremost, a proper perspective is gained of the successive steps in advance in our knowledge of the subject.

That one attack of many of the infectious diseases protects the individual against subsequent attacks, or renders those subsequent attacks mild and harmless, has been known through the ages; nay, more, for centuries in India and the East advantage has been taken of this fact, and, to protect them against the severe disease, individuals—chiefly children—have been purposely inoculated with matter taken from those suffering from a particular form of infection, or (and this not only in the East) have been made to sleep in the same bed, etc., it having been found that disease so communicated to those enjoying good health is apt to assume a mild form. In other words, infectious disease, under ordinary conditions, "selects" those of weakly constitution, or temporarily in poor condition, and gains a stronger hold than it does when conveyed to those previously sound in health. Such a method of inoculating smallpox, then endemic throughout Europe, and terribly rife, was introduced into England from Constantinople by Lady Mary Wortley Montagu, and became extensively practised there and elsewhere in Europe in the middle of the eighteenth century, until the danger of the process became so evident that it had to be given up. The very mildness of the inoculated disease led to carelessness on the part of the patient and those around him, and, while the patient became immunized, his *entourage* became infected; the disease became more and more common as a consequence.

The next step, and this definitely in advance, must always be associated with the name of Edward Jenner; not that he was the first to note that cowpox conveyed to man protected against smallpox, or, indeed, to inoculate with cowpox to this end. One or two others had practised the method sporadically before him, but without fully testing the results or making them generally known. Jenner went into the matter as thoroughly as it was possible for him to do at that period, tested with smallpox virus those whom he had "vaccinated" (*vacca*, a cow), and found them resistant; and by the publication of his methods and results before the Royal Society, in 1796, brought the matter to public knowledge and public use, and thereby converted what had been the greatest endemic scourge into a relatively rare disease, capable of control. Thanks to the process of immunization properly carried out, smallpox is today non-existent in the German Empire, save for cases introduced over the borders, and affects other countries in inverse proportion to the rigor of their vaccination laws and the stringency with which these are enforced. The essence of Jenner's advance was that, conveying a mild disease, harmless, non-infective, save by direct contact, he protected against an often fatal and always disfiguring disease. But how these results were brought about he could not explain; he held that he was dealing with a modified form of smallpox, and in this we now know that he was right. In modern terms, he employed a germ attenuated by passage through another species of animal to set up a mild attack. One hundred and twelve years have elapsed, and even today we are not positive what is the organism of smallpox.

With the next and greater epoch the name of Pasteur[1] must ever be associated. He it was who, first isolating the causative agent of an infection, found the means of attenuating it (1880), of making it so weak that, when inoculated, it set up a transient illness, after which the animal was found protected against the natural infection. The chickens around Paris were being decimated by a virulent diarrhœa (chicken cholera); Pasteur isolated the organism, a minute bacillus, and noted that old cultures did not kill the chickens inoculated; utilizing these chickens for subsequent inoculations with powerful fresh virus, he found that they did not succumb; and he possessed the genius to recognize the full significance of the observations; not that something had gone wrong with his experiments, but that by keeping, the culture had become attenuated, and that here he had at hand a means of conferring immunity by inoculating the chickens with attenuated virus.

That a plague of diarrhœa in a poultry yard, studied by a professor of chemistry, should be the seed from which has grown the vast development of latter years is a strange fact, but fact, nevertheless. Armed with the knowledge gained from the study of chicken cholera, Pasteur and his lieutenants, Roux and Chamberland, attacked next the subject of anthrax, a disease enzootic in certain parts of France and causing a

[1] Compt. rend. de l'Acad. de Science, 90: 1880: 239.

great annual loss to the farmers. The simple means of attenuation employed in the first case was here of no use; old cultures were as virulent as were new, and this, it was found, because the bacilli were spore-producing, and the spores formed during the early days of growth, and remaining dormant in the culture fluid, when they developed possessed all the properties of the bacilli in which they had been formed. Some method had to be found to lower their virulence. Toussaint, in 1880, had already published a method of attenuating the bacilli, namely, by heating the blood of an infected animal to 55° C. for a few minutes. The bacilli in such blood, we now know, contain no spores. Chauveau, later, gained similar results by taking fresh cultures of the bacilli and heating them momentarily to 80° C. Both these methods undoubtedly attenuated the bacilli; either continued for a little time would cause the death of the organisms. A variation of a few seconds in the treatment would thus make a very material difference in the grade of attenuating the bacilli; in fact, by neither could exactitude be obtained. To obtain practical results exactitude in dosage was essential, and his training as a chemist led Pasteur to seek after exact reactions. Thus, after many trials, a way was found, namely: it was discovered that spores were not produced when the bacilli were cultivated close to the maximum temperature limit of growth. Grown at between 42° C. and 43° C., the bacilli became slowly attenuated, until, in thirty days, growth ceased altogether, through the weakening and death of the bacilli; between the eighth and the thirtieth day the loss of virulence was progressive, and, what is more, subcultures made from the original flasks of growth in the high temperature incubator, when kept at 37° C. did not regain their original virulence, but maintained for generations the grade of attenuation impressed upon the original culture by growth for a certain number of days at the high temperature.

Here, then, he possessed a method of accurate graduation, and now he was able to demonstrate that progressive inoculation of sheep and cattle, employing in each case first a weakened culture, then, some eight days later, when the reaction had subsided, inoculating with a more powerful one, gave immunity against large injections of the most powerful virus. His method was so precise that it was found of immediate benefit, and with its general adoption the reduction of the anthrax mortality in France was very remarkable. As a practical indication of its value (for at the time Koch vigorously criticised Pasteur's method, and even to-day many German text-books do not, in our opinion, appraise at its full value this great achievement), it may be stated that for some years French insurance companies refused to insure farms in the infected districts unless the sheep and cattle had been "vaccinated," and even supplied their own veterinarians, to make sure that the treatment was properly carried out.

Even more remarkable was the genius displayed in dealing with rabies—a condition in which, for the first time, Pasteur came to deal with disease in man. Here, even at the present moment, we are

doubtful as to the causative agent, and Pasteur was literally working in the dark; notwithstanding, he succeeded in gaining virus of definite grades of intensity with which to inoculate. First, it was determined that the virus was constantly present in the brain and cord of dogs affected with the disease; that an emulsion of this nerve matter inoculated into the animals of the laboratory would set up the disease in them, and that the most rapid and sure method of inoculating the disease was by the subdural method, by trephining the animal and introducing the matter beneath the dura mater. But with matter obtained thus from different rabid animals, the period of inoculation in the inoculated animals was very variable, and often very long; it was necessary to make it constant and, if possible, to shorten it. And here Pasteur discovered that he could intensify the virus. He had, two years before, made certain remarkable observations upon "rouget du porc" (swine erysipelas), finding that by passage of a germ through a series of pigeons he increased its virulence for pigeons, through rabbits for rabbits, but that, whereas the virus rendered more virulent for pigeons was also more virulent for swine, with the rabbit virus the results were the contrary. Just as smallpox from man passed through a series of calves or monkeys[1] is rendered less virulent for man, so with the rabbit "rouget" for swine. This was the first case in which this was definitely proved. Since then several like instances of *exaltation* or *attenuation of virulence by passage* have been reported. Now, he found that he could intensify his rabies virus by passage through rabbits until, after some two hundred passages, he had brought down the incubation period with remarkable regularity to six days; further passages reduced it further, but slightly and very slowly. He now possessed a "virus fixe," or sufficiently constant for purposes of obtaining attenuated material of definite grades of lessened virulence. We have said that the causative agent is unknown. Pasteur took the rabbit's cord, under strict aseptic precautions, and, falling back upon his chicken cholera experience, tested the effects of exposing it to the air for several days and drying it over caustic potash. As a matter of fact, he found that by this means it eventually lost all its virulence, and—not to enter into details—he was able to elaborate the method of developing immunity in man and protection against the disease by daily inoculations of emulsions of such dried cord, beginning with that dried twelve days, and devoid of all virulence, and gradually ascending until the most virulent material was injected. The remarkable success of this method in a disease which in man has so long an incubation period that preventive inoculations can be practised during that period, is known to all.

We have described these observations in a little detail, not to remind the reader of the greatness of Pasteur's genius, though that is worth the doing, nor, again, to impress the moral of the need in studies upon immunity to gain material of known and constant strength, though that is most important, but more particularly to impress the fact that

[1] Vide Copeman, Jour. of Path., 2:1894:407

each specific disease is a special entity, having characters of its own that have to be taken into consideration and dealt with along special lines.

It may, indeed, be as Moore[1] has lately suggested, and others before have mooted, that rabies is not a microbic disease, but due to the transference of an enzyme, which, by autocatalysis, increases itself. Until clear proof of the existence of such transference is afforded, we are content to be skeptical. While drying and oxidation, as employed by Pasteur, would result in weakening and destroying an enzyme, it would have a like effect upon a non-spore-bearing microbe.

The next great step forward was the determination by Salmon and Theobald Smith, in Washington, in 1886, that immunity against hog cholera is to be gained by the inoculation of products of growth of specific organisms—observations which during the next few years were abundantly confirmed in connection with a large number of pathogenic organisms (tetanus by Brieger and Kitasato; diphtheria, by Roux and Yersin; Bacillus pyocyaneus, by Chantemesse and Charrin; and the list might be extended). It was thus definitely established that (1) *the symptoms of infectious disease are caused by the diffusible products of bacterial activity*, and (2) *that immunity is more particularly the development of the capacity to neutralize those products.* But it soon became obvious that here, again, the different pathogenic bacteria did not all possess like properties. With one group the filtered culture fluids were eminently active; with another group they were, if not wholly inactive in producing immunity, so weak as to be practically of no value, although immunity in this latter group could be induced by inoculating minute doses of the living cultures. We owe more especially to Pfeiffer,[2] in 1891, and to his studies upon the cholera spirillum, the recognition wherein the difference lies. In those cases immunity can also be induced by inoculating the killed bacilli. Whatever processes happen within the organism (and we are still uncertain regarding these) in cultures outside the body, the toxins are present, but do not diffuse out of the bacteria into the culture. We now speak of these as *endotoxins* (p. 497).

As to the chemical constitution of these toxins, the observations so far have led us, as already noted, to no sure conclusions. For this reason the recognition by Ehrlich,[3] that there exist vegetable toxins (*phytotoxins*) that can be isolated in a state of relative purity, has been of distinct importance. Abrin (from the Abrus precatorius, or jequirity bean), ricin (from the castor oil plant), robin, and crotin have all been found to possess toxic properties resembling those of toxins proper; and, what is more, as Ehrlich showed, it is possible to immunize against them. Another class of albuminoid bodies, the snake venoms, were shown by Calmette, in the same year, 1894, to belong to this category.

[1] Jour. of State Med., 1904.

[2] Zeitsch. f. Hygiene, 11: 1892: 393.

[3] Deutsch. med. Woch., 17: 1891: 976.

Coincidently, while one series of observers was investigating the properties of the offensive toxins, another set was giving their attention more to the defensive mechanisms of the animal body. Traube, in 1874, and Lister,[1] in 1881, noted that blood to which putrefying matter was added had, within certain limits, the power of remaining sweet, and deduced that it had definite bactericidal properties. Metchnikoff, from 1884 onward, demonstrated with wonderful ingenuity the powers of the leukocytes to take up and destroy bacteria, and, what is more, to become adapted to and destroy bacteria from which, at first, they were repelled. Flügge and Nuttall[2] were the first to demonstrate under the microscope and by cultural methods the destruction of bacilli by the fluids of the organism. The solution of bacteria, whether within the cells or in the fluids of the body, must clearly be a chemical process, and if the bacteria produce specific chemical substances, it would seem certain that the organism provides particular chemical substances to counteract them. To Hankin, of Cambridge, whose brilliant work has been arrested by routine departmental work in India, belongs the credit of first isolating (1888) defensive bodies from the tissues, and showing that these neutralized the toxins. Independently, Buchner, a little later, made like observations, terming the bodies he isolated *alexines*. These two laid the foundation of our knowledge of the *antibodies*.

More immediately, however, in the direct line of advance during the next few years were the observations of Richet and Hérieourt,[3] and of Babes and Lepp,[4] that the blood serum of animals immunized against pyococci and rabies, respectively, conferred immunity on other animals. These observations led up to the great work of Behring and Kitasato[5] (1890) upon tetanus and diphtheria, work which not merely showed that immunity could thus be conferred by the serum of immunized animals, but that cure could be attained by the inoculation of such serum into those already affected—in tetanus, if the inoculations be made during the incubation period; in diphtheria, after the disease has definitely showed itself. With the development of the practical methods of employing diphtheria antitoxin Roux's name must always be associated. These observations showed the existence of another form of immunity, termed by Ehrlich *passive* immunity, not brought about by the reaction of the infected animal, but due to introduced antitoxic substances, in contradistinction to the *active immunity* induced by such reaction.

Thus, in 1890–91, these men established the fundamental data of immunity. Since then there have been great advances in detail, in confirmation of the results here indicated, in further analysis and deter-

[1] Trans. Internat. Med. Cong., London: 1: 1881.
[2] Zeit. f. Hyg., 4: 1888: 253.
[3] Compt. rend. de l'Acad. de Sci., 107: 1888
[4] Ann. de l'Inst. Pasteur, 3: 1889.
[5] Deutsch. med. Woch., 1890: 49.

mination of the nature and mode of action of the bodies which we have grouped under the general terms of toxin and antitoxin. Of these the greatest was first indicated by Pfeiffer's work upon the cholera spirillum, but its meaning was only comprehended through Ehrlich's[1] studies and Bordet's[2] able work upon the process of hemolysis. We refer to the recognition of immunity being dependent, in most cases, not upon one, but upon two, bodies, the one, "complement," present in the normal organism; the other, the "specific immune body," developed in reaction to the presence of the toxins. Of, it may be, equal importance, is the discovery of Preston Kyes,[3] that a body of approximately known character and composition, lecithin, can take the place of one of these (for thereby we come nearer to an exact chemical knowledge of the process of immunity), and, for the same reason, the earlier demonstration by Martin and Cherry,[4] that the toxin and antitoxin form a chemical compound, stands out as one of the landmarks of more recent advance.

At a relatively early period Hildebrandt showed that immunity could be obtained against the action of various enzymes by progressive inoculation of the same. Ehrlich discovered the production of antitoxins against the plant poisons (phytotoxins); Phisalix and Bertrand, Calmette, and Fraser, independently, antitoxins against snake venom; Ehrlich and Bordet, the formation of cytolysins, *i. e.*, the development in the organism of substances which protected against and destroyed the cells of other species or of other individuals of the same species, these being developed as the result of progressive inoculation of the particular order of cells.

The widespread interest taken in these investigations, opening up, as they have done, a new world, and the eager participation in the researches in all parts of the civilized world, is sufficiently indicated by the names we have mentioned in this rapid sketch. French and German and Russian, English and American, Japanese and Australian, each and all are to be credited with one or other notable advance. And as the discovery of the new world, while it rounded geographical science, doubled the data with which the student of geography had to become familiar, so these discoveries of pathogenic bacteria, the nature of their action, and of the reaction to them, while they have wonderfully rounded our whole conception of the processes of disease in general, have undoubtedly doubled the data the medical student of today must master, as compared with the student of a quarter of a century ago.

[1] Wertbestimmung des Diphtheriheilserums, Jena, 1897

[2] Ann. de l'Inst. Pasteur, 12: 1898.

[3] Berl. klin. Woch., 1903; loc. cit.

[4] Proc. Roy. Soc., 63; 1898: 423, and Brit. Med. Jour., 1898; ii: 1120.

CHAPTER VII.

IMMUNITY—(CONTINUED).

THE VARIOUS ORDERS OF IMMUNITY.

HAVING afforded this short account of the development of the study of immunity, it is unnecessary to continue in the strict chronological order; to discuss first what we know concerning toxins and antitoxins, and the development of immunity to infectious disorders. On the contrary, it will, we think, be found more helpful to take into consideration, first, the simpler cases of bodies of known constitution; next, those in which, if still we are not fully acquainted with the chemical composition of the agent against which immunity is obtained, we, nevertheless, are able to isolate that agent, and can be assured that we are dealing with substances of constant value. Having done this, we can with greater security consider the data associated with the more complicated cases, in which we deal with the reaction to bodies which so far we have been unable to isolate in a state of purity.

Immunity against Substances of Known Constitution.—Beyond the fact that there exists such an immunity, the data so far gained from the study of immunization lead us, unfortunately, a very short distance. It is a matter of familiar knowledge that there exist arsenic eaters in Syria who can accustom themselves in the course of a few years to the consumption of four times the ordinary fatal dose with no effect beyond a sensation of general well-being. If this be the case in man, and Hausmann[1] has lately called it in doubt, no such definite immunity can be conferred upon animals of the laboratory. Most observers have obtained nothing beyond merely negative results; have found rabbits and dogs to become increasingly susceptible. Even Besredka,[2] though he discovered the cause of this ill success, can only be said to have induced a trifling immunity. Nevertheless, his observations are of great interest.

The normal peritoneal fluid contains fairly abundant leukocytes, in the proportion of 66 per cent. of mononuclears to 33 per cent. of polymorphonuclears (in the rabbit). Inject an arsenical salt into the peritoneal cavity, whether in solution or in suspension, and if the dose be fatal, there is an almost immediate *hypoleukocytosis*, the diminution especially affecting the polymorphonuclears. Employing Metchnikoff's terminology, there is a negative chemiotaxis. If the dose kill-

[1] Arch. f. Pharmakodynamic, 2: 1903, and Deutsch med. Woch., 1903

[2] Ann. de l'Inst. Pasteur, 13: 1899: 49, 209, and 465.

the rabbit in less than twenty-four hours, the reduction continues and becomes more and more marked. If the dose be below the fatal, there is, at most, a transitory hypoleukocytosis, followed by a hyperleukocytosis and increase, particularly in the number of polynuclears, so that the peritoneal fluid may become quite milky. This leukocytosis, first seen in the peritoneal fluid, subsequently affects the blood also.

If a sparingly soluble salt be exhibited, while in fatal cases it is untouched and found lying free on the peritoneal surfaces, in other cases it is taken up by the "polymorphs" and hyaline mononuclear leukocytes, and can be seen within them in the form of fine colored granules. If soluble salts be employed, the same process evidently occurs, for, if the blood be drawn with due precautions against clotting and be rapidly centrifugalized, the serum and red corpuscles afford no signs of the presence of arsenic: the layer of white corpuscles alone shows its presence.[1] The nearer the dose is to the fatal limit, the larger and more pronounced the stage of hyperleukocytosis, and where a sparingly soluble suspension had been given, Besredka found that in the course of days the foreign granules in the leukocytes became finer, until at last none was to be recognized.

That there are also fixed phagocytes was further obvious; the liver in all cases contained arsenic in excess of other organs. Employing sparingly soluble salts, it would seem that the leukocytes break down, or otherwise discharge their contents, which are taken up by the liver cells by absorption, from which they are slowly discharged into the bile. The poison is also slowly passed out from the kidneys. It appears to produce its fatal effects by action upon the nervous tissue, for one one-hundredth of the dose which produces death when inoculated under the skin leads thereto when injected directly into the brain, and, injected thus, sets up all the symptoms of acute arsenical poisoning.

These are the basal facts. Now, as to the production of immunity. Besredka took advantage of the stage of hyperleukocytosis. With a solution of arsenical salts of such a strength that 10 c.c. surely kills a rabbit of given weight in forty-eight hours, he found that, injecting 2 c.c. of this under the skin at night, and then giving the fatal dose (10 c.c.) subcutaneously the next morning, no ill results ensued. Arsenic is very slowly eliminated; the animal had in its system more than the fatal dose; 12 c.c. usually caused death in twenty-four hours or less, and yet animals so treated recovered. Examining into the matter, it was found that the preliminary dose had caused a pronounced polymorphonuclear hyperleukocytosis. The consequence is that, absorbing the poison, these leukocytes remove it from the blood and body fluids, and so prevent it from reaching the nervous system in sufficient concentration to set up fatal effect.

[1] This is an observation of some importance; it has been freely taken for granted that leukocytes absorb soluble substances, like all other cells, and possess the power of selective absorption. This, to our knowledge, is the first positive demonstration of that selective absorption.

This, so far, is not immunity of the classic order; it is in line with the phenomena of Issaeff's "resistance period" (p. 499). At most, a grade of positive protection is given.

But there is more to be said. If immunity of this order be produced in a rabbit, and the animal be bled six or eight days later and the serum taken, that blood serum is found to have acquired new properties. Whereas the serum of an ordinary rabbit is absolutely without effect when injected into an animal which has received a fatal dose, 8 c.c. of the serum of a treated rabbit injected into a fresh animal either at the same time as, or antecedent to, a minimal fatal dose of arsenic, acts as a preventive, and the animal recovers from the poisoning.

This latter is what we term *passive immunity;* a substance not elaborated by the animal under experiment, when introduced into its organism, acts as an antidote—aids the system in neutralizing or destroying the poison.

It is obvious that the serum of a rabbit that is actively immunized against arsenic comes to contain something not present in recognizable amount in the serum of the normal rabbit.

What is this something? That we do not know. We only know that it is not arsenic-containing, is not a combination of the arsenic given to the first animal with its cell substance; for if the serum be obtained with all due care, despite the fact that the methods at our disposal indicate the presence of extraordinarily minute traces of arsenic, the serum may give absolutely negative reaction; and yet that same serum exhibits these protective properties when injected into a second animal.

If Besredka be correct—and he is a worker of distinction—the only conclusion to be reached is, that as the organism becomes accustomed to the presence of arsenic, its cells elaborate something which is capable of combining with or neutralizing that arsenic, and this body, whatever its nature, passes over into the fluid of the blood, where it can be detected for eight days and more.

But the existence of this phenomenon is denied by later workers. Ehrlich, indeed, lays down with great precision that antibodies can only be produced by the reaction to substances which are capable of direct assimilation, and enter into synthetic union, with the cell substance. He draws the distinction between alkaloids, glucosides, and other drugs, that these, while entering the cell substance and acting upon it, do not become fixed by the cytoplasm, but can be dissolved out, whereas, the whole group of toxins, to be presently noted, do become assimilated and fixed (p. 476). Ford,[1] however, has recently obtained a definite experimentally induced immunity against a glucoside isolated by him from the poisonous mushroom, *Amanita phalloides*. There are also indications that arsenic and other metals become "fixed" in the liver. It would seem, therefore, that Ehrlich advances too far in hypothe-

[1] Jour. of Infect. Diseases, 3:1906:191; Jour. of Exp. Med., 8:1906:137; and Jour. of Biol. Chemistry, 2:1907:273.

cating that only a limited order of chemical substances is capable of becoming built into the cell substance.

With regard to morphine, Faust's[1] observations are of importance. When injected subcutaneously into the ordinary dog, the greater part of the morphine is discharged through the bowels. By gradually increasing the amount injected, a point was reached at which at last the excretion through the intestine ceased. Analysis of the tissues in such animals showed that it was not retained within them. The only conclusion is that the organism gradually, under increasing doses, gains the power to dissociate the morphine. Where this happens, and what the process is, demands further investigation. There are indications that similar dissociations, or destructions, are developed in the process of immunization to alcohol, strychnine, and cocaine. In none of these cases, however, has so far any sure evidence been obtained of antitoxin production. The cases that have been recorded fail to stand criticism.

It may be that in all this group there are developed processes of another nature. Ransom, for example, has shown that cholesterin, which is a common constituent or by-product of the tissues, neutralizes saponin, and several observers have noted that the loosely combined sulphur of the organism can neutralize highly poisonous nitrites up to a certain point by converting them into more harmless rhodan compounds. If we regard the antitoxins as more particularly albuminoid compounds, split off from the cell molecule, it may be that in these other cases there is induced an increased production of non-albuminous bodies, capable of neutralizing one or other poison. But it may also be that more exact research and the employment of other methods show eventually that the processes are of the same nature as those obtained with the bodies we shall next study, and that Ehrlich's distinction, useful as it has been, is not absolute.

Immunization against Albuminoid Vegetable Poisons: Phytotoxins.—There are, as already indicated, certain vegetable poisons of a proteid nature, as distinct from the more usual alkaloids and glucosides, and these are extremely toxic. Abrin, ricin, robin, and crotin are the best-known members of the group. The seeds of the prayer bead, or jequirity, and of the castor oil plant both yield when suitably treated bodies of this proteid nature. They are, it may be, compound proteins. Thus, the former, abrin, has been resolved into an albumose and a globulin, destroyed at different temperatures, both producing similar symptoms. It is still a matter of debate whether the toxic properties are due to the actual globulin or albumose, or whether each has associated with it a third substance, which is the actual toxin. Nay, more, it has been suggested that the toxin is not so much an actual substance as a property; that the albumose and globulin have a force inseparable from them, comparable to the conferment of magnetism

[1] Arch. f. exp. Path. u. Pharm., 44: 1900. This has been confirmed by Cloetta, ibid., 50: 1903.

upon previously non-magnetized iron—a suggestion in line with that we have noted in connection with ferments (pp. 59 et seq.).

As the result of a very full study of ricin, Cushny[1] came to the conclusion that the poison is itself a protein, a globulin, or is so bound to a proteid that the usual methods will not bring about separation. Heating to 51° C. leads after a considerable period to coagulation, with loss of its toxic properties. It is so powerful that 0.04 mmg. per kilo kills a rabbit; or, according to Ehrlich, 1 gram is adequate to kill a million and a half guinea-pigs, with symptoms of acute œdema, inflammation, and necrosis of the tissues in the region of the injection. It is to be noted that there is a *period of incubation* before the symptoms make their appearance, in this resembling what we are familiar with in connection with the bacterial poisons. After seeming to be quite well for four or five days following upon inoculation, the rabbits suddenly show symptoms, and die in the course of a very short period. This, it is true, strongly suggests the action of a ferment and the accumulation in the system of some second substance able to directly combine with or act upon the cell substance. But Cushny could obtain no signs of accumulation of poison in the blood, nor of the presence of any new toxic substance possessing properties differing from those of the ricin injected.

Ehrlich was the first to call attention to the fact that, if mice or other animals be fed upon slowly increasing doses of ricin, they gain immunity such that they can take one hundred times the fatal dose with impunity. To immunize by subcutaneous inoculation, very much smaller doses have to be employed, and care has to be taken that the animal recovers from any signs of local or general disturbances before a second dose be given. But the immunity can be carried to such an extent that these animals will now stand *five thousand times the lethal dose*. In other words, it is possible to obtain an extreme grade of active immunity.

If the serum of animals thus highly immunized be mixed with ricin outside the body, it is found that the poison is rendered inert, and the mixture inoculated into another animal in large amounts is without any serious effects. The indications point to the fact that there is thus brought about a union between the poison and a substance formed by the body and present in the blood, and this union appears to resemble the formation of a double salt (p. 468).

Striving to analyze what happens in poisoning with ricin, and in the production of immunity to the same, we are met with a series of very curious facts. In the first place, the ricin is seen to have two properties which are separable. In toxic doses it causes agglutination of the blood corpuscles, and this agglutination can be well brought about outside the body, a mixture of a sufficiency of the poison with defibrinated blood causing the corpuscles to clump together and to be precipitated, the supernatant fluid becoming quite clear and limpid. And this agglutinating power marches hand-in-hand with the toxic properties of the substance, so that the extent of agglutination has

[1] Archiv f. exp. Path., 41: 1898: 439.

been used by various observers as an index of toxicity. But, as Flexner has shown, the agglutination and the consequent thrombosis and blocking of the vessels is not the essential cause of the lethal action of ricin. The essential poisonous properties are shown in the extensive focal necroses in the liver and other organs. Indeed, as Müller has pointed out, under the action of pepsin and hydrochloric acid, *the agglutinative action is destroyed without the toxicity being diminished.*

Are we dealing here with a mixture of two substances or with one very complex molecule, which is capable of undergoing slight chemical change without all its specific functions being destroyed? In this connection there are observations of very considerable interest. If ricin be heated to 100° C. for two hours, it undergoes coagulation and is rendered wholly inert, so that large doses may be injected without any toxic effects showing themselves, and yet animals treated with this modified toxin are found to become immunized.[1] The modified ricin *is no longer poisonous, but is still able to set up those changes in the organism which result in the production of an antibody.*

In this connection we may refer to robin, the active principle of the seeds of the *Robinia pseudacacia*. This is a proteid body of the same order as ricin, but much weaker in its effects; yet the blood of animals immunized against it becomes strongly antitoxic to ricin. As Ehrlich suggests, robin may be a toxoid of ricin. In this relationship there is no question regarding duality of the active substance. We have to regard the molecule of the poison as becoming so modified by heat that it cannot enter into *harmful* combination with the cell substance of the animal inoculated, but not sufficiently modified to prevent it reacting, to a certain extent, with that cell substance, and thereby stimulating the production of antitoxins.

Yet another remarkable fact has been noted. If sufficient ricin be added to the serum of immunized animals, with its contained antiricin, so as to make a neutral and inert mixture, which, upon inoculation, produces no toxic effects, that mixture *is still capable of producing active immunity* when injected into the species of animals which yielded the antiricin. It is clear, therefore, that in this combination between toxin and antitoxin the toxin is not destroyed; it continues to exist as such in the combination, and is able to stimulate to production of antiricin by the organism, although it is unable to cause toxic effects.

Little is known regarding the process whereby the antiricin is developed —regarding the cells which give rise to it. During the incubation period there has been noted an increase in the leukocytes, but the general opinion is that the leukocytes play here but little part of the process of immunization. That the stroma of the red blood corpuscles with which the agglutinin becomes connected plays any part is extremely doubtful. We shall refer later to Römer's suggestive observations on the site of production of antiabrin (p. 472).

[1] Such modified toxins Ehrlich terms *toxoids*. We shall meet with them again in discussing bacterial poisons.

Obviously, the presence of the ricin in the system leads to the active production by the tissues and passage into the blood of a substance which is able to neutralize large amounts of ricin. Is this directly derived from ricin? Is it a substance normally present in the tissues which is developed and poured out in increased quantities under the stimulus of the ricin? Or, on the other hand, is it a product new to the organism?

Once an animal is immunized against ricin it may be bled and re-bled, and still its blood continues to be antitoxic; its tissues *have acquired the habit of discharging antitoxin*, a fact which scarce favors the view that this antiricin is directly derived from the ricin injected. According to Bashford, the most careful studies fail to reveal that the blood serum of the normal rabbit or guinea-pig has the faintest sign of the presence of an antiricin present under normal conditions. *We are here dealing, it would seem, with the development of a substance wholly new to the organism*—a fact of considerable importance in connection with the theory of adaptation. Something wholly beyond any principle of "survival of the fittest" is requisite to explain this new development.

Immunization against Substances of Unknown Constitution.—Ferments and Antiferments.—The toxins in their properties so closely resemble ferments that it might be expected that, at least as regards unusual ferments or ferments out of place, a series of facts would be ascertained closely parallel to what has been determined in regard to the former set of substances. And this is so, though with certain differences, which, in our opinion, form the only serious *data*—as distinguished from *hypotheses of mode of action*—upon which he found a distinction between the two orders of bodies. Hildebrandt[1] showed, in 1893, that repeated injections of emulsin (which inverts glucose into lactose and galactose) lead to a tolerance of the same, due to the development in the organism of an antiferment. The development of such antiferments was confirmed by von Dungern[2] as regards the proteolytic enzymes of bacteria, and more especially by Morgenroth[3] as regards the rennet ferment. Morgenroth demonstrated that, as the result of the repeated injections of goats with rennet, their serum became able to neutralize that rennet; and, further, that this reaction is quantitative, a given amount of serum rendering inactive a fixed amount of rennet solution of known strength. But just as an animal immunized against a specific microorganism is not rendered immune to microbes which, morphologically and in cultural characters, are evidently closely allied, so such immunization of an animal with animal rennet will not protect against rennet ferments obtained from plants (*e. g.*, cynarase, gained from the *Cynara cardunculus*); or, more exactly, the blood serum will not prevent the latter from coagulating milk.[4] In like

[1] Virchow's Arch., 131: 1893: 5.

[2] Münch. med. Woch., 1898, and Centralbl. f. Bakt., abt. 1: 24: 1898.

[3] Centralbl. f. Bakt., abt. 1: 26: 99, Nrs. 11 and 12, and 27: 1900.

[4] Briot, Thèse de Paris, 1900.

manner, Sachs[1] has demonstrated the development of an antipepsin; Gessard,[2] of an antityrosinase; Moll,[3] of an antiurease (urea-splitting enzyme); Schütze,[4] of an antisteapsin (fat-splitting enzyme), and of an antilactase (enzymes which split milk sugar), etc.

An important distinction between the immunization against these enzymes, or, at least, against enzymes which normally are in relationship to the organism, and that against bacteria and their toxins, is that the development of anti-enzymes is limited, and does not become extreme.[5] This, it may be, has its explanation in a surplus of such anti-enzymes, disturbing normal metabolism and absorption of foodstuffs, and so stimulating sundry cells to produce anti-anti-enzymes, whereby a regulating mechanism is set up preventing the anti-enzymes from accumulating in the organism beyond a certain point. Another explanation is afforded by certain remarkable observations of Beitzke and Nanberg.[6]

According to these observers, the serum of animals immunized against emulsin possesses the property of synthesizing glucose and galactose into lactose; it combines, that is, the products of the ferment action. The process, it is true, is a slow one, and may be, after all, but a special case of reversibility of enzyme action, but, if confirmed, it would suggest that between enzymes and anti-enzymes a self-limiting circle is developed.

It is worthy of note, also, that bodies of the nature of antiferments to the normal enzymes of the organism are normally present in the organism; an antirennin, or antirennins, have been isolated from normal blood, and of particular interest is the discovery of Weinland[7] that the cells of the gastric mucosa contain antipepsin, amplified by Pollack's[8] determination that pancreatic extract similarly contains an antiferment against the digestive action of the pancreas. Here we have gained at last the needed explanation why the digestive organs do not digest themselves.

So, also, it has to be noted that there are certain common enzymes of the organism against which, so far, observers, by injection of these ferments, have been unable to obtain anti-ferments. If *fibrin ferment*, for example, be inoculated into an animal, no antifibrin ferment is produced—only precipitins; although Bordet has brought forward evidence that the inoculation of *fibrin-containing* blood into another species of animal stimulates the production of an antibody. No

[1] Fortschr. d. Med., 20: 1902: 425.

[2] Ann. de l'Inst. Pasteur, 15: 1901.

[3] Hofmeister's Beitr., 2: 1902.

[4] Zeitsch. f. Hygiene, 48: 1904: 457 and Deutsch. med. Woch., 30: 1904: 308. 1904.

[5] So far, to our knowledge, there are no adequate studies upon the upper limit of development of antibodies in relationship to enzymes which, in their activities, are foreign to the animal body (as are the toxins).

[6] Verhandl. d. Deutsch. Pathol. Gesellsch., 1905: 160.

[7] Zeitsch. f. Biol., 44: 1902.

[8] Hofmeister's Beitr., 6: 1904

antipepsin or antidiastase, so far, has been developed. It may be that here some principle is in action, as already suggested, inhibiting the development of antibodies to ferments which are widely distributed throughout the organism; for peptic and diastatic ferments, it must be remembered, are not developed by the gastric and salivary glands alone, but, as shown by the results of autolysis, are producible by the cells of all organs, and the same is true of fibrin ferment, as indicated by the process of coagulation necrosis; that just as in normal assimilation the cells are not stimulated to produce antipeptones and anticarbohydrates, so the normal cell enzymes, when absorbed and presented to the cell, set up no antagonistic reaction. The general principle would seem to be that molecules which afford particular side-chains are not stimulated to produce these in excess in the presence of free side-chains of the same order: still less does that presence stimulate them to produce antibodies to their normal side-chains. We thus are not inclined to lay great weight upon the distinction between normal ferments and toxins, more particularly when we recall that, as in tuberculosis, a similar lack of reaction, or imperfect reaction, may present itself toward bacterial products.

To this matter of the parallelism or identity between enzymes and toxins we shall return later, when we have noted the data bearing upon the production of antitoxic bodies proper. We shall leave until then the discussion of the action of enterokinases, etc.

Toxins and Antitoxins.—That certain bacteria produce diffusible, poisonous substances, or toxins, was noted very early in the study of bacteriology; indeed, even before specific forms of bacteria were distinguished, it was observed that putrefying material afforded substances like Panum's sepsin, which were intensely toxic; and when Koch introduced the method of growing pathogenic bacteria upon solid media, and the solution of gelatin was found by Fermi and others to be due to proteolytic enzymes, it was natural that observers should conclude that the toxic action of bacteria in the body was due to a similar excretion or diffusion out from the bodies of bacteria of ferment-like substances.

We now know that, *in vitro* at least, and probably, also, in the body, this diffusion out of toxins by living pathogenic bacteria is the exception, and not the rule. Nevertheless, a very important step forward was made when Roux and Yersin studied the diffusible toxins (exotoxins) of the diphtheria bacillus, and Brieger (though less thoroughly) those of the tetanus bacillus. The toxins of both of these organisms were discovered to be of extraordinary virulence, or to have intense toxicity. By no means could they be gained in a pure state. Nevertheless, the impure precipitate gained, for example, by salting out, or precipitation by phosphates, and present in only minute amounts, was found so powerful that with the diphtheric toxin 0.0002 mg. would kill a guinea-pig of 250 grams within three days.

At a relatively early date (1887) it was shown (by Salmon and Smith) that such diffusible toxins inoculated into animals would produce

immunity, but the most notable advance was made when, in 1890, Behring, with his colleagues, Kitasato and Wernicke, demonstrated that when such immunity was produced, the blood serum of the immunized animals contained substances which would neutralize the diffusible toxins, and so discovered the *antitoxins*, proving, further, that *such immune serum injected into animals suffering from either tetanus or diphtheria would in them neutralize the toxins and induce a condition of passive immunity*. The more intimate studies upon the development of protective substances by the organism date from this discovery. It became necessary, in the first place, to determine with as great an accuracy as possible what was the advisable dose of antitoxin to be administered in order to neutralize the toxin; to do this a standard toxin had to be developed. What should constitute the minimal lethal dose had to be agreed upon—the smallest amount which would surely kill a given animal (guinea-pig) of normal size (250 grains) within a given time (four days). We owe to Ehrlich the fullest studies upon this subject and the most important deductions from the data obtained in these studies.

Behring had noted that outside the body in the test-tube the antitoxin acted upon and neutralized the toxin. (Like observations had also been made by Kanthack,[1] for snake venom and its antitoxin, and by Denys and Van der Velde[2] for leukocidin (the leukocyte-destroying substance obtained from cultures of pyococci), and by Ehrlich for ricin and antiricin.) Now, Ehrlich established clearly that this action *in vitro* follows the laws regulating the formation of double salts: (1) If an amount, x, of a particular antitoxin solution neutralizes an amount, y, of a particular toxin in a given time, then $3x$ is requisite to exactly neutralize $3y$; (2) the higher the temperature (below the limits beyond which the antitoxin became inert) the more rapid the reaction; and (3) the reaction proceeds more rapidly in concentrated than in dilute solution. Obviously, while the formation of antitoxins is a vital process, the reaction between these and the toxins is purely chemical, occurring outside as well as within the organism. These conclusions were confirmed when Martin and Cherry and Brodie demonstrated, by their filtration experiments, that, whereas toxin alone will pass, as the latter showed, through gelatin filters under high pressure, there is no passage when they have been acted upon by antitoxins, *i. e.*, they have undergone combination with the same.

Toxins.—What, then, are toxins? Unfortunately, no precise definition would appear to be possible. To describe them, as is often done, as poisons against which it is possible to gain immunity by means of antibodies, is to include under this term a very large number of different substances—bacterial products, venoms of various animals, animal

[1] Jour. of Physiol., 13, 1893. (Continental writers are apt to pass over without due recognition this important and early observation of Kanthack.)

[2] La Cellule, 1896.

cell substances, sundry vegetable poisons and enzymes as a body, whether of animal or vegetable origin. It seems difficult, however, to approach any clearer definition, and, for practical purposes, this is adequate. If we attempt to characterize them more closely, we note: (1) that they are, one and all, the products of cell metabolism; (2) that they act in most minute doses; (3) that they diffuse with difficulty; (4) that [illegible] not one of them has surely been obtained in a state of purity.

We are accustomed to regard all these bodies, if not as proteins proper, nevertheless as closely allied thereto. It must be remembered that the evidence here is presumptive and far from being positive. Like proteins, they are of colloid nature, as indicated by their low diffusibility. But as a body they are not absolutely non-diffusible. Nothing like a splitting off of amido-acids can be determined, as with proteins proper. Nor, again, when obtained in a state of relative purity, do they necessarily afford those two characteristic reactions of proteids, namely, the biuret reaction and Millon's test. But, on the other hand, they act in such extraordinarily small amounts, that to gain from them recognizable amounts of amido-acids would be beyond the scope of the chemist; and the same is true of the two reactions above noted. For these tests a certain minimum of material must be present; with the toxins, it may well be that we are below that minimum.

On the whole, although we have to admit that the evidence is far from complete, it is most satisfactory to regard the toxins, and particularly the bacterial exotoxins, as cleavage products of protein metabolism, and as approximating in their nature to primary, non-polymerized, protein molecules. In favor of this view are the observations of Arrhenius and Madsen upon the rate of diffusion of toxins compared with salts and (definitely proteid) antitoxins, in which it was found that the former occupy a position between the latter two; their molecules are thus evidently larger than those of crystallizable salts, but smaller than those of the ordinary proteins.

But Arrhenius and Madsen[1] were dealing only with exotoxins—diffusible toxins; their observations do not apply to the less diffusible endotoxins. And here we encounter identically the same problem regarding chemical constitution that we noted with the diffusible extracellular, and the non-diffusible intracellular ferments, so that, taking merely bacterial toxins as a body, it is extremely doubtful if we are justified in regarding them all as cleavage products. It appears to be a sounder course not to speak of *toxins*, as a whole, as a specialized group of chemical substances, but of *toxin action*, and the capacity to elicit the production of antitoxins as a property of the protein molecule and of sundry of its dissociation products. Toxin action, that is, may be regarded as a form of enzyme action which may manifest itself either in

[1] Festchr. z. Eröffnung d. Serum Instituts, Kopenhagen, 1902.

connection with large and complicated protein molecules or with molecules dissociated from the cell, so few in number and so small (relatively to the complete protein molecule) as to render chemical detection difficult. Nay, it may well be that the almost constant association of "toxins" with albuminous matter is an indication that the toxin action is a property of this albuminous matter which may still be retained by certain molecules, the products of dissociation of the same, when an attempt is made to separate toxin from albumin.

It is our duty to point out that this is not the usually accepted view; it is almost universal to regard toxins as a particular class of *chemical* substances and to neglect the consideration of toxin action as a *physical* property of matter, having a particular molecular arrangement. This view, it will be seen, includes all the phenomena of immunity as coming under the heading of enzyme action and the reaction of the same.

Not to confuse the reader, we will, however, continue to speak of toxins and describe their properties in the accepted way. In the succeeding paragraphs it will be the toxins in the narrower sense —the bacterial exotoxins—that we have mainly under consideration. Inoculated into the blood of an untreated animal, these disappear with relative rapidity; in some cases, three or four minutes after inoculation the blood is found innocuous. This, in the non-immunized animal, is not due to any process of neutralization occurring in the circulation, but to an absorption by the cells of various tissues, and by the leukocytes. That this is so can be determined by making extracts from the various organs. Doing this, the organs become separated into two classes. If, for example, as Ransom[1] pointed out, tetanotoxin be employed, while the blood loses its toxicity, extracts from all the organs, with one exception, are found toxic. That one exception is the brain and nerve matter. Wassermann and Takaki[2] found that, while less was true of man, the horse, and the guinea-pig, in the rabbit the liver and spleen manifest the like properties. This does not mean that none of the tetanotoxin has been taken up by these three organs, but the very reverse. In all the other organs the absorbed toxin is in loose combination, and can easily be separated; it is, at most, "adsorbed." In the nervous tissue (more particularly the gray matter), and in the rabbit's [illegible] and spleen, it enters into intimate combination, and cannot be [illegible]d. The combination, as shown by the last two observers, [illegible]clantly confirmed, can be demonstrated outside the body, [illegible] substance is found to completely neutralize tetanus toxin added [illegible] in definite proportions, the emulsion being without effects when injected into other animals. And, as Milehner has shown, if such a mixture, properly made, be centrifugalized, the supernatant, clear fluid is wholly free from the toxin, which is not the case when kidney or other organ of the guinea-pig is employed. Flexner and Noguchi[3]

[1] Zeitsch. f. Physiol. Chem., 31: 1901: 282.
[2] Berl. klin. Woch., 35: 1898: 5.
[3] Jour of Exp. Med., 6: 1902: 277.

have shown the occurrence of this same binding of the neurotoxic component of snake venom with brain matter.[1]

We call attention to these joints because everything indicates that *it is those cells and tissues which anchor the toxins that eventually develop the antitoxins.* The mere loose adsorption of the toxin is not sufficient for this purpose.

Here Metchnikoff[2] has recorded a very important observation. The tortoise is uninfluenced by tetanus toxin, and after inoculation it is found that none is found in its brain or other organs, and no amount of injections of the toxin will in it produce antitoxins. The alligator, while similarly showing no nervous effects upon inoculation, is found to have the toxin bound in certain organs, *but not in the nerve matter*, and in it successive inoculations lead to abundant antitoxins appearing in the blood. Ford[3] has, by other methods, demonstrated that antitoxin production only occurs in individuals whose cells have the specific power of binding the toxin.

For specific antitoxins to be produced, there must first have been a direct union with, and action upon, the cell substance on the part of the toxin. As Ehrlich points out, alkaloids only enter into the looser combination, and to this is to be attributed the non-formation of anti-alkaloids. With Wassermann, we can in this respect compare alkaloids and toxins to saccharin and sugar. Both act on sundry cells and give the sensation of sweetness; the latter only undergoes assimilation.

The observations of Metchnikoff demonstrated clearly that to stimulate the production of antitoxins it is not necessary that the toxins so act upon the cells as to set up the symptoms of disease. Ehrlich has, indeed, shown that by subjection to heat and other methods the diphtheria toxin can be so modified that its toxic action is greatly lowered or entirely lost; it may be rendered quite harmless, and yet, inoculated, such modified toxin leads to the development of antitoxins. The existence of these modified toxins, or *toxoids*, and their capacity to induce immunity afford proof that the toxin molecule consists of at least two subordinate groups—one that anchors the toxin on to the cell substance, the *haptophoric* group of Ehrlich's terminology; the other, the *toxophore*, which, when present, so influences the cell activities as to set up toxic disturbances.

A further proof of the existence of these two constituents has been afforded by Morgenroth.[4] He took three frogs and injected tetanus toxin into them without obvious effect, for at ordinary temperature

[1] This same binding with specific cells has been abundantly proved as between the red blood corpuscles and "toxins" which lead to hemolysis—tetanolysin, staphylolysin, ricin, snake venom, etc. Sachs found that spider venom (arachnolysin), which has no action on guinea-pigs' erythrocytes, remained in solution on centrifugalization, but, added to rats' erythrocytes (which it destroys), the supernatant fluid, upon centrifugalizing, was free from it.

[2] Traité de l'immunité, Paris, 1901.

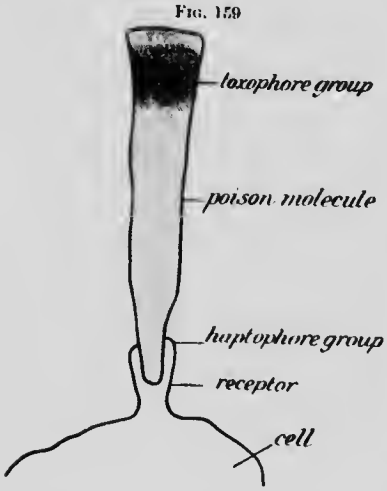
[3] Zeitsch. f. Hygiene, 40; 1902; 363.

[4] Arch. Internat. de Pharmako-dynamie, 1900.

these cold-blooded animals are insusceptible to tetanus. These he kept for three, four, and five days to some weeks in the cold. Had the toxin been still circulating in the blood the subsequent injection of tetanus antitoxin would have neutralized it; had it been excreted, again no symptoms would have developed. But now, upon warming these frogs, symptoms of tetanus appeared. The only possible explanation is that the toxins had become anchored to the nerve cells, etc., and, being so combined, could not unite with the circulating antitoxins. But, if so, then *the haptophoric constituents must unite with the cell substance in the cold, and the toxophoric constituents only become active when the temperature is raised.*

Ehrlich has brought forward evidence of the existence, more particularly in old toxin solutions, of a series of modifications of the toxins: protoxoids, syntoxoids, epitoxoids, and bodies which have little affinity to antitoxins. These last he has termed *toxones.* The active toxins themselves may also exhibit variations in their avidity to combine with antitoxins, and in this way he has distinguished between proto-, deutero-, and tritotoxins.

FIG. 159



The Antitoxins Proper.—Mode of Development.—It is evident from the above that the toxins enter into combination with the cell substance, and as we find that when this combination occurs the toxin becomes neutralized, it becomes most probable that the particular cells in which the toxins become anchored are those which eventually discharge into the blood the substances—antitoxins—which are capable of neutralizing them. The conclusive proof of this local development of antitoxins has been afforded by Römer, not, it is true, with bacterial toxins, but with abrin. This, it has long been known, has a peculiarly powerful effect upon the conjunctiva. By the exhibition of increasing strengths of abrin in the right conjunctiva of a rabbit, Römer[1] gained a local immunity, so that the conjunctiva was no longer sensitive; then, at the beginning of the third week, before this should affect the organism in general, he killed the rabbit, took the conjunctivæ, and triturated each separately with a fatal dose of abrin. The injection of the emulsion from the right (immunized) conjunctiva was without effect; the like injection from the left was fatal. Thus, clearly, the cells which had absorbed the abrin had developed and contained anti-abrin in sufficient amounts

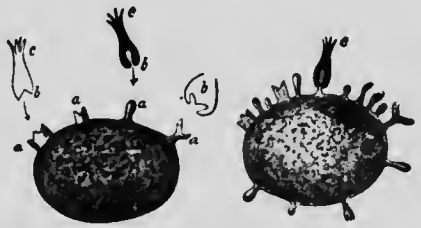
[1] Arch. f. Ophthalmologie, 1901.

to neutralize the poison. And, while there is evidence that certain leukocytes—Metchnikoff's macrophages—play an active part in this development, it is obvious that they are far from being the only cells involved.

How, then, is the antitoxin developed? It used to be thought that there was a direct conversion of the toxin into antitoxin. This certainly is not the case, for the amount of antitoxin is altogether out of proportion to the amount of toxin injected. We have exactly the same continued production of the antitoxins as noted in the case of anti-abrin (p. 465). Knorr[1] has shown that toxic unit in a horse (immunized against tetanus) leads to the production of about 100,000 antitoxin units, and McFarland[2] has made similar observations. *While the toxins stimulate the cells in the first place, it is the cells which assimilate the necessary constituents and build up and discharge the antitoxins.*

The Side-chain Theory.—How are we best to picture the manner in which this is brought about? Here Ehrlich's conception of the process is the only one which seems to be satisfactory. We have already noted

FIG. 160



Cells with various receptors or haptophorous groups of the first order (*a*) adapted to combination with the haptophorous groups (*b*) of various chemical compounds brought to them. It will be noted that there is no mechanism by which the toxophorous elements of the molecules (*c*) can be directly attached to the cell. (McFarland, after Ehrlich.)

that the cell substance enters into relatively firm combination with the toxin, just as it combines with constituents of the foodstuffs in order to assimilate them. We have seen, also, that the toxin possesses a haptophorous constituent which unites with the cell substance, and this whether the toxin is actively toxic or not; or, in Ehrlich's terminology, whether it possesses an active toxophorous constituent or not. Now, if we predicate these constituents for the minute toxin molecules, the specific matter of the relatively large cell molecule must be very much more complex. If the toxin molecule has its haptophore, whereby it anchors itself on to the cell substance, so we must imagine that the cell molecule has not one but several orders of "anchors," whereby it attracts and combines with itself all the various orders of foodstuffs. The cell molecule, that is, also possesses haptophores, which, in this case, Ehrlich terms *receptors;* and it is to some special order of anchor

[1] Münch. med. Woch., 1898: 321 and 362.

[2] Text-book of Bacteriology, third edition, loc. cit.

that the haptophore of the toxin molecule becomes attached. These receptors, it will be seen from what we have said regarding the constitution of the proteidogenous or biophoric molecule, are *side-chains* (p. 50); and certain orders of unsatisfied side-chains must be regarded as having affinity for, attracting and combining themselves with the toxin molecules. Nay, more, it is with one particular portion of the toxin molecule (the haptophorous) that the combination is effected; these may or may not have a toxophorous moiety. That is not concerned in the act of combination, but, when present, after the combination has taken place, it may so affect the total constitution of the molecule as to lead to grave cell disturbances.

This is the groundwork of Ehrlich's now celebrated "side-chain theory," and up to this point we think our readers will agree with us that the theory is well grounded upon experimental data, and is strictly in harmony with our general conceptions of cell activity. But this simply carries us to the point at which the toxin has become associated with the cell substance. We have simply reached the point at which the toxin, unless too strong for the cell, or unless too many toxins have become joined on to the receptors of a given cell, is neutralized. We may speak of such neutralizing receptors as intracellular antitoxins. Now we have to explain how there is set up a discharge of free antitoxins into the blood, and here it is that, while forced to accept it, we cannot but feel that the theory is deductive, and on less secure ground.

The very fact, as pointed out by Cobbett,[1] that the blood serum of human beings who have never suffered from diphtheria contains a recognizable amount of diphtheria antitoxin would suggest that antitoxins are not primarily specific; in other words, that the cells of the body normally discharge substances capable of combining with and neutralizing diphtheria toxins. To this it may be objected that human beings may be subject to what we have termed "subinfection" with diphtheria. But the same is true also of horses' blood serum (Wassermann[2]); and when, as von Dungern[3] has shown, rabbits' blood serum contains an antitoxin against the poison of starfish eggs, our point becomes established. *There is, that is, a normal discharge into the blood plasma of a large number of potential antitoxins*, of bodies having affinities for one or other toxin, and it is only when these toxins gain entrance into the system that the particular antitoxins become developed in relatively enormous quantities.

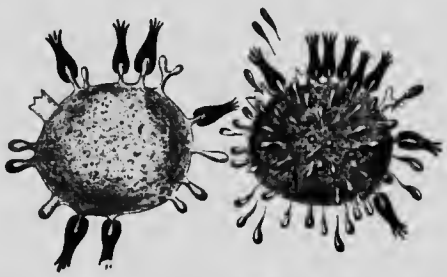
If, with Ehrlich, we regard these as discharged cell receptors or side-chains of particular orders, then we have to assume that the very act of combination of the toxin molecules with the receptors stimulates the cell substance to reproduce more of these particular receptors than are necessary, and that the overproduction is discharged out of the cell. This assumption, it is true, appears to accord strictly with the facts of the case; but we find it difficult to picture the process whereby

[1] Centralbl. f. Bakt., 26: 1899.
[2] Zeitsch. f. Hyg., 19: 1895: 408.
[3] Zeitsch. f. Allg. Physiol., 1: 1901.

this overproduction is brought about. Ehrlich bases himself upon Weigert's law of inertia—the law, namely, that once a cell is stimulated to perform a certain act, it continues to perform that act for some time after the stimulus has ceased to act. But this production of antitoxins continues for a longer period than was contemplated by Weigert, and that law does not explain why the anchoring of the toxin by a particular side-chain acts as a stimulus to the production of new side-chains of the same order.

While offering these criticisms, it must not be thought that we are opposed to Ehrlich's theory; on the contrary, we accept it almost in its entirety; only at this one point it seems to us that the chain of events depicted has some weak links. Ehrlich throughout purposefully speaks in most general terms of the constitution of the cell, and draws no distinction between cytoplasm, paraplasm, and nucleoplasm. He, in fact, leaves it an open matter which portion of the cell is the seat of the changes demanded by his theory. The conception we have given

FIG. 161



Ehrlich's conception of cation of the cell haptophores, or receptors, to compensate for the loss o ralized and removed by the toxin molecules.

of the cell structure (p. 137) leads us to consider that a poison can only interfere seriously with cell activities when either mediately or immediately it tells upon the nuclear biophores. *We would regard a toxin molecule diffused into or absorbed by the cytoplasm not, with Ehrlich, as becoming fixed to the biophore, but rather as detracting and dissociating a side-chain from the biophoric molecule.* The next stage would depend upon the number of toxin molecules gaining entrance to the cell, and, it may be, upon their ferment-like activity. An excessive number would lead to such a dissociation of the biophoric molecules as to entail biophoric dissolution and cell death. *The known facts regarding the extraordinarily minute, unmeasurable quantities of toxin capable of causing death of relatively large animals leads us to believe that* ferment action *must play a part; namely, that the toxin molecule, having dissociated one side-chain, becomes liberated from this and free to dissociate another side-chain, until, dissociating the biophore more rapidly than that can build itself up, it causes dissolution of the same, and cell death.* Along these lines the difference between toxins and alkaloids, and other

cell poisons which can readily be dissolved out of the cell, is that the latter, if they set up cell disturbances, do this by a single act of union and dissociation, the latter by the repeated enzyme-like attraction and dissociation of side-chains from the cell molecules. So far as they go, the histological appearances of the nuclei—of the brain cells, for example, in cases of tetanus—are in favor of such nuclear dissolution.

Where, on the contrary, the action is not so intense, the dissociation of a side-chain by a toxin molecule is followed by the building up or assimilation by the biophore of another to replace it. Here, also, to explain subsequent events, the toxin molecule must be regarded as endowed with enzyme-like properties. The loss of a single side-chain cannot, no more than any other momentary stimulus, set up the habit of manufacturing side-chains in excess of the needs of the individual cell; but if for some little period that molecule is dissociating side-chains of a particular order, but these are reformed more actively and in excess of the rate of destruction, it appears to us possible to realize the gradual development of a habit of production and casting loose of these side-chains which shall continue long after the primary stimulus has ceased to act. That toxins in a potentially active state may remain in the cells for weeks is demonstrated by Morgenroth's observations upon the tetanotoxins in frogs, to which we have already referred[1] (p. 471). The diagram opposite gives more fully our conception of the way in which the toxin acts in this respect.

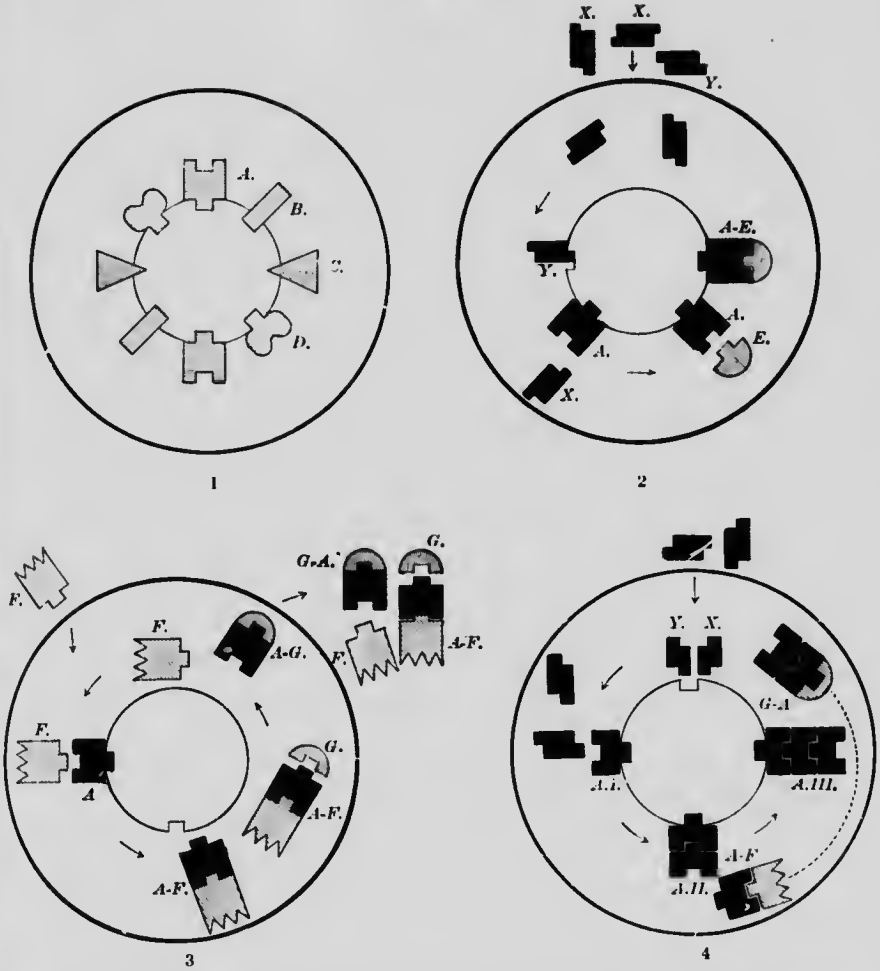
It is, we would emphasize, *the continued existence of the toxins for some little time within the cell, but not as a part and parcel of the biophoric molecules, that best satisfies the conditions of the case, i. e.*, the development of the habit of side-chain, receptor, or antitoxin production. And these, developed in excess of the needs of the cell, become discharged into the circulating medium.

On the Nature of the Union of Toxin with Antitoxin.—While, as we have pointed out, these two become united, the union is not of such a nature that the two components undergo modification in the process. We can, that is, by the employment of appropriate means, recover or separate one, at least, of the constituents without loss of its original properties. Thus, with pyocyaneus toxin-antitoxin (Wassermann), or snake venom toxin-antitoxin (Calmette), if the compound (in solution) be heated up to a certain point, the antitoxin is destroyed, and the mixture regains its toxic properties.[2] There is, further, a series of observations to the effect that a combination of toxin and antitoxin which

[1] Along the lines here indicated Morgenroth's observations are capable of explanation, not so much as evidence of the existence of haptophores and toxophores (though they afford this also), as of persistence of the active poison within the cells, which poison is only able to manifest its results when, by abnormal temperature conditions, the cell metabolism and side-chain production is so lowered that now the toxin gets the upper hand.

[2] But, as a general rule, it must be noted that toxins are more sensitive to heat than are antitoxins; heating such more sensitive toxins, they are apparently converted to toxoids, which still remain attached to the antitoxins.

FIG. 162



The author's conception of side-chain and antitoxin production. 1. The biophoric molecule situated within the cell, and possessing side-chains of various orders, *A*, *B*, *C*, *D*. 2. Mode of formation of side-chains. Free molecules (*X*, *Y*) diffuse into the cell (or are produced within the cell by dissociation of more complex molecules, also absorbed): these are attracted by an unsatisfied affinity of the biophore, and are built up by it to form the side-chain *A*. Such side-chain, when formed, may become satisfied by attracting to it other (foodstuff) molecules, such as *E*, having the right order of haptophorous grouping. It is conceivable (but not shown in the diagram) that molecules of the *E* order may not merely satisfy the side-chain, but detach it so that the compound *A-E* becomes free in the cytoplasm, or discharged from the cell (active katabolism). 3. A toxin molecule *F* diffusing into the cytoplasm has a stronger affinity for the side-chain *A* than has the biophore, combines with it and detaches it. But when detached and free in the cytoplasm other molecules (*F*) present in the cytoplasm have now a stronger affinity for the *A* moiety of the compound *A-F* and combine with it, liberating the toxin moiety *F*, which again becomes free in the cytoplasm and capable of dissociating another side-chain *A*. Or the compound *G-A* may become discharged from the cell (circulating antitoxin), and then in the altered surroundings the intracellular toxin molecules *F* may exert the greater affinity and joining with the *A* moiety become neutralized. It is the *G-A* compound, and not the side-chain *A* alone, that constitutes the extracellular antitoxin. 4. In the presence of abundant *X* and *Y* molecules the side-chains *A* become built up in series, and this whether attached to the biophore or free in the cytoplasm, the more there are freed by the action of the toxin, the greater under these conditions will be the production of antitoxins. Thus, the presence of the toxin molecule *F* stimulates the cell to the production of increased numbers of the molecules of the particular side-chain order upon which it exerts specific action.

is absolutely neutral for individuals of one species is fatal for those of another.

This has been explained by Weigert as due to the presence in the blood of the second animal of substances having a stronger affinity for the antitoxin moiety, in consequence of which the toxin becomes set free. Aschoff affords the alternative explanation, that in the first animal (the mouse, for example, treated with a tetanotoxin-antitoxin mixture) tissues other than the nerve cells can combine with the toxin, as, indeed, has been shown to be the case, and that so, with subcutaneous inoculation of what for the mouse is found to be a neutral mixture, there is, nevertheless, an excess of free toxin. If, now, this same mixture be inoculated into a guinea-pig whose other tissues have not this affinity for the toxin, such free toxin is capable of exercising its full effects on the nerve cells.

Of late years several obvious departures from the simple law of the formation of double salts have been noted in the reaction between toxin and antitoxin—exceptions which it is difficult to explain adequately. We shall not here mention all, but would refer to Jacobi's conscientious discussion of the subject. Of these, the most remarkable is Danysez's phenomenon, first noted with ricin, and later found to obtain with a great number of toxins by von Dungern[1] and Sachs.[2] If the amount of toxin has been accurately determined which, added to a given amount of antitoxin serum, completely neutralizes it, and if, now, half the amount of the toxin only be added, then if, at a later period, the other half be added, the result is not a neutral, but a poisonous, mixture. More antitoxin has now to be added to bring about neutralization.

A possible explanation of this phenomenon is to be found in Ehrlich's recognition of multiple toxins and toxoids. It is not unlikely that in a toxin solution, besides the active toxin proper, having the greatest avidity for antitoxins, there are present toxoids with less affinity, which, when the amount sufficient for complete neutralization is added, do not combat with the antitoxin; when only a fraction of that amount is added, are taken up by the unsatisfied antitoxin molecules. By this means, when further toxin solution is added, the molecules cannot find adequate antitoxin molecules with which to unite.

An enzyme-like action on the part of the toxins would also explain the phenomenon. We freely admit that, observing in general the remarkable obedience of toxin-antitoxin mixtures to the law of multiple proportions, it would at first sight appear that toxins do not act like ordinary ferments. Nevertheless, as we have already shown from Morgenroth's observations, in relationship to antibodies, ferments do obey this law; a given amount of antirennet serum renders inactive a fixed amount of rennet solution. More suggestive of enzyme action is Behring's[3] observations that if a mixture of tetanus toxin and anti-

[1] Deutsch. med. Woch., 1904: 275 and 310.
[2] Centralbl. f. Bakt., 37: 1904.
[3] Beitr. z. Exper. Therapie, 1904: 7.

toxin be taken in which the toxin is in excess, there is a marked increase in toxicity when the mixture is diluted with water. This, as Jacobi indicates, suggests hydrolytic dissociation.

In general the law of multiple proportions is strongly in evidence, *i. e.*, if 10 volumes of antitoxin neutralize 100 of a toxin solution, 100 volumes of antitoxin are found to neutralize 1000 of the same toxin. The combination, however, is not immediate; while it is relatively rapid with diphtheria, in tetanus preparations it is slow, requiring often some hours; the age of the antitoxin preparations also introduces variations in rate.

On the Action of Antitoxin upon Toxin within the Organism.—We cannot leave this subject without discussing the mode in which antitoxins introduced into the organism bring about the cure of infection. Experimentally, we find that the smallest amount of antitoxin is required, and the least evident disturbance of the organism occurs, when toxin and antitoxin are introduced simultaneously; and here, again, least of all when the two have been in contact for some period.[1]

When symptoms are already present, much larger quantities are required, and when the disease has been active for some days, no amount of antitoxin will arrest the fatal result. But, as just stated, the antitoxin can, under certain conditions, arrest the disease, even when symptoms are present, and when clearly the toxins have already gained entrance into the cells. These, indeed, are the conditions under which diphtheria antitoxin is most often employed in practice, with brilliant results. It is evident, therefore, that the antitoxins can act upon toxins which already have become bound in the cell, but that, just as with the lapse of time the toxin *in vitro* becomes more and more firmly bound to the antitoxins, so in the cell *in vivo* there is a similar increasingly firm anchoring of the toxin to the receptors, until eventually the free antitoxins introduced from without are unable to loosen the union. That this is so is confirmed by several observers of the phenomena of so-called "cure *in vitro*," as observed in connection with hemolytic agents. For a certain period it is found that the addition of an antihemolytic serum to blood corpuscles which have absorbed hemolysins will remove and neutralize these "toxins," but with longer interaction the "antitoxin" is without effect.

This very fact that foreign antitoxins entering the cell can arrest the infective process appears to us to support our contention that the toxins, at a time when they are already setting up active cell disturbances, *are not in direct combination with the biophores, but are acting upon them from without*—in the cytoplasm. We would conceive antitoxins intro-

[1] Thus, as Wassermann has demonstrated, if a fresh neutral tetanus toxin-antitoxin mixture be introduced subcutaneously, symptoms of the disease will, nevertheless, manifest themselves if the animal has, beforehand, been treated with adrenal extract. That, by contracting the arteries, prevents the absorption of the antitoxin by means of the circulation, and the toxin is still able to make its way to the higher centres along the nerves. If the two have been in contact for two hours previously, no symptoms show themselves.

duced into the system as: (1) neutralizing any free toxin molecules in the circulating fluids of the body, and so preventing their action upon the cells, and (2) as gaining entrance into the cells, and there not so much acting directly upon the toxin molecules present (for those are already combined) as affording to the biophores that excess of side-chains necessary to build them up again and to neutralize the toxin molecules should they become temporarily free—as, in short, affording to the cell physiological rest, together with the particular assimilable matter which has been used up by the activity of the toxin.

CHAPTER VIII.

IMMUNITY—(Continued).

If enzymes cause reaction and, under certain conditions, the development of antibodies which neutralize their action, it becomes probable that other diffusible cell products, and more particularly those of an essentially organic nature and proteid type, will be found to have the same properties. And this, as a matter of fact, has been found to be the case.

PRECIPITINS.

The first discovery of these bodies was, it is true, not the simplest example. If, as pointed out by Kraus,[1] in 1897, one inoculates an animal with fluid cultures of typhoid, cholera, or plague bacilli, and then, after some days, gains some of the blood serum of that animal and adds a little to the germ-free culture fluid, a specific precipitate appears in the mixture. The same results appear when the fluid of growth *minus the microorganisms* is used for inoculation. We know that is the proteid substances present in the broth which cause the reaction, whether these become modified in particular directions, by the growth therein of the particular bacteria, and in part, perhaps, have been excreted by those organisms, or whether they are unaltered, for simple broth will bring about a like result. Through the inoculation of these constituents of the broth antibodies are developed and appear in the blood, which, combining with the bodies present in the culture fluid, cause a precipitate. Such antibodies, first known as *coagulins*, are now grouped together as *precipitins* and of them a large number have been developed by treating (injecting) animals with protein-containing fluids of various orders, and, these not merely of animal, but also of vegetable origin—milk, horse serum, eel serum (Bordet[2] and Tschistovitsch), egg albumin (Meyer), globulin from sheep and ox blood, peptones (Wassermann), human blood serum (Uhlenhuth), albuminous urine, pleural exudate, etc. (Mertens, Leclainche and Vallé, and others), muscle albumin (Schütze), serum albumin, pseudoglobulin (Ide), casein and milk albumin (Hamburger), vegetable albumin (Schutz), wheat, rye, and barley albumoses (Kowarski).

And these are to a large extent specific; thus, to give simple examples,

[1] Wiener klin. Woch., 1897: 736.

[2] Ann. de l'Inst. Pasteur, 13: 1899. A full study of the literature is afforded by Nuttall, Journal of Hygiene, 1:1901: 367, and of the whole subject of blood precipitation, in his Blood Immunity and Blood Relationship, Cambridge, 1904.

the blood serum of an animal treated with wheat albumose will cause a precipitate in a solution of wheat albumose, but none in solutions of rye or barley albumoses, and, as Bordet showed, the serum of rabbits treated with cows' milk will cause a precipitate in cows', but not in goats' milk,[1] and several others have shown that the serum of rabbits injected with human blood will cause a heavy precipitate in human blood serum, but none in goats' or dogs' blood serum. Here, indeed, we possess an excellent medicolegal method for detecting the presence of human blood. Certain precautions, however, as pointed out by Nuttall, have to be taken into account. The specificity, as, indeed, might be expected, is not complete; the more nearly allied two animals are the greater the probability that their proteins of one or other order will be of closely similar constitution and lead to the production of allied antibodies, and this is found to be the case. Grünbaum has shown that the precipitins developed by injecting into other species of animals the blood of the gorilla, chimpanzee, and ourang-outang will each of them cause precipitates in the blood serum of all three species of ape *and in that of man*, although they are without effect upon the blood sera of lower animals. Conversely, as indicated by Nuttall, if a given precipitin leads to precipitation in a series of bloods from different animals, it is an evidence that they are "of the same blood" and genetically closely allied, and these data of Grünbaum are to be accepted as new and convincing evidence of the consinship between man and the higher apes. A like common reaction is found in the blood sera of different species of birds, amphibia, reptiles, etc.

While this is the case, it has to be emphasized that *the precipitation is most marked with the homologous serum, i. e.*, with the serum of the species against which the proof animal was inoculated, and if this precipitin-containing serum be diluted, a point will be reached at which it will still react in a given time with the homologous serum, but not with others. And, indeed, as showing that there are even differences in the constitution of the proteins of individuals of the same species it has been repeatedly noted that the reaction is most complete with the blood or other protein-containing fluid of the *individual* animal that has afforded the material for inoculating the proof animal.

We see, also, another order of allied phenomena, indicating that the different proteins of the one individual have certain constituents in common, so that the precipitin developed by inoculating the one protein is capable of associating itself with, or acting upon, other proteins, although, again, not to the same extent as it acts upon its specific protein. Thus Besredka has found that the serum gained by injecting animals with *cell-free blood serum* will, added to blood, cause *hemolysis*, *i. e.*, will act on erythrocytes, liberating their hemoglobin. So, also, the serum of rabbits, injected with human muscle albumin, is intensely hemolytic. And, we may add, this action of the red corpuscles is

[1] As pointed out by Moro, Wiener klin. Woch., 1901:1074, the specificity here is not complete.

extremely common on the part of the sera of animals injected with cells of various orders.

The Nature of the Precipitate.—When we come to inquire what are these precipitins, and what the substances precipitated by them, we meet with difficulties. We know so little regarding the inner constitution of protein bodies. Thus, to take the latter question first, it is generally held that the *precipitable substance* is the main proteid constituent of the fluid used for purposes of injection; the resulting precipitate is so large—the amount of casein precipitated, for instance, when milk has been used to develop the precipitin, is very considerable; and when we use what we regard as a simple protein, egg albumin, or globulin from the blood, the precipitin acts specifically upon these substances. Thus, what we may term the common-sense view is that these particular proteins are specifically acted upon. The critical, or hypercritical, view is that we know next to nothing about the constitution of proteins, and that there may be an intermediary *tertium quid* produced which, in its fall, brings down with it the bulk of the protein.

Jacobi instances as a parallel the case of ricin, which, added to blood, precipitates the corpuscles, so that the fluid becomes quite clear, the ricin having no action upon the hemoglobin, but upon the stroma of the red blood corpuscles. The illustration appears to us far-fetched; we fail to see how, under the circumstances, the ricin if it acts upon the stroma of these corpuscular elements, could do anything else. Welsh and Chapman's[1] argument is more weighty: that it is not the test protein that supplies the main bulk of the precipitate, but the antiserum. Quantities of the test protein many times too minute to yield an appreciable precipitum with ordinary proteid precipitants may yield distinct precipitates with the specific antiserum.

Let us admit that in the fall of the main protein other substances, including other proteid bodies, are apt also to be brought down;[2] whether linked to the precipitable substance, or directly acted upon by the precipitin, or as a purely mechanical matter, we cannot, in most instances, state with sureness. The sensible view, undoubtedly, is that the precipitin acts directly upon the main constituent of the precipitation. This view demands, it is true, that we admit the existence of an enormous number of proteid bodies; that, for example, the globulins in the blood of different species are distinct bodies, for otherwise the specific action of the precipitin on one particular serum becomes inexplicable. But this we are already prepared to admit; the widely different percentage composition in C, H, N, O, etc., gained by the various observers who have analyzed hemoglobin, has already shown us that this must be the case. What is true of hemoglobin is likely to be true of other proteins.

[1] Proc. Roy. Soc. B., 78: 1906: 297.

[2] Thus, Delme and Hamburger have shown that a precipitin developed against horse serum will, if added to the serum of a horse immunized against toxins, bring down the antitoxin along with the serum proteids.

As regards the *precipitins*, these resemble, in properties, the other antibodies producible in blood serum; they can be precipitated by various reagents, can be isolated from the bulk of proteins present in that serum by fractional precipitation, *i. e.*, by adding successive increments of ammonium sulphate and filtering off the successive precipitates that show themselves, the precipitins being brought down along with certain globulins within certain narrow limits, can be redissolved, along with these globulins, and so on. Here a like question presents itself: Are these particular euglobulins, or pseudoglobulins, the precipitin; in other words, is the precipitating property a function of the modified globulin (for the two cannot be separated), or are we to regard the precipitin as a distinct chemical entity, brought down at the same time as the globulin? The fact above noted, that the two cannot be separated, again renders the former the more direct and practical view, the one that should, provisionally, be accepted. But here, also, the indications are that we must admit the existence of a multiplicity of these modified globulins, and that even in the one blood serum more than one of these proteins may be developed possessing these powers of precipitating.[1] These globulins appearing in the blood serum of the inoculated animals, it must always be kept in mind, appear there as the result of cellular reaction and activity, and, if different orders of cells coincidently take up the inoculated material, there is nothing improbable in their reactions varying and in their discharging into the blood bodies—precipitins—showing some variation in constitution.

Lastly, we may note the existence or possibility of development of *precipitoids* corresponding in properties to the *toxoids* and of *anti-precipitins*.

AGGLUTININS AND AGGLUTINATION.

Gruber and Durham[2] were the first to make a special study of the phenomenon of agglutination, which has previously been noted cursorily by Metchnikoff,[3] Charrin and Roger,[4] Pfeiffer,[5] and several others who had made growths of bacteria in the serum of immunized animals. In June, 1896, Widal published his paper, in which he showed that, during the course of an attack of typhoid, the blood serum of the patient acquires the power of clumping typhoid bacilli to which it is added. Already, in March of the same year, Grünbaum, working under Gruber, had observed this phenomenon, and but for an unfortunate delay in the publication of his paper, for which he was not to blame, what is now known as the Widal reaction would have been

[1] This has been conclusively demonstrated by Pick, Beitr. zur Chem. Physiol u Pathol., 1: 1901: 351 and 445, and coincides with Durham's observations upon agglutinins, to be presently noted.

[2] Münch. med. Woch., 43: 1896: 285. [3] Ann. de l'Inst Pasteur, 5: 1891: 473

[4] Compt. rend. Soc. de Biol., 1889: 667.

[5] Pfeiffer and Issaeff, Zeitsch f. Hyg., 17: 1894: 355

known by his name. As it was, Gruber had already, some months prior to Widal's publication, announced the general principles of the method. The test should, therefore, be known as the Gruber-Widal, or the Grünbaum-Widal.

Agglutination consists in the clumping of free bacteria suspended in physiological salt solution, or broth, when there is added to the same some of the homologous serum—*i. e.*, serum of an animal which has been inoculated with bacteria of the same species. With this clumping, the bacteria, if previously motile, become motionless. The reaction is obtained with a great number of pathogenic bacteria—typhoid, coli, dysentery, tuberculosis, pyocyaneus, plague, anthrax bacilli, cholera spirilla, pneumococci, streptococci, pyococci, etc. It is specific to this extent that, *with relatively high dilutions of the homologous serum, the specific bacteria* alone *exhibit clumping;* non-specific, to the extent that, with more concentrated serum, bacteria of allied species may also exhibit agglutination. Such specific agglutinins may be present in the blood serum, not merely during an infection, but for months, and even years, after, though the statement is made that, unlike antitoxins, as a result of removal by bleeding they are not readily reproduced. The reaction may be followed under the microscope, but is more easy to follow by the naked eye, by observation of the gradual flocculus formation and sedimentation, whether in pipettes, long tubes, or watchglasses. Only with concentrated solution is it of rapid development; toward the upper limit of dilution it shows itself slowly. Most English and Continental observers recommend the use of the unaltered homologous serum, as permitting more exact dilution. For diagnostic purposes, the dry method elaborated by our late colleague, Wyatt Johnston,[1] after Widal had shown that the agglutinins are unaltered by drying, has, throughout North America, been found to give equally accurate results.

The Properties of Agglutinins.—Here it is not our purpose to enter into the fine details of the process of agglutination; these will be found carefully recorded by Ewing, Cabot, and other writers upon the blood and its properties. Our object is to note the main facts bearing upon the agglutinins in their relationship to immunity, and to the other bodies now under discussion. They are, relatively, highly resistant bodies, withstand drying for many months, even when freely exposed to the air, are little affected by light or putrefaction; the majority, in a moist condition, can be heated to 62° C. without loss of properties, although some (*e. g.*, tuberculosis agglutinins) are rendered inactive at 56° C. Like the antitoxins, they may be present in normal serum. Thus, normal human serum has been found, when concentrated, to cause agglutination of many bacteria—B. coli, B. typhi, B. pyocyaneus, Spp. choleræ, and *danubicus*, and pyococci. Even when diluted thirty times, it may clump the typhoid bacilli; or,

[1] Centralbl. f. Bakt., 21: 1897: 523; Brit. Med. Jour., 1896: ii: 1629, and Johnston and McTaggart, Montreal Medical Journal, 25: 1897: 709.

one hundred times, the pyococcus aureus. And the same is true of animal sera. In general, fœtal blood, and, indeed, that of healthy children under seven years, has very feeble agglutinating powers, a fact which would suggest that processes of subinfection play some part in the development of these normal agglutinating powers. Clumping is produced both with living and dead bacteria, and can be developed in the blood serum by the inoculation of dead cultures. As shown by Stäubli,[1] the sixteenth part of an agar culture of the typhoid bacilli suffices, when injected, to cause the appearance of relatively abundant agglutinins, and J. McCrae,[2] in our laboratory, was able to obtain their production even when the bacilli were enclosed in celloidin capsules. Other observers have gained agglutinins by feeding animals with the homologous bacteria, without setting up obvious infection. By inoculation of cultures, the agglutinating power of the serum can be so increased that, in dilutions of 1 in 1,000,000, Van der Veldt[3] gained clumping of B. typhosus; and with 1 in 2,000,000, Durham[4] was able to "clump" the B. coli.

In general agglutinins show evidence of development in from three to six days after the first injection; after this they increase with considerable rapidity. McCrae found that after removal of the celloidin capsules they rapidly disappeared from the blood, and it may well be that the cases which have been noted, particularly with typhoid, in which they have been present a year or more after injection, are cases of latency of the bacilli within the organism, for the existence of "typhoid carriers" is now well established. Their mode of disappearance is not wholly understood. They have repeatedly been determined in the milk of nursing mothers, and have been detected in the tears. This would point to their excretion; there is a certain amount of evidence that they undergo destruction in the liver and spleen, but the observations upon their presence in the urine are very discordant.

As to where the agglutinins are formed observations are curiously conflicting. According to some authorities, extracts of the leukocytes of animals injected with one or other microbe afford no agglutinins. Van Anden found in certain cases only that the spleen, bone-marrow, and lymph glands contained more agglutinins than did the blood, while others have determined that removal of the spleen has no effect in the production of these bodies, and several observers have throughout found less agglutinins in the organs than in the blood, while Figari and others have brought forward evidence to show that in the intravascular blood (plasma) agglutinins are wholly absent, only appearing with coagulation and in the serum, and yet others have suggested that in the circulating blood there occur free agglutinins, which gain full activity under the

[1] Centralbl. f. Bakt., Abt. 1: 36: Nr. 2.

[2] Jour. of Exp. Med., 5: 1901: 635. The same has been noted by d'Espine and Mallet, Revue Méd. de la Suisse Romande, 1907.

[3] Bull. de l'Acad. Roy. de Méd., Brussels, April, 1897.

[4] Lancet (Lond.), 1898, i: 15.

influence of the oxygen of the air. From this it will be seen that despite very numerous observations, we are still in complete ignorance.

Group Reactions.—Of late years, a very extensive literature has made its appearance upon the specificity of the agglutinins. With regard to Pfeiffer's phenomenon (p. 497), the Berlin school had demonstrated that this was remarkably specific, and at first it appeared that this was true with regard to agglutinins and the Gruber-Widal reaction. Very soon, however, it was found that a serum that would agglutinate the typhoid bacillus would agglutinate also the B. coli—to a less extent, it is true, but, nevertheless, definitely. At first this was ascribed to the existence in the serum employed of normal agglutinins, and the complication it was thought would be overcome by employing high dilutions. To this day there are those like Paltauf, who, save in connection with the B. coli group, would ascribe all aberrant results to the presence of these normal agglutinins. They base themselves upon the strong specificity of the reaction with the different allied species of spirilla and the clear results gained with the plague bacillus.

But when one has personally dealt with sera which will agglutinate two distinct species when diluted in the one case to 1 in 1000, in the other to 1 in 300,[1] dilutions far beyond the limits of normal agglutinins, it is impossible to accept this explanation. The conclusion is inevitable that both the typhoid and the colon bacilli and their allies exhibit what are termed group reactions. With these we must accept with Achard that it is not the agglutination in itself that is specific, but the grade to which it is developed.

The most satisfactory explanation of this "group agglutination" has been afforded by Durham,[2] in his study of the B. enteritidis. According to him, a given bacillus introduced into the system may cause the development not of one, but of several different agglutinins, and some of these may, likewise, be developed when bacteria of other species are introduced. If bacillus I possesses the agglutinogens a, b, c, d, e, stimulating the production of agglutinins A, B, C, D, E, and bacillus II has similarly agglutinogens d, e, f, g, h, causing the production of agglutinins D, E, F, G, H, then, if bacillus I be introduced into its homologous serum, there will be the strongest reaction, but bacillus II will also show a reaction with the same serum, although not so perfect, for although agglutinins A, B, C are unable to influence it, agglutinins D and E can.

We arrive thus at the conception of "idio-agglutinins," or specific agglutinins proper, developed by each species, and common, or group agglutinins which are able to act upon more than one species. In short, agglutinins come into line with what Ehrlich and Morgenroth have demonstrated must be the case with amboceptors and with what has been noted regarding precipitins.

Relationship of the Agglutinins.—Although agglutination frequently precedes bacteriolysis, it is obvious that agglutinins and bacterio-

[1] Adami and Chopin, Jour. of Med. Research, N. S., 6: 1904: 469.

[2] Brit. Med. Jour., 1900 and Journal of Exp. Med., 5: 1901: 353.

lysins are distinct bodies. Both, it is true, are thermostable and both become attached to the bacterial substance, both occur in the blood serum, and are to be found there for some time after infection, but as shown by Pfeiffer and Kolle,[1] bacteriolysis may occur without a sign of agglutination, and after inducing immunity, the blood serum, months ater, may still be strongly bactericidal when it has completely lost the power of agglutinating.

There is, further, as well shown by Evans,[2] no relationship between the agglutination and protective powers of a given blood; the blood of a typhoid convalescent agglutinated at 1 to 500 had a bactericidal value of 5 units, whereas another, which only agglutinated at 1 to 20, had a bactericidal value of 500,000 units. And lastly, as pointed out by Ehrlich and Morgenroth, bacteriolytic action is arrested by subjecting the serum to a heat of 56° C. (which destroys the complements), whereas agglutinins are unaffected by this temperature. This indicates a further difference, namely, that the bacteriolytic amboceptors can only act in the presence of a complement. Nor, although they have many features in common, are the agglutinins identical with the precipitins. Bordet has shown that agglutination can occur without any sign of precipitation.

The Nature of the Agglutination Process.—Of the many views regarding the nature of the agglutination process, that of Bordet is the most acceptable. As the result of the action of the agglutinins, he postulates an alteration in the molecular attraction or tension between the bacteria and the fluid medium. In the first phase of the process there is a junction of the agglutinins with the constituents of the bacterial cell; the second is purely physical, the salts in the medium playing a part in the process. It is, in short, a process of the same nature as the gathering of red corpuscles into rouleaux; in fact, a series of observations upon the agglutination of red corpuscles and other cells have been made which in many respects parallel those observed in connection with bacteria. As Sir Lauder Brunton[3] has shown, if matches (to represent bacilli) or disks of cork (to represent erythrocytes) be covered with hard soap and thrown into water, they float about free and isolated until that water is slightly acidulated, when they immediately draw into clumps. Render the water faintly alkaline, and the clumps, if broken up, will not form again. More recently, Albrecht[4] has demonstrated that red corpuscles, as a matter of fact, possess such a fatty (lecithin) containing surface layer as is demanded in Brunton's experiment, and in ignorance of the latter he comes to a like conclusion regarding the mechanism of agglutination. Through alteration in the physical condition of the environment he concludes that the surface of corpuscles (and bacteria) becomes so modified as to lead to the physical attraction and adhesions of the bodies.

[1] Centralbl. f. Bakt., 20:1896:129.
[2] Jour. of Path., 9:1903:42.
[3] Ibid., 7:1900:53.
[4] Abh. d. Deutsch. Pathol. Gesellsch., 5:1903:7.

IMMUNIZATION AGAINST CELLS. CYTOLYSIS AND THE CYTOLYSINS.

It has long been known that the inoculation of a foreign blood is likely to set up grave if not fatal disturbances, and even the inoculation of the blood of another animal of the same species has been found so dangerous that, recommended in man for a time in cases of grave wasting disease, experience has led to its being given up entirely. Experimentally we find that it may lead to dissolution of the red corpuscles of the host and to intravascular coagulation. We owe to Bordet and his brilliant observations a fuller knowledge of this process of *hemolysis* or solution of the corpuscles, observations that can easily be confirmed and that have led to abundant studies upon the destruction of cells of other nature by the organism; so that now there is abundant literature upon the wider subject of *cytolysis*, and incidentally not a little light has been thrown upon the subject of cell destruction in general within the organism. Bordet showed that if an animal, A, be inoculated with successive small amounts of the blood corpuscles of an animal of another species, B, within a few days (not immediately), upon bleeding A and obtaining some of its blood serum, that serum added to the blood or blood corpuscles of B, outside the body, will cause the dissolution of B's red corpuscles, so that the fluid becomes "laked," or, if inoculated into the vessels of any animal of B's species, will cause an extensive intravascular destruction of the erythrocytes. The inoculation of the corpuscles leads to the appearance in the serum of a *cytotoxin*, or *cytolysin*.

In rapid succession, by a long series of observers, similar cytolysins or cytotoxins were demonstrated as being developed when cells of various organs were injected into an animal of another species. From their free condition spermatozoa soon suggested themselves for such experiments, and Metchnikoff and Landsteiner independently demonstrated the existence of *spermatoxins* (the spermatozoa of bulls being injected into rabbits). Leukocytes were similarly suitable objects, and Metchnikoff, by inoculating polynuclear and mononuclear leukocytes respectively, gained cytotoxins acting specifically on one or other form. These *leukotoxins* are also known as *leukocidins*. Ciliated epithelium was shown to have its cytotoxin (*trichotoxin*), as have kidney cells(*nephrotoxin*), liver cells (*hepatotoxin*), pancreatic, adrenal, and, in fact, every form of animal cell that has been tested. Not only do the sera so gained act on the particular form of cell in the test-tube, but inoculated into the vascular system of animals of the species affording the original cells, the subjects of cytolysis, the cytotoxins act preëminently on the organs containing these particular cells, setting up grave degenerations of the same. Charrin has gone so far as to demonstrate that a hepatotoxin acting specifically upon the liver cells of the goat will pass through the placenta and lead to degeneration and atrophy of the liver of the fœtal kid.

The exhibition of such cytotoxins is most effective when an animal

is inoculated with the cells of a widely different species, but, as shown by Ehrlich and Morgenroth, if the red corpuscles of one goat be injected into another, its serum is capable of laking the blood of other goats, a fact which might perhaps be expected from the clinical observation that the serum of one patient (even without inoculation) may lake the blood of another. There are thus *isolysins* as well as *heterolysins* (lysins active in another species). But it is impossible to develop experimentally *autolysins*, that is, to bring about cell destruction by any method of reintroducing into the organism the separated cells of the one individual, a fact which is parallel perhaps to what was noted regarding the impossibility of gaining anti-enzymes to the common enzymes of the organisms.

Also, it has to be observed that while these cytotoxins are specific to the extent that they act most powerfully upon the one particular cell form through which they were derived, they are liable to have some action on other forms of cells. This is not wholly surprising when we remember that all the cells of the organism have a common origin, and are likely thus to have certain constituents in common. Particularly the liability of cytotoxins in general to induce hemolysis has been often noted.

Here again, by the cautious inoculation of an animal of the susceptible species with progressive small doses of cytolysins, *anticytolysins* can be developed and serum obtained which will neutralize the action of the cytolytic serum.

Bacteriolysins.—We have until now been silent regarding what is quite the most important of this series of cytolysins. Just as inoculation of *animal* cells leads to the production of bodies causing the destruction of those cells, so has the inoculation of *vegetable* cells a like result; *bacteriolysis* and the *bactericidal* activity of the blood serum is of the same order as the cytolysis here described.

The existence of this bacteriolysis was known years before the other cases; but although Bordet's observations upon the cholera spirillum demonstrated the nature of the process it is through his later observations upon hemolysis and through the researches of Ehrlich and his pupils on cytolytic phenomena in general that we have gained our grasp—such as it is—of the phenomena of bacteriolysis in particular. We believe that the student will gain a clearer understanding, if we detail first the main facts regarding the cytolysis of animal cells and then pass on to bacteriolysis.

The Mechanism of Cytolysis.—To repeat Bordet's fundamental experiment: The serum of guinea-pigs' blood has normally very little effect upon rabbits' blood and blood corpuscles; but if a guinea-pig has injected into it rabbits' blood corpuscles its serum becomes in a few days extremely active (such serum is termed *immune*). If now a suspension of rabbits' red corpuscles be taken and have a little of this serum added to it, there results extensive dissolution of the corpuscles, with escape of the hemoglobin and "laking." So as to obviate any complicating appearance of precipitins, we now inoculate the centrifugalized

and washed *red corpuscles* and use a suspension of such washed corpuscles for the test.

But if we warm the G. P. serum to 55° to 60° C., the hemolytic action is wholly arrested. It is usual to speak of such warmed serum as *inactivated serum.*

Now to this mixture of washed corpuscles and inactivated serum add a little blood serum from a normal, untreated guinea-pig or rabbit, and immediately the hemolysis takes place.

Or, briefly:

Normal non-immune G. P. serum + washed R. erythrocytes . .	=	No hemolysis
Active (unheated) immune G. P. serum + washed R. erythrocytes	=	Hemolysis
Inactivated (heated) immune G. P. serum + washed erythrocytes	=	No hemolysis
Inactivated immune G. P. serum Normal G. P. or R. serum Washed R. erythrocytes	=	Hemolysis

It is obvious that heating the treated guinea-pigs' serum has destroyed something which is restored by adding normal blood serum, or otherwise that there is something present both in unheated immunized guinea-pigs' serum, and in normal guinea-pigs' serum which is a necessary factor in the process of hemolysis.

But this is not the only factor, for non-immune G. P. serum is without effect in the corpuscles. There must, therefore, be a second body present and developed in the serum of the immunized guinea-pig which is equally essential; and it is the combined action of these two which leads to the hemolysis.

The existence and combined action of these two factors can similarly be demonstrated in every case of cytolysis.

We speak of the body developed in the serum of the immunized animal as the *immune body.* We shall also refer to it, for reasons presently to be given, as the *intermediate body.* The body present both in the normal and the immune serum, which is indeed a normal constituent of all healthy sera, is, most commonly, referred to as the *complement.* The term is not wholly fortunate, for while admittedly this body is necessary for the completion of the process, the term tends to suggest that it is accessory rather than, as we now regard it, the essential agent in the cell destruction. Many—altogether too many—alternative names have been given to these two bodies, to recite which at this point would only cause confusion; we will tabulate them at a later period.

We can demonstrate that both are present in the cytolytic serum in the following manner. Take the cytolytic serum in two parts:

1. Heat the one part to 55° to 60° C. This, as already noted, destroys the complement and leaves the immune body unaltered, that being only destroyed by a heat of 70° C. or over.

2. Cooling the cytolytic serum to 0° C., add to it the washed cells, upon which it has a specific action, these having also been carefully cooled down to 0° C. At this temperature cytolytic action is arrested. But, while this is the case, as first demonstrated by Ehrlich and Morgen-

roth, the immune body attaches itself to the washed cells, and now, by carefully filtering it at zero, *a complement-containing serum can be gained free from the immune body.* And if now the cells in the filter be washed so as to remove all traces of the serum with contained complement, the cells may be suspended in physiological salt solution and brought to room temperature without showing the least trace of cytolysis. But, if the filtrate of (2) be now added, cytolysis rapidly ensues; or, if again this filtrate be cautiously added to (1) and to the mixture the particular cells be added, then the reaction occurs, although, in this case, it is not always perfect. Through the action of heat, as we now know, the complement may be converted into *complementoids*, which combine with the immune body, and while unable to disintegrate the cells, nevertheless, to a greater or less extent, prevent the active complement added later from combining and completing the reaction. In general, however, as shown by Sachs, the complement has a greater affinity to the immune body than have these complementoids.

Fig. 163

Combination of cell *a*, amboceptor *b*, and complement *c*. The amboceptor may unite with the cell, but cannot affect it alone. The complement cannot unite with the cell except through the amboceptor, having no adaptation to the cell directly.

These observations—and they have been repeatedly confirmed—indicate very clearly that for cytolysis to occur there must first be combination between the immune body and the cell, and that then the additional combination of the complement brings about the cell disintegration, the immune body alone having no disintegrating action. They do not, it is true, exclude the possibility of the immune body and complement being in state of loose combination in the serum, but even if so, it must be through the immune body that such a combination attaches itself to or acts upon the cell. It is for this reason that the immune body is also referred to as the *intermediate* body, or *amboceptor*, it being regarded as capable of a double attachment seizing on to both cell and complement. That such combination between complement and immune body actually takes place has been shown by Preston Kyes in his observations upon cobra poison, to which we shall refer later, in which he showed clearly that lecithin acts as a complement, the cobra poison acting as the immune body in the destruction of the red corpuscles, and poison and lecithin becoming combined to form a most active and rapid hemolytic agent. The existence of such compounds strongly supports Ehrlich's view of the intermediary nature of the immune body, as against Bordet's that the immune body first acts directly on the cell and then, also directly, the complement.

The Immune or Intermediate Body (Amboceptor).—There have been very numerous observations made upon these two constituents, immune body and complement. The more important results must here be indicated, for largely through methods introduced by Ehrlich, the reactions obtainable approach the procedures of the chemist

in their exactitude. We are dealing with bodies having well-defined properties; a precise amount of the complement-containing normal serum must be added to a particular quantity of the inactivated serum (containing immune body) to act completely on a given mass of cells; anything more or less leads to an imperfect reaction.

Multiplicity of Amboceptors.—Regarding the properties of immune bodies, it must in the first place be recognized that these are multiple. It is found, for instance, that goats' blood serum will dissolve both guinea-pigs' and rabbits' red corpuscles. If the proper amount be taken to hemolyse G. P. corpuscles, the serum still contains amboceptors capable of attaching themselves to rabbits' corpuscles and (with the complement) causing their dissolution, or otherwise, the goats' serum contains one set of immune bodies having affinity for the guinea-pigs' corpuscles, another for the rabbits' (Ehrlich). In like manner, Neisser has shown that when a serum is at the same time hemolytic and bacteriolytic for certain bacteria, the bacteriolytic power may be removed by letting it act upon the bacteria, and it still retains its hemolytic powers. We shall show that the same is true for the immune bodies or amboceptors which are developed to act against specific bacteria. *We have to acknowledge then a pronounced multiplicity of immune bodies.*

Multiplicity of Receptors.—But, as a corollary, it must be equally admitted that *the cells have multiple affinities, or as Ehrlich terms them, receptors.* The very fact that red corpuscles are capable of being acted upon by so large a group of diverse substances as the phytotoxins (ricin, etc.), snake venom, spider and scorpion venom, bacterial products, and hemolysins proper can only be explained on the supposition that the corpuscles have manifold affinities. The alternative that there is some common atom group in all these different lysins having an affinity for a special atom group in the red corpuscles is shown to be wrong, or at least inadequate to explain the whole series, because, as regards hemolysis alone, the same hemolytic serum will not act on the red corpuscles of all members of one species. Inoculate a goat with the corpuscles of another goat, and the serum developed will not hemolyse the corpuscles of all goats indifferently; it will act on some specimens, but not on others. As Aschoff expresses it, employing an illustration of Durham's regarding agglutinins, if we regard the goats' corpuscles as capable of possessing a possible full series of receptors a, b, c, d, e, f, then if we treat a goat with corpuscles possessing only the receptors a, b, c, its serum will come to contain amboceptors for a, b, c, and not for d, e, f. Such serum coming into action with the goats' corpuscles possessing receptors a, b, c, will actively destroy them; possessing only a and c, will destroy them, but not so actively; possessing receptors d, e, f, will have no action.

While this is the case, it is also evident that certain amboceptors appearing in the serum of different species, if not throughout identical, may, nevertheless, be so closely allied structurally that, as regards any particular reaction, they may replace each other, their molecular constitution, in certain respects, causing them to have like affinities.

Amboceptoids.—Whether amboceptors can undergo modification; whether, for example, bodies can be developed which will combine with the complement but not with the cell, is still a matter of some debate. Wechsberg,[1] it may be, encountered such amboceptoids in dogs' blood, in which he gained "Complementablenkung" (diversion of complements), but found that there was no action on the cell. In Ehrlich's terminology the body or bodies in question possessed a complementophile group, but no cytophile.

Anti-amboceptors.—Regarding these, *i. e.*, the production of antibodies by inoculating a third animal with the immune bodies developed in the second, it has to be noted that so far they have not been surely determined in connection with hemolysins. Pfeiffer and Friedberger,[2] Bordet,[3] and Ehrlich and Sachs have, however, produced these against other cytolytic agents. The first of these produced them by inoculating cholera immune serum into animals, and made the interesting observation that the anti-immune body so developed hindered the action of typhoid immune serum also. On the other hand, the anti-immune bodies developed from the amboceptors produced in immunity against the different snake venoms are strictly specific in their action.

Seat of Development of Immune Bodies.—This we shall discuss when dealing with the origin of antibodies in general (p. 517).

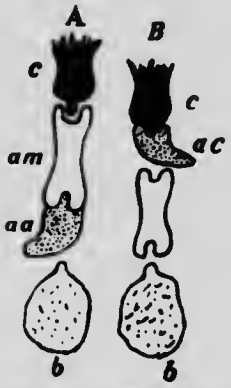
Complements.—There has been and continues to be discussion as to whether in a given blood one or more complements exist. It will be seen that the evidence is in favor of their being a *multiplicity of complements*. Bordet more particularly has championed the unitarian theory. A given complement-containing serum, he showed, will, when added to inactivated immune hemolytic serum, activate it and cause hemolysis. Similarly, added to inactivated immune bacteriolytic serum it causes bacteriolysis. But if now such complement-containing serum, after acting upon the blood corpuscles, be tested with inactivated bacteriolytic serum it has no effect, and *vice versa*. This, he concluded, indicated the existence of one complement active in both processes, and used up in the first. And Kyes' observations upon the hemolytic action of snake venom appear at first and up to a certain point to favor this contention. Kyes found that if a watery solution of cobra poison be shaken up with a solution of lecithin in ether, the neurotoxic element in the venom remained in the watery solution; the hemolytic combined with the lecithin and could now be gained as a definite compound of lecithin—a lecithide insoluble in ether and so distinct from lecithin proper and possessing intense hemolytic powers. He showed, further, that in all respects such lecithin acts as a complement, and that not merely for cobra venom, but for other snake poisons; that where cobra poison injected alone causes hemolysis, the action is to be explained by the preëxistence of lecithin as a constituent of the corpuscles; that the mere

[1] Wiener klin. Woch., 15: 1902: 337.
[2] Centralbl. f. Bakt., 34: 1903 and 37: 1904.
[3] Ann. de l'Inst. Pasteur., 13: 1904.

existence of lecithin is not sufficient; all erythrocytes contain lecithin, but not all are laked by cobra poison; therefore the lecithin, to act, must be in a free or disposable state.

To this extent lecithin, a body capable of crystallization, and therefore a definite chemical compound, is a complement common for a large number, at least, of hemolytic snake venoms. But, if this be so, everything indicates that lecithin is able to form a large number of compounds or, more exactly, to become attached to and an intimate portion of various cell substances. In the organism, at least, the lecithin may be very variously combined; and we are justified in supposing that under intravascular conditions the complement action of lecithin is not necessarily exerted by it as a free substance; but that, combined, it is capable of uniting the cobra poison, *provided* that in the combination the particular affinity for the poison is unsatisfied.

Fig. 164



Schema of neutralizing action of *A*, anti-amboceptor, and *B*, anti-complements, respectively. In *A*, the amboceptor cannot combine with the cell receptor *b* because of the junction of the anti-amboceptor *aa*. In *B*, the amboceptor can unite with the cell receptor, but cannot be activated because of the junction of the anti-complement *ac* with the complement. (After Levaditi.)

A like chain of reasoning would seem to harmonize Bordet's observations with those we are about to note.[1] If, as shown by Ehrlich and Morgenroth, goats' or horses' blood serum be filtered (through Pukall's filter), two complements are obtained, the one passing through with difficulty, the other under certain conditions coming through the filter alone; the former acting upon the immune bodies from rabbits' blood, the latter on those in guinea-pigs' blood. Neisser and Döhring were able to make a similar separation in human blood serum. Further, it has been noted that in some cases the complement is thermostable, in others thermolabile. From these and other observations, Ehrlich and Morgenroth concluded that (1) *in every normal serum there exists a series of complements*, and again that (2) *in different animals there exist a certain number of identical complements* either absolutely identical or identical so far as regards their haptophore groups (*i. e.*, having identical affinities toward the cell, but not being throughout of the same composition). As above suggested, one common type of substance may be the basis of complements of all orders, but the modifications and accretions this gains in different species and different individuals may determine whether there be asso-

[1] Jacobi, loc. cit., p. 68, brings together other convincing proof in favor of the plurivalent hypothesis, notably Ehrlich and Marshall's observations upon an anti-complement found present by chance in a specimen of human ascites fluid and its capacity to inhibit the lytic complement in some cases and not in others.

ciation with particular immune bodies or not. As Aschoff points out, this variation in the properties of the complements has a practical bearing upon the relative benefit gained by different individuals from the injection of preventive sera.

Variation in Amount of Complement.—And, we may add, the amount of complement present is also a factor. There are numerous observations indicating that, in the course of disease and by experimental methods (Abbott and others), the amount may become greatly reduced, and that through their relative absence protective sera fail to antagonize the bacteria.[1] On the other hand, it may be increased by the injection of indifferent substances, blood plasma, broth, etc., and such increase may, in part, explain the favorable results of Issaeff's method.

Complementoids and Anticomplements.—If a serum which has been heated up to the point at which it is inactivated and the complement as such destroyed, the existence in it of complementoids is demonstrated from the fact that anticomplements become developed in the serum of the inoculated animal, just as toxoids (p. 471) will induce antitoxin formation. Such anticomplements when added to an active serum arrest its activity.

Structure of the Complement.—The existence of these complementoids, together with the consideration previously detailed, would indicate that the complement is formed of two essential parts, the haptophoric portion, whereby it attaches itself to the immune body; the toxophoric or zymophoric or cytotoxic, which is the essential agent in bringing about cell destruction. This latter may be destroyed or modified (complementoid), whereby, although the altered complement combines with the immune body, no cytolytic results ensue, and active complement is prevented from uniting. A like absence of the cytoxic moiety must be predicated for the anticomplement. The former also may be modified so that the complement is unable to join on to one or other amboceptor.

BACTERIOLYSIS AND BACTERIOLYSINS.

While the essential data bearing upon the destruction of bacteria and the production of bacteriolysins are identical with those of cytolysis in general, it has seemed better to treat the subject separately, so as to present it to the reader in a clearer light when he is more fully prepared to grasp the main details.

Already, thirty years ago, Traube[2] concluded that the blood was able to destroy bacteria. In 1881, Lister noted that extravascular blood kept sweet despite the addition of small amounts of putrefying material, *i. e.*, that within certain limits it arrests the activities of putre-

[1] Vide Ehrlich and Morgenroth, Berl. klin. Woch., 31: 1900 (phosphorus poisoning); Metchnikoff (chronic suppurations), Ann. Pasteur, 14: 1900: 577; Bentivegna and Corini (hunger), Lo Sperimentale, 5: 1900: d'l Inst. 490.

[2] Jahr. d. Schles. Ges., 1874.

factive microbes, in 1884, Grohmann[1] published confirmatory results; v. Fodor[2] followed the course of the destruction in intravascular blood, noting a preliminary destruction followed by increased proliferation: facts which were confirmed by Flügge and carried yet farther by Nuttall,[3] working in his laboratory, who found that the destruction could occur in fluids containing few leukocytes such as the aqueous humor and pericardial fluid, and that so the destruction was not, as Metchnikoff had laid down, essentially intracellular. He made the further important observation that a heat of 56° C. destroyed the bactericidal activity of sera and other body fluids. From these observations we pass to the more definite studies of Hankin and of Buchner and his school upon the nature of the essential bactericidal substance—Buchner's alexine—while here must be noted the important observation of Vaughan and McClintock,[4] confirmed by A. Kossel,[5] that the nuclei of leukocytes contain nucleinic acid, which in itself is a definitely bactericidal substance. Here also must be mentioned, what we must discuss in more detail later, Metchnikoff's observations upon phagocytosis, the determination more particularly by Buchner and his pupils that leukocytes afforded the main source of the alexines found in the body fluids and the objections that have been raised to these conclusions.

The next great step forward was undoubtedly the observation by Pfeiffer that the cholera spirillum (and the same was quickly shown to be the case with the majority of pathogenic bacteria), contains what we now term *endotoxins* in contradistinction to the diffusible toxins of the diphtheria bacillus, and that immunity against these bacteria is therefore, produced by means other than the neutralization of diffusible toxins which had already been shown to occur by von Behring. These observations led to the demonstration by Pfeiffer and Bordet of the complex nature of the bactericidal process; in short, to the demonstration of the existence of complements in normal sera and the development of immune bodies or amboceptors in the immunized animal.

Further, it was noted that forms which, like the diphtheria bacillus and the B. pyocyaneus, afford diffusible toxins contain at the same time endotoxins, and that the process leading to the destruction of such bacteria by the organism (as distinct from the neutralization of their toxins) is identical with that occurring in cytolysis.

Pfeiffer's Reaction.—The basal methods for studying bacteriolysis have been afforded by Pfeiffer and Bordet. Pfeiffer has described two methods of gaining his reaction which in principle are, however, identical.

1. Take a guinea-pig that by successive inoculations has been rendered highly immune to virulent cholera spirilla and introduce into its peritoneal cavity five to ten times the ordinary fatal dose of an agar culture of the cholera spirillum.

[1] Inaug. Diss., 1884. [2] Deut. med. Woch., 1886: 617, and 1887: 745.
[3] Zeitsch. f. Hygiene, 4: 1888: 253.
[4] Medical News, 1893. [5] Arch. f. Physiol., 1893: 164.

2. Or, inject into the *normal* guinea-pig a like dose of the spirillum mixed with an excess of cholera immune serum from another guinea-pig.

In either case, by removing with a pipette some of the peritoneal fluid from time to time, it is seen that the injected bacteria undergo destruction, and this apart from any phagocytosis and in a remarkable manner. They become motionless, swell, become rounded and like micrococci; therewith (more particularly in the peritoneum, not so clearly *in vitro*) they become progressively smaller, their substance undergoing solution, as Pfeiffer described it, like sugar in water. Radziewski[1] has carefully followed the reaction in Sp. cholera, B. pyocyaneus, B. typhi, B. pneumoniæ, streptococcus pyogenes, B. mallei.

Metchnikoff and Bordet showed that the identical process occurred *in vitro*, and that the bacteriolysis could be brought about by taking definite proportions of bacilli, inactivated (heated) immune serum, and normal serum, the latter containing the amboceptors, the latter the complement (although they use different terms for the two, which to avoid confusion we do not mention). Not to repeat ourselves unduly we may sum up in brief sentences the main facts that have been ascertained regarding bacteriolysis and *mutatis mutandis* for all the different forms of cytolysis.

1. Bacteriolysis is brought about by the interaction of amboceptors and complements upon the bacterial body.

2. Antibodies, including both amboceptors and complements, may be found present in the blood of normal animals, and this not only in the serum, as Gengou has urged, but in the plasma (von Dungern and others). These are not, that is, entirely derived from the dissolution of leukocytes at the time of the removal of the blood. The amount of amboceptors is small, however, compared to what may be developed by specific inoculation.

3. The amboceptors are multiple; an animal immunized against both cholera and typhoid provides a serum which after destroying the cholera spirilla will, added to typhoid bacilli suspended in normal serum, destroy these also.

4. By immunization of animals against a specific microbe specific immune bodies are developed acting (specifically) upon the species of microorganism employed for inoculation.

5. This specificity, while, as Pfeiffer has shown with the cholera spirilla and strains of the same, it may be very strongly marked and practically absolute, may in other cases be more diffuse; thus Löffler and Abel[2] found that typhoid immune serum had a slight bacteriolytic action upon some strains of B. coli, and Dünschmann[3] that quarter evil (Rauschbrand) serum could act on the bacillus of malignant œdema. Such "group action" on the part of amboceptors is but slight compared with what is seen in the case of agglutinins (p. 487).

6. It is possible to develop temporarily non-specific protective powers

[1] Zeit. f. Hygiene, 37: 1901: 1.
[2] Centralbl. f. Bakt., 19: 1896: 51.
[3] Ann. de l'Inst. Pasteur., 8: 1894: 403.

on the part of the organism. Such increased resistance against pathogenic bacteria in general may be developed at the height of inflammation, or, as Isaeff has shown, by preliminary inoculation of various fluids (sterile broth, urine, physiological salt solution, etc.). Such increased protection is temporary—Isaeff's resistance period—and has no effect on the blood serum; it disappears in ten to fourteen days. His observations indicate that it is associated with increased leukocytic activity. We must recognize, that is, that the organism employs more than one means to protect itself.

7. The antibacterial amboceptors as a class are unaffected by heating for several hours to 60°, but are destroyed at 70°.

8. They are not immediately produced upon inoculating animals with bacterin; usually three or more days elapse before they are recognizable in the blood.

9. Once developed by the organism, they are to be recognized in the blood serum for a considerable period, varying with the different species, but extending in some cases to a year and more.

10. If they disappear from the blood serum, a relatively very slight inoculation of the specific microorganism will result in their reappearance in abundance.

11. They may be developed either by progressive inoculations of the living microbes, by larger doses of the killed microbes, or by a combination. Such inoculations (Haffkine, Wright, etc.) may be employed to produce immunity in man against cholera, plague, typhoid, streptococcus infections, etc.

12. The complements of different animals are not necessarily identical, and for this reason the immune serum developed by one species will not necessarily protect another; thus anthrax immune serum will protect one species and not another (Sobernheim). Vibrio Metchnikovi immune serum gained from the rabbit will protect rabbits, but not pigeons; i. e., while the amboceptors produced to combine with the bacteria will so combine whether they encounter the bacteria in rabbits' or in pigeons' blood, in the second case, the complements afforded by the pigeon blood, being different, will not combine with the amboceptor, and the bacteria are not destroyed.

13. So also there may be more than one order of complement; in the same blood there may be those of more than one order. Normal rabbits serum heated to 56° loses its power of activating cholera and typhoid immune serum, but can still act upon anthrax bacilli.[1]

14. Virulent bacteria possibly possess more specific receptors than non-virulent, a larger amount of the amboceptor-containing immune serum being required to neutralize and destroy them. An alternative view is that virulent bacteria produce more antibodies of the nature of aggressins (p. 749) which antagonize the action of the amboceptors.[2]

15. *Anti-amboceptors* which can readily be obtained in hemolytic studies are not so easily gained against bacteriolytic agencies. The

[1] Bail, Centralbl. f. Bakt., 27: 1900: 50 and 517.

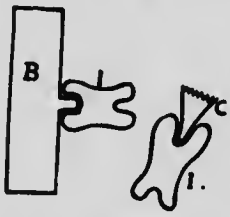
[2] Wechsberg, Zeit. f. Hygiene, 39: 1902: 1

haptophoric constituents of the amboceptors tally with the corresponding bacterial receptors, and it is unlikely that these amboceptors inoculated into normal animals (to develop anti-amboceptors in their blood) will find in the organism of those animals receptors which correspond with those of the bacteria; unless such receptors be present the anti-amboceptors cannot be developed (Friedberger).

Nevertheless, occasionally such have been found, as Pfeiffer and Friedberger[1] chanced to gain anti-immune sera which neutralized the protective action of goat typhoid and cholera immune sera in guinea-pigs, by inoculating rabbits with a goat typhoid and goat cholera immune sera respectively (*i. e.*, the sera of immunized goats).

16. **Diversion of Complement.**—Lastly, a word must be said regarding a peculiar phenomenon first noted by Neisser and Wechsberg.[2] If a suspension of bacteria be taken in a normal serum containing sufficient complement to cause bacteriolysis when a known amount of inactivated serum is added (*i. e.*, containing *x* amboceptors), then if, say, 10 *x* amboceptors be added, instead of the solution of the bacteria being hastened, the opposite occurs; it may be wholly arrested. There is evidently a diversion of the complements, the excess unattached amboceptors have a greater avidity or attraction for the complement molecules than have those that have become partially satisfied by attachment to the bacteria, or, conversely, it may be that the avidity of the bacterial receptors is greater for amboceptors pure and simple than for the combined amboceptors plus complement.

Fig. 165



Diversion of complement: when there is excess of amboceptors 1, those which have not combined with the complement molecules *C* are supposed to enter more readily into combination with the bacterial receptors *B* than do the compound amboceptor-complement molecules.

The phenomenon has been variously explained: Thus Metchnikoff suggests agglutination of the bacteria by the excess of inactivated serum, or the presence in the excess serum of sufficient anticomplements to take the place of the complements. Gruber also has suggested anticomplements already present and made active by the addition of large doses of inactivated serum. To us the simplest explanation appears to be afforded by the following diagram, namely: an amboceptor which is within the sphere of influence of a complement, and is being attracted by it, is less likely to succumb to the attraction of the cell receptor than is an amboceptor not subjected to such influence, and so the receptors become satisfied by unlinked amboceptors.[3]

17. From the practical point of view, that of establishing passive immunity by inoculating immune serum, it is of importance to recall

[1] Berl. klin. Woch., 1902: 204.

[2] Verhandl. d. Internat. Cong. d. Hygiene, Brussels, 1901: 697 and Münch. med Woch., 1901, Nr. 18.

[3] Buxton, Jour. of Med. Research, N. S., 8: 1905: 431.

what has already been said regarding the variation in the amount of complements in the individual and the reduction these may undergo in the course of disease, as also the fact that the complements in the blood of one animal do not necessarily correspond with those of another, and are not so active in the blood of that other animal as are the complements proper thereto. Thus, passive immunity and the destruction of bacteria are not always complete. Mixed immune sera are thus sometimes found more satisfactory than the immune serum of a single animal or species; or it might be suggested that as a final result normal human serum is most likely to afford the right order of complements for human patients, a relatively small amount of serum containing, it is found, sufficient complement to satisfy a large bulk of amboceptors.

ANIMAL VENOMS.

We have already more than once called attention to the toxic action of animal venoms—the venom of snakes, scorpions, certain spiders, etc.—and should in strict order have considered them after the toxins, but, as we shall point out, in some respects they are more nearly allied in their mode of action to the cytolysins and occupy thus an aberrant position. Here it may be briefly noted that, by cautious repeated injections, whether of minute quantities, or, better, of the modified toxin, into the lower animals, antitoxins—antivenins—can be obtained to all the animal venoms. Such antivenins were first obtained against cobra poison by Phisalix and Bertrand,[1] Calmette, and Fraser by different methods of procedure. Calmette's[2] antivenom from the horse has been produced extensively, and has been found of service in cases of actual snake bite in human beings. It was with such antivenom that Kanthack[3] first demonstrated the neutralization of toxin and antitoxin *in vitro*. Since then there have been produced experimentally the following: antiscorpion venom (Calmette), anti-arachnolysin (against the poison of the spider, *Epeira diadema*, Sachs),[4] antiphrynolysin (against toad poison [Bombinator bufo], Pröscher),[5] antisalamander poison (Phisalix), anti-eel poison, antifish poison, etc.

Needless to say, it is snake venom that has attracted the greatest attention, and that has materially contributed to our knowledge of toxic actions, and here Kyes,[6] Flexner and Noguchi,[7] and others have demonstrated that the raw poison contains several separate toxins—a hemolysin, a neurotoxin, a nephrotoxin, an endotheliotoxin, etc. Nor have all of these the same mode of action. The majority act directly, but others,

[1] Compt. rend. Soc. de Biol., 1894.

[2] Ibid., 1894. Fraser, Brit. Med. Jour., 1895: ii: 416.

[3] Jour. of Physiol., 3: 1893.

[4] Hofmeister's Beitr., 2: 1902.

[5] Hofmeister's Beitr., 1: 1901.

[6] Berl. klin. Woch., 1902: Nrs. 38 and 39. Also in Ehrlich's Ges. Abhandl., 1904: 413.

[7] Jour. of Exp. Med., 6: 1901-5: 278.

like the hemolysin, require the intermediation of a complement. We seem, indeed, with these venom hemolysins to have a series of bodies intermediate between or at least indicating the relationship between the toxins which act directly on the cell and those which for their action require the intermediation of a complement. Both spider and toad poison act directly, indeed rapidly, upon the red corpuscles and give rise to bodies having all the characters of antitoxins. Cobra venom acts immediately on the red corpuscles of some animals (*e. g.*, the guinea-pig), has no action on others (ox, sheep, goat), but can be activated in the latter cases by the addition of the blood serum of another animal (*e. g.*, guinea-pig). That added blood serum must contain the complement; and in the case of the susceptible animals we can only conclude that the erythrocytes already possess an endocomplement. As a matter of fact, as already noted (p. 494), Kyes demonstrated that if lecithin does not constitute this endocomplement, at least it can act as a complement and so bring about the hemolysis.

This very remarkable series of facts suggests that in all toxic actions proper we may similarly have to deal with endocomplements, whereby the whole body of cases here considered fall into a common group, the only difference being that in some cases the complement is supplied by the blood serum, in the others it is already present as an endocomplement in the cell acted upon. Fascinating as is the suggestion, there is as yet no adequate further evidence afforded in its support, unless, indeed, the evidence recently afforded by Levaditi[1] that washed leukocytes can slowly take up and digest bacteria, can be accepted as an indication that the same cell can produce both amboceptor and complement. But evidence that a complement is necessary to bring about the action of the diphtheria toxin on the cell, or of the diphtheria antitoxin on the diphtheria toxin, is quite lacking.

OPSONINS.

Another class of substances present in the blood serum and factors in the bacteriolytic process, has been shown to exist by Wright and Douglas. As with the agglutinins, it is difficult to realize the exact nature of their activity. These observers, employing Leishman's method of observing phagocytosis by leukocytes outside the body and under the microscope, have made out that, under ordinary conditions, the polymorphonuclear leukocytes do not freely take up and digest bacteria unless certain thermostable substances be present in the serum, which, in consequence of their auxiliary action, they term opsonins,[2] and to the presence or relative absence of these substances they attribute to a large extent the eventual destruction of bacteria by phagocytic activity or their continued multiplication within the organism. They find, for example, that the leukocytes from a person suffering from chronic furun-

[1] Ann. de l'Inst. Past., 1905.

[2] From "*opsono*," I cater for.

culosis or other pyococcic or streptococcic diseases are able to take up abundant cocci if removed from the patient's blood serum by centrifugation and placed in the serum of a normal healthy individual. In fifteen minutes, kept at 37° C., such leukocytes may each have taken up from fifteen to thirty cocci added to the suspension, whereas under the same conditions the leukocytes in the patient's own serum may have been almost inert. And contrariwise, the leukocytes from a healthy individual placed in the blood serum of the patient may also show scarcely any activity. Phagocytic activity is, therefore, not merely a matter of leukocytic activity, but is favored and stimulated by the action of some substance in the blood serum. How this acts is still a matter of some debate.[1]

Independently, but later, Neufeld[2] has described what are evidently the same bodies, as *cytotropic* substances. He has found that the serum of animals immunized against streptococci, pneumococci, and erythrocytes contains substances which act upon the bacterial cells or erythrocytes in such a way as to favor their ingestion by leukocytes. Like Wright, he finds that they are thermostable, that they can be heated to 59° C. for half an hour without being destroyed, and that they become fixed by the microbes, but not by the leukocytes.[3]

To obtain Wright's phenomenon certain precautions are necessary: (1) The bacteria employed must be in an emulsion, so made that the individual microbes are separate and not massed into clusters. (2) The emulsion must not be too thick, *i. e.*, too great an abundance of bacteria by overlying the leukocytes in the preparation gives false ideas regarding the extent of phagocytosis. (3) The observer must have considerable training so as to reduce or render constant the personal factor in the bacterial counts. It is better that the counter should not know beforehand the history of the preparation he is engaged upon. (4) The same pipettes should be employed for the same stages of the process, so as to ensure accurate mensuration and mixture. (5) The greater the number of leukocytes counted, the less the possibility of error. These are but some of the more obvious precautions; there are abundant minute details of technique as developed by Wright, all making for accuracy, but with the greatest perfection of technique, it has to be admitted, that the limit of experimental error remains high.[4] Nevertheless, as the accompanying examples show,[5] in the hands of a careful worker closely accordant results are obtainable.

Experiment I.—Rabbits' serum mixed with emulsion of staphylococci and human leukocytes (from seven persons) in the proportion of 3:1:3. Phagocytic count obtained by counting the number of cocci in 35 polymorph leukocytes and then calculating the number per leukocyte:

[1] Wright and Douglas, Proc. Roy. Soc., 72: 1903: 357; 73: 1904: 125, and 74: 1904: 159. See also Bulloch, Practitioner, November, 1905.

[2] Deut. med. Woch., 1904. [3] Centralbl. f. Bakt., 38: 1905.

[4] Vide Fitzgerald, Whiteman, and Strangeways. Bull. of Comm. for Study of Special Diseases, 1: 1907: 115.

[5] Bulloch and Atkin, Proc. Roy. Soc. Lond., 74: 1905: 381.

								Cocci per leukocyte.
1.	Rabbits' serum	+	cocci	+	corpuscles of	W. B.	(normal male)	= 9.8
2.	" "	+	"	+	"	F. T.	" "	= 9.3
3.	" "	+	"	+	"	O. G.	" "	= 9.7
4.	" "	+	"	+	"	R. D.	" "	= 9.6
5.	" "	+	"	+	"	C. H.	" "	= 9.0
6.	" "	+	"	+	"	H. M.	(an anemic female)	= 9.9
7.	" "	+	"	+	"	S. M.	(male, facial acne)	= 9.0

Here it will be seen that, using the same serum, but different leukocytes, the counts are practically identical; differences between 9.0 and 9.9 do not exceed the limits of error of observation. In experiment II the sera are different, but the leukocytes of one individual are employed throughout.

Experiment II.—Various human sera + cocci + one kind of leukocyte (from a normal male individual):

							Cocci per leukocyte.
1.	Serum of	W. B.	+ cocci	+	corpuscles of	W. B.	21.3
2.	"	F. T.	+ "	+	"	"	20.3
3.	"	O. G.	+ "	+	"	"	21.1
4.	"	R. D.	+ "	+	"	"	20.0
5.	"	C. H.	+ "	+	"	"	19.8
6.	"	H. M.	+ "	+	"	"	15.5
7	"	S. M.	+ "	+	"	"	14.0

Here it will be seen that there are more differences; not much between the sera of the healthy males, but that of the anemic H. M. stimulates to a distinctly lessened phagocytosis, while the slightest of all is induced by S. M., who suffered from a disease, acne, due to growth of this particular microbe, the pyococcus.

These observations of Sir A. E. Wright have thus far been abundantly confirmed in numerous laboratories. It has been demonstrated that:

1. In a large number of infections protective substances (opsonins) exist in the blood serum.

2. The opsonin is thermolabile; more correctly, the *natural* opsonins are, in the main, thermolabile; the serum containing them is "inactivated" if heated to 56° C. for a few minutes, and very largely inactivated if heated only to 50° C. for a longer period. Recent observations show, however, that there are opsonins and opsinins; some produced after preliminary vaccination are relatively thermostable, being little affected by a temperature of 60° C. (Muir and Martin, Hektoen, Rosenow).

3. The opsonins act upon the bacteria, so that the latter can subsequently be ingested by the leukocytes.

4. When different bloods are compared, the variable factor is the serum, and not the leukocytes. This is not the same as stating that leukocytes of different individuals do not vary in their phagocytic activity. In certain diseases of the hemopoietic system, as shown by Ledingham,[1] apart from changes in the opsonic content of the serum,

[1] Lancet, London, June 16, 1906. See also Shattock and Dudgeon, Proc. Roy. Soc. of Medicine, 1: 1908: Medical sect., 169.

these may vary greatly in their phagocytic power, and this variation may explain occasional aberrant results. But, as a rule, the variations in the cells are so slight compared with the range of variation of opsonic power of sera that it may be neglected. So also the matter is not affected by the fact, brought out in Metchnikoff's laboratory, that slowly—after an hour or more—some slight ingestion of bacteria is seen to take place by leukocytes suspended in normal saline solution and in the absence of serum and opsonins. Such observations do not indicate that opsonins do not exist. In a normal serum at body temperature within fifteen minutes normal polymorphs take up abundant bacteria; not an occasional coccus, but from thirty to fifty may be counted in a single leukocyte. This difference between the effects of a normal serum and of an inactivated serum or physiological salt solution is very striking.

5. The specific opsonin is used up when bacteria are added to a serum, so that on removing the bacteria the serum used with a second portion of the same emulsion is inactive.

6. The opsonins become combined or at least absorbed, by the bacteria, so that these bacteria removed after treatment and placed in an inactivated serum are freely taken up by leukocytes mixed with the same.

7. That there is a definite combination is suggested by the fact that, whereas the opsonin in serum is destroyed by a heat of 60° C., the mixture of serum and bacteria that has undergone opsonization may be heated to 60° C. for long periods without abolition of the opsonic effect (Bulloch and Atkin).

8. There is multiplicity of opsonins, or otherwise they are largely specific. Contrary to or rather modifying the earlier results of Bulloch and Western, several observers, notably Simon, Potter, Ditman and Bradley, Russell, Hektoen, and Rosenow, have brought forward data proving that there is a common opsonin in normal serum (which is thermolabile), whereas, after vaccination there are developed specific opsonins (some at least of which are thermostable). Following injection of bacterial vaccines, there is an increase of opsonins which react specifically.

9. By careful vaccination with measured small quantities of dead cultures of various pathogenic microbes (pyococcus aureus, gonococcus, B. coli, B. tuberculosis, etc.), it is possible to increase markedly the opsonizing power of the serum of the individual. Such vaccination is followed by what Wright terms the "negative phase," during which the specific opsonin becomes reduced in amount; secondly, there is a positive phase of increased opsonic power of the blood serum.

10. Regarding phagocytosis as the main process by which bacteria are destroyed within the organism, and the opsonins as the means whereby the bacteria are prepared for ingestion, Wright has concluded that the relative amount of opsonins in a given serum gives an indication of the defensive powers of the individual; for this purpose he has established an "opsonic index." This is the ratio between the average number of bacteria found within 20 to 40 polymorphonuclear leukocytes of an emulsion made with the patient's serum and the number found in

the same number of like leukocytes in an emulsion made with normal serum, the latter being taken as 1.0. For greater sureness a "pooled normal serum" may be employed, *i. e.*, a combination of the sera of five or more apparently normal individuals.

In most infections the index is found to be below 1.0. With carefully measured subcutaneous injections of dead specific bacteria there results a rise of the opsonic index, and this rise corresponds to an obvious improvement in the general condition of the patient and the local manifestations of the disease. By carefully watching the index it is possible by successive vaccinations to bring up the index in successive steps, until it reaches and exceeds the normal, and coincidently in these diseases a very material improvement is to be recognized, if not complete arrest of the morbid process. This is particularly the case with conditions due to the Pyococcus aureus. Good results are also obtainable in certain cases of gonorrhœa, B. coli infections, tuberculosis, etc., although, in the latter disease, it cannot be said that the opsonic index affords clear indications.

The want of certainty in the readings has, indeed, rendered many very skeptical regarding the full carrying out of Sir A. E. Wright's technique; but while it has to be admitted that all do not react similarly to successive vaccinations, and that even in his own practice Wright encounters not a few obstinate cases which do not react satisfactorily to his vaccinations, on the other hand, in certain infections, more particularly of a chronic or subchronic type, there are such remarkable cures that it is impossible not to see that the method, if not complete, has in it a material advance upon any previous attempts at treatment by vaccination and elevation of the resistant powers of the organism during the progress of a disease.

AGGRESSINS.

As pointed out some years ago by Ainley Walker,[1] as also by Welch, in his Huxley[2] lecture, if the cells of multicellular organisms coming into relationship with bacteria and their products are stimulated to produce antibodies, we may premise that bacteria, as living cells, encountering the cells of the organism and their products, are, under favorable circumstances, stimulated to produce reciprocal antibodies, and to produce them in increasing amounts. It is in this way that we best explain those phenomena which we group together under the term "exaltation of virulence" by passage of bacteria through a succession of animals of one species. Now the virulence of an organism is not merely dependent upon the production of toxins in the strict sense. This is immediately evident when we consider the case of the cholera spirillum, the anthrax bacillus, and other microbes which produce endotoxins almost exclusively. We have not a particle of evidence that, when these become more virulent, the production of exotoxins undergoes increase;

[1] Jour. of Pathol., 8: 1902: 34.

[2] Brit. Med. Jour., 1902: ii: 1105.

the filtered culture fluid from a twenty-four-hour culture of the most virulent strain produces as few symptoms as does that from the most attenuated strain. Nevertheless, inject the attenuated bacilli into the organism, and phagocytosis is immediate; inject the virulent, and there is no phagocytosis. In other words, the indications are that the living virulent microbes excrete or discharge substances which are not toxins proper, but which, nevertheless, have an inhibitive or "anti" action upon the cells of the orgmism, substances which are not necessarily taken up by the body cells leading to their destruction, but either neutralize the action of the opsonins or directly repel the body cells, the repulsion being greater than the attraction exerted by the other bacterial substances.

Of late, certain interesting observations have been made by Bail[1] and others which demonstrate the existence of bodies of this order. Inoculating cholera and typhoid bacilli into the pleural and peritoneal cavities, he set up local infection. Taking the inflammatory fluid containing the bacteria, he removed the latter by centrifugalization and killed the few remaining organisms in the decanted supernatant fluid by antiseptics, or by heat at 44° C. This clear fluid has no toxic properties; it may be inoculated with impunity into animals of the same species. When, however, it is inoculated into an animal along with a *sublethal* dose of the particular (homologous) microbe, an acute lethal result follows. His associates, Kikuchi, Weil, and Hoke, report like results with dysentery, chicken cholera, and pneumonia organisms. Instead of the bacteria of a sublethal dose undergoing destruction, they multiply. There is something in the inflammatory exudate that has paralyzed the protective agencies of the body. The production of these aggressins is the more active the greater the resistance to the bacteria. They are produced in greater quantities during the strife between the bacteria and the body cells, while little is produced in the test-tube. Some, however, are so produced; they are, that is to say, normal products of bacterial activity. Thus, Kolle found that when bacteria are grown in pleural fluid or blood serum in the test-tube, or even in distilled water, then develops a substance which, when the sterile culture fluid is inoculated along with a sublethal dose of the bacterin, leads to fatal results.

An immunity may be developed against the sterile aggressin-containing fluids, and this immunity may be transferred from one animal to the other by inoculation of its immune serum.

Bail regards these aggressins as new undescribed substances; others regard them as free bacterial receptors, holding that these discharged receptors combine with the amboceptors, producing, as it were, a diversion of the amboceptor, so that the bacteria themselves are not attacked, and thus continue to proliferate. But even granting this, it is obvious that these receptors are not of the nature of endotoxins or of exotoxins, for the fluid containing them is devoid of toxic effects. At the most,

[1] Arch. f. Hygiene, 52: 1905; Heft 3 und 4. See also Wassermann and Citron, Deutsch. med. Woch., 1905: 1101.

if of the nature of receptors, they are haptophorous and devoid of a toxophorous moiety.

The existence of these aggressins very probably explains certain observations of Wright,[1] Douglas, and Reid[2] which have been confirmed by Opie,[3] namely, that exudates produced by the local growth of a given pathogenic microbe contain no opsonins. More correctly it may be, that there is not an absence of opsonins under these conditions, but a neutralization of the same, by the bacterial aggressins. It may, indeed, be suggested that the aggressins are to the bacterial organism what the opsonins are to the animal.

ANAPHYLAXIS.

Yet another order of phenomena deserves notice in this connection. From the early days of the employment of antidiphtheritic serum, occasional cases have been reported of sudden death following upon the inoculation of the serum. In 1906, Rosenau and Anderson[4] were able to collect nineteen such cases out of the literature. The symptoms may come on within five minutes of the treatment, with collapse, unconsciousness, and convulsions; milder cases, of urticarial rashes with some nausea, are comparatively common, and it has been clearly proved that they are induced not by the toxins or antitoxins, but by the serum, horse serum producing identical effects. Along with these cases of serum sickness, attention may be called to the fatal effects which have followed the transfusion of the blood of sheep and other animals into man, in cases of grave anemia. Such transfusion led to after-effects so severe—high fever, hemorrhages, and intravascular clotting—and was so often fatal, that it was rapidly given up. Some cases, not so severe, showed merely urticaria with fever.

Experimental observations upon these phenomena have led to some very remarkable results. If a moderately large dose of a foreign serum be injected into an animal, either subcutaneously or into the peritoneum, no immediate effects are produced, and the animal in a few days becomes immunized to that serum. But, if instead of a dose of 5 c.c. of foreign serum, a guinea-pig be given as little as $\frac{1}{100000}$ of a c.c., and now in twelve days a second injection of 5 c.c. be given, the guinea-pig is apt to die, it may be, within a few minutes, or at most a few hours. Instead of being rendered immune, the very opposite result has been brought about; the animal has been "sensitized," rendered much more susceptible to the foreign serum. This process of sensitization has received the name of *anaphylaxis*.

It has been found that in herbivorous animals the same results may be gained by feeding with the foreign serum. Gay and Southard[5]

[1] Proc. Roy. Soc. Lond., 74: 1904: 147.
[2] Ibid., 77: 1906: 194.
[3] Jour. of Exp. Med., 9: 1907: 515.
[4] U. S. Hygienic Laboratory Bulletin, No. 29, Washington, 1906. See also Pirquet and Schick, Die Serumkrankheit, Leipzig und Wien, F. Deuticke, 1905.
[5] Jour. of Med. Research, 16: 1907: 143.

and others have shown that the subjects of anaphylaxis exhibit hemorrhages in the stomach, cecum, lungs, spleen, heart, and adrenals; these appear to be associated with a definite fatty degeneration of the capillary endothelium. Further, the blood of the sensitized animals comes to contain a substance which, when the blood is injected into other guinea-pigs, sensitizes them. In man and omnivorous animals, a single dose has sometimes the effect that the two doses possess in rabbits and guinea-pigs.

Such sensitization is so wholly opposed at first sight to all our experience in experimental immunity, that a totally different explanation would seem necessary. Various theories have been adduced, of which the only one that appears to us satisfactory is based upon Vaughan's[1] remarkable studies upon bacterial and other proteins. In a long series of papers, from 1901 until the present time, he has shown that the bacterial proteins may be split up into two portions—the one poisonous, the other non-poisonous—and now, taking what is apparently the most innocuous of proteins, namely, egg white, he has determined that the same is true of this also. One may inject the white of three hens' eggs into the peritoneal cavity of a rabbit, with no untoward effects. Nevertheless, by extraction of the purified egg albumin with 2 per cent. sodium hydroxide in absolute alcohol, two bodies are obtained: one poisonous, soluble in absolute alcohol, the other non-poisonous, and insoluble. This poisonous moiety, apparently of proteid nature, kills just as promptly as that obtained from the proteins of the colon or typhoid bacillus; the minimum fatal dose for the guinea-pig ranges from 8 or 10 up to 100 mg., according to the grade of purification.

Vaughan and Wheeler find that animals may be sensitized to egg albumin either with unaltered egg white, *or with the non-poisonous moiety, but not with the poisonous moiety.* What is more, *the non-poisonous moiety does not sensitize to itself*, but only to the unbroken egg white.

These facts can only be satisfactorily explained on the supposition that, under the conditions of these experiments, when a small dose of a foreign protein is introduced into the organism, for it to be assimilated the cell substance has affinity for the non-poisonous moiety. The same results ensue, it is seen, whether the whole egg white or only its non-poisonous residue be exhibited. The cells become habituated to attract to themselves the non-poisonous moiety alone, and to form and discharge a series of receptors which combine with this. When, therefore, after this habituation or immunity has become established (in ten or twelve days), the unbroken egg white is again exhibited, the cells—and these receptors—actively attract this non-poisonous moiety, liberating the poisonous moiety, which now, free in the body fluids, enters the blood, circulates to the brain, and there sets up those disturbances, more particularly in the respiratory centre, which leads to death. For as Besredka[2] has shown, and Vaughan confirms, the toxic action in these

[1] Jour. of Infectious Diseases, 1907: 476, gives a full bibliography of the publications from the University of Michigan bearing upon the subject.

[2] Ann. de l'Inst. Pasteur, 21: 1907: 117 and 384.

cases is cerebral in type. Vaughan and Wheeler show very clearly that the second dose must contain enough egg white to furnish a fatal dose when split up in the animal body.

But why do we obtain these anaphylactic results only when the preliminary injection is relatively minute, and why, under ordinary conditions of exhibiting a first dose of fair size, do we on the contrary gain immunity to the whole protein? Here we would suggest that the principle of dissociation of ions may be invoked. Just as when a relatively minute quantity of NaCl is dissolved in a large quantity of water it undergoes dissociation into its Na and Cl ions; but when the amount is large this dissociation is largely wanting, so with the introduction of a minute amount of a protein into the system, that protein undergoes dissociation into its poisonous and non-poisonous moieties. The liberated toxic substance is too minute in amount to have any effect; the body cells attract and attach the non-poisonous moiety alone. When, on the other hand, a large preliminary dose is given, from the very concentration of the introduced protein, ionization and dissociation does not occur; the protein then acts as a body possessing haptophorous and toxophorous constituents, and the cell substance attracts and acts upon the molecules as such, accustoming itself to deal with the whole molecule. Bound thus into the cell, the toxophorous moiety has no deleterious effect, for, as above noted, it acts specifically not upon the body cells in general, but only upon certain cells of the nerve centres, and under ordinary conditions of inoculation the molecules of the foreign protein become taken up and bound to other cells, and do not then enter the general circulation in amounts sufficient to tell upon the nerve cells. This entrance into the general circulation may happen in transfusion experiments, or in preliminary doses of protein in large amounts, and in this way we may explain the lethal effects of serum sickness. In other words, where a large preliminary dose is given the organism becomes immunized to the whole protein, and not merely to its non-poisonous moiety.

CHAPTER IX.

IMMUNITY—(Continued).

THEORIES OF IMMUNITY.

To master and to keep level with the vast number of individual observations that are now being poured out upon this one subject of immunity is in itself a life's work. Appalling as must be the mass of data contained in the last two chapters, to the reader who approaches the subject for the first time, these represent but a selection of the more important and generally accepted observations, and such conclusions as we have already drawn represent a sifting of opinions often very widely at variance. To have indicated and discussed the divergent views would have expanded those two chapters into two volumes. As it is, we have detailed but one theory—that of Ehrlich—and have not carried that to its conclusion. Now, it is for us to sum up, so far as is possible, the reasonable deductions that, we think, may be drawn from the data afforded, treating immunity and the process of immunization not as a subject apart, but as a branch of pathology, and indeed of general biology, so that our conclusions harmonize with those that are to be gained from the study of other vital reactions.

We note, in the first place, that all the toxins, or, to be quite clear, all those bodies which, gaining entrance into the system, lead to the formation of "antibodies," are themselves either cell substances or the products of cell activity, and that the antibodies are likewise the products of cell activity. The two groups, in fact, are seen to be curiously similar in very many properties—reflections one of the other. A little consideration shows that this is not surprising; were we bacteria, we would regard the animal antibodies as toxins and our own toxins as protective antibodies, or, at least, as preparatory digestive ferments. It may well be that the bacterial toxins, being developed by organisms extremely low down in the scale of living beings, are of simpler constitution than the antitoxins developed by warm-blooded animals, but when we ascend to the venoms of vertebrate animals, we find that the cobra discharges a hemolytic *toxin*, which in its properties and mode of action is identical with the hemolysin formed as an *antitoxin* in the serum of warm-blooded animals consequent upon inoculation with erythrocytes. Here clearly whether we regard the hemolysin as a toxin or an antitoxin depends wholly upon the point of view. So far does this parallelism or reflection proceed, that as Welch suggested in his well-known Huxley lecture, where two living organisms, the animal and the microbe, are pitted against each other, the increase in virulence which

may be acquired by the latter may be the expression of the development by it of anti-antitoxins (which from the point of view of the microbe are simple antitoxins) corresponding to the development of antitoxins by the warm-blooded organism, and tending to neutralize the same.

We are dealing, it will be seen, throughout his whole study, with the methods in which the living matter, whether animal or vegetable, reacts toward other living matter, whether animal or vegetable, and the products of the same which come into contact with it, and although the statement may at first encounter appear to be both novel and extreme, further thought will confirm it; the problems of immunity narrow themselves down to special problems bearing upon the digestion and assimilation of unusual proteid matter, or, at least, of the primary products of cell metabolism.

Metchnikoff, indeed, would regard immunity [illegible] matter of digestion and adaptation to the same by one order of cells, the phagocytes, free and fixed, and it will be well before proceeding [illegible] to note his main observations and arguments, for they have had extraordinary influence in stimulating work upon this subject, [illegible] as we shall see, his conclusions do not, in their essentials, oppose the more generally accepted theory of Ehrlich; they are the expression of the same views regarded from another aspect, in some respects wider, in others narrower;[1] wider in that throughout it keeps prominently in the foreground that immunity, like all other vital processes, is a matter of cellular activity, whereas the study of sera and their properties which constitutes the main method of the Ehrlich school is apt to cause neglect of this fact; narrower in that it is essentially morphological, and thus largely overlooks the fact that chemical processes underlie morphological phenomena, and again, that it would refer every important reaction to one order of cells, the leukocytes and other potential phagocytes, and somewhat obstinately is unwilling to credit other cells and tissues with any part in the process of immunization.

THE PHAGOCYTOSIS THEORY.

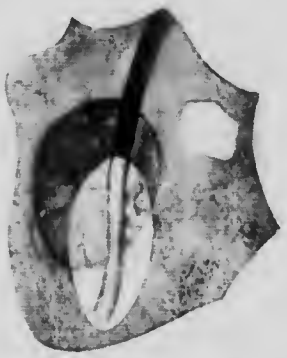
We have already, on several occasions, called attention to the basal facts regarding phagocytosis, and have shown that the unicellular organism and sundry cells in the multicellular organism have the power of actively taking up foreign particles, organized and living, organic and inorganic, and that this process of phagocytosis is primarily nutritional—a means whereby the individual cell gains food material; that particles so taken up, if unfitted for assimilation, are discharged; if capable of affording food material, stimulate the formation of a digestive

[1] M. Metchnikoff has detailed his theory in his work "L'immunité dans les maladies infectieuses," Paris, Masson, 1901, of which an English translation has appeared. We would, however, recommend the student for practice in French to read it in the original, for it is of sustained interest and great value. A digest of his views is given by him in German in the fourth volume of Kolle and Wassermann's Bacteriologie.

vacuole around them, in which vacuoles we have indications of the presence of digestive ferments, and lying thus in the fluid the foreign matter is seen to undergo solution, until all that remains are a few granules of unassimilable debris which become eventually cast out.

Among such foreign bodies these phagocytic cells are able to take up the various microbes, animal and vegetable. They can, indeed, as abundantly proved by Metchnikoff, take them up in a living condition, and, observing what happens, whether in the unicellular organism, like the amœba, or in the free leukocytes, cells of higher animals, we observe that there is the same formation of digestive vacuoles and destruction of the microbes by digestive processes. This under favorable conditions. And, as a matter of fact, the more carefully we study under the microscope the processes occurring within the organism during the course of infection, the more we become convinced that phagocytosis, whether by leukocytes or by endothelial cells, or by the newly developed "embryonic" fixed tissue cells, is extraordinarily common, and is obviously a most important factor in the destruction of pathogenic organisms and in the cure of infectious disease. There is, indeed, not a single disease due to known animal or vegetable microbes, where there is definite reaction on the part of the organism, in which at one period or other of its course phagocytosis, and that often very extensive, has not been observed. One has but to inject into the peritoneal cavity of one of the animals of the laboratory a little of the fluid culture of some mildly pathogenic microbe and examine a drop of the peritoneal fluid, or make a smear from the surface of the omentum in the course of a few minutes to a few hours (the time varying according to the virulence of the microbe), to find abundant leukocytes containing the bacteria in different stages of digestion. Or, more instructive still, take, after Leishman's method, a few drops of human blood from the finger, dilute, centrifugalize, pipette off the layer of white corpuscles and suspend these in the serum, add to the suspension a small platinum loopful of a suspension of some pathogenic microbe—the pyococcus aureus, for example—and place the mixture for a quarter of an hour in the incubator at 37° C. Upon examining a drop of the mixture under the microscope, the number of bacteria seen within the leukocytes and that have been taken up in this short time is very remarkable.

Fig. 166



Mode of destruction of a bacillus (B. anthracis) by a cell. A digestive vacuole has formed around one portion of the bacillus, and that portion has lost its power of staining. (After Metchnikoff.)

There can then be no question regarding the importance of phagocytosis as a factor in the destruction of microbes that gain entrance into

the system. There may be a question, however, whether it is the one supreme method of destruction of microorganisms and what is its relationship to the development of continued immunity. For the wandering cells of the organism, we know, have but a short life period, and if they gain the power of destroying bacteria they do not convey it to their descendants, for such descendants normally, we believe, do not exist. Before answering these questions there are other properties of the phagocytes which we must recall.

In the first place, with very virulent microbes no phagocytosis may show itself; there is a *negative chemiotaxis;* the leukocytes are not attracted, and those in the neighborhood, acted upon by the strong toxins, undergo dissolution. In the second we observe that in a typical localized infection, such as the abscess we described (p. 393) or in the pneumonic lung, for a considerable period the phagocytosis, if in evidence, is insufficient to destroy the microbes; the mere act of taking up living bacteria does not necessitate their destruction, and the number taken up may not correspond to the rate of proliferation; only at a later period, if the infection results in healing, does the phagocytosis become adequate. To explain these phenomena Metchnikoff invokes the property of *adaptation.* By accustomance, by dealing at first with small amounts of less concentrated toxins the leukocytes gain the power of withstanding and neutralizing larger amounts until a negative chemiotaxis or a weak positive becomes converted into an active positive chemiotaxis; and whereas at first the digestion was feeble, now it becomes powerful and rapid in action. These conclusions we cannot but accept; we have in Metchnikoff's remarkable studies the most convincing examples of the development of individual cell adaptation.

All these considerations, however, throw no light (1) upon the observations made, from 1888 onward, by Nuttall and others upon the destruction of bacteria *within the tissues* without the intervention of leukocytes; (2) upon the destruction of bacteria *in vitro,* by serum and other body fluids devoid of cell contents; (3) upon immunization against soluble bacterial exotoxins and the development of antitoxins, and, in fact, upon the development of antibodies against ferments, phytotoxins, and soluble "toxins" of all orders. How are all these phenomena brought within the terms of the theory?

As to the first, that such destruction takes place cannot be controverted; it is most obvious in Pfeiffer's original method of gaining his reaction in the peritoneal cavity of the guinea-pig immunized against cholera or typhoid; the peritoneal fluid is found to contain relatively few leukocytes and abundant swollen and globular bacteria undergoing destruction. Metchnikoff ascribes this extracellular destruction to a preliminary *plasmolysis* or *leukolysis,* to a destruction of leukocytes, whereby their digestive ferments become liberated into the plasma and able to act upon the bacteria in an extracellular manner. This view, that it is the leukocytes that in the main afford the bacteriolytic substance, is supported by the observations of Denys and his pupils and of Buchner and his pupils, that if a "sterile" suppurative inflammation be induced, as

by the introduction into the pleural cavity of finely powdered glass or alcuronat (a vegetable protein), the exudate, rich in leukocytes, possesses distinctly more pronounced bactericidal properties than does the blood plasma and other body fluids, or even the blood serum of the same animal. Metchnikoff admits fully that the amboceptors (his *fixateurs*) pass out and become free in the ordinary plasma. These he regards as discharged by the leukocytes, but he is unwilling to accept or suggest excretion by the living leukocytes as an explanation of the presence of the complement (his *cytase*),[1] and he adduces certain important observations made by his pupil Gengou[2] in support of his contentions and as a proof that the plasma, even of an immunized animal, contains no complements. Gengou's statements are certainly most positive. If, employing Freund's method, the blood of an animal be received direct into paraffined test-tubes, there is no destruction of leukocytes and no clotting. Such blood centrifugalized yields according to Gengou a plasma wholly devoid of complements. Therefore—concludes Metchnikoff—the complement (cytase) present in ordinary serum was derived from the dissolution of leukocytes—they act normally as intracellular enzymes—and the theory of phagocytosis becomes expanded to this extent, that destruction of bacteria is recognized as being brought about either intracellularly by the digestive action of the leukocytes, or extracellularly by the enzyme-like action of the cytase, or complement, working through the intermediation of the fixateur, or amboceptor. But within the infected organism such liberation is infrequent, and throughout, it is cells which are potentially phagocytic that give origin to the antibodies.

Further, to complete the outline of Metchnikoff's theory, it has to be noted that he recognizes two broad groups of phagocytes, each having the power of acting more particularly upon one set of substances; the *microphages* (polymorphonuclear leukocytes, eosinophiles, etc.), and the *macrophages* (hyaline leukocytes, endothelial cells, and fixed phagocytes); the former he finds more particularly active in opposing the bacteria of acute disease, the latter those of chronic disease, as also acting upon cells. Instead of a multiplicity of complements, as demanded by Ehrlich,

[1] Here it may be well to afford a table of the various terms employed by different observers to indicate these two bodies, the amboceptor or immune body and the complement respectively:

SYNONYMS.	
Amboceptor.	*Complement.*
Intermediate body.	Addiment (Ehrlich's first name).
Immune body (R. Pfeiffer).	Cytase (Metchnikoff and Bordet).
Fixateur (Metchnikoff).	Alexine (Buchner).
Sensitizer or	
Substance sensibilatrice (Bordet).	
Preparator (Müller).	
Copula.	
Desmon.	

[2] Ann. Pasteur, 15: 1901: 68 and 232. See also Levaditi, ibid., 15: 1901: 894, and 16: 1902.

he recognizes only two—macrocytase developed by the macrophages and microcytase by the microphages. The immune bodies he regards as derived also from the leukocytes.

His grounds for this are the following: In immunizing an animal against erythrocytes, spermatozoa, and other cells it is seen that the foreign cells are taken up by one order of cells, the macrophages. It is these cells alone that are directly involved, and thus, in the process of digesting, the cells must develop the antibodies. Of these, the amboceptors (fixateurs) are secreted, the complement (macrocytase) remains within the cell.

If, finally, these are the deductions to be drawn from cases in which we are able to follow the fate of discrete bodies, such as bacteria and various cells, where we can see that *within the organism* it is the phagocytic cells that act upon them, and where we can determine that these phagocytes afford the antibodies, then it is justifiable to assume a like activity on the part of the potentially phagocytic cells in the case of soluble toxins.

These latter conclusions are far from having been accepted in their entirety, and we must briefly note some of the more important contradictory observations. As regards *plasmolysis* affording an adequate explanation for the liberation of the complement in Pfeiffer's reaction, Durham and Gruber have pointed out that the destruction of leukocytes in the peritoneum is only apparent. Following upon the introduction of the bacterial culture, the leukocytes are not destroyed; they become clumped or balled upon the surface of the omentum and mesentery (these observations, however, do not exclude wholly the dissolution of a certain number of the leukocytes). Pfeiffer has pointed out that the presence of increased complements in connection with Buchner's aleuronat experiment does not necessarily indicate that these are derived from broken-down leukocytes, and shows that if leukocytes so gained be centrifugalized and carefully washed they afford not a trace of complement. (To this Metchnikoff objects that the repeated washing has artificially removed the cytase—but if they pass out with such ease under these conditions, may they not also diffuse out freely in the living organism?) Several observers also have given the "lie direct" to Gengou's observations. The majority, however, have not employed his method, using other means (oxalate, leech extract, etc.) to arrest the coagulation of the blood—methods which possibly lead to alteration in the leukocytes and liberation of the complements. But Lambotte,[1] employing the same paraffined test-tubes, detected the definite presence of complements in the centrifugated plasma (not, so far as we can see, in the same amounts as when clotting has occurred and certain leukocytes have undergone dissolution).

Nor is it possible, in the light of Ehrlich's observations, to accept Metchnikoff's dictum that there are only two cytases (complements); and lastly it is, in our opinion, impossible to harmonize Metchnikoff's

[1] Centralbl. f. Bakt., Abt. I, 34; 1903; 153.

theory with the observations of Wassermann, Ransom, and others that tetanus and other toxins are absorbed by the nervous tissues and there neutralized. In connection with hemolysis Metchnikoff lays down very precisely that it is the cells which absorb the "toxin" that furnish the antibody. The same process of reasoning would lead us to conclude that the nerve cells which neutralize the tetanotoxin are capable of furnishing the antitoxin. In our experience one of the most marked features both of nerve cells proper (and it is the gray matter which mainly absorbs the tetanus toxin) and of neuroglia is that whether in general septicemias or in localized bacterial inflammation of the brain and cord, neither of these forms of cells show a trace of phagocytosis. Of all the cells of the body, they may be said to be the least potentially phagocytic. Römer's striking observations, already noticed (p. 472), upon the local production of anti-abrin in the conjunctiva of the rabbit are absolutely opposed to this narrower view.

On the other hand, as regards hemolysis in general, we would accept Metchnikoff's view rather than that of Ehrlich regarding the production of the hemolysins. These, by the supporters of the side-chain theory, are regarded as being developed by the red corpuscles, according to the general law that the cells which absorb the toxin produce the antitoxin. Metchnikoff shows that when foreign erythrocytes are injected into the body they are taken up by the macrophages; it is these cells in the spleen and elsewhere that more probably provide both hemolysins and antihemolysins. If, that is, a hemolysin be developed by inoculation of erythrocytes of another species, that hemolysin, it is true, inoculated into animals of that other species acts directly upon the red blood corpuscles and leads to the liberation of their hemoglobin; but in the organism the stromata of the destroyed blood cells are taken up by endothelial and other cells, and these living persistent cells it must be that produce the antibodies. The same must be true in connection with the development of the hemolysin in the first place. The brief existence of the erythrocyte, its incapacity to reproduce itself and convey acquired properties to its descendants, are also against the supposition that these cells actively produce antibodies. We have, indeed, the observations of Calmette[1] and Jacobi[2] that the red corpuscles of animals rendered highly immune to such hemolytic agents as cobra venom and ricin still remain highly susceptible to the hemolytic action of these poisons, and Ehrlich[3] himself has regarded an apparent exception, recorded by Kossel in the case of the rabbit immunized against eels' blood, as due not to the acquirement of antibodies by the corpuscles, but to the loss or exhaustion of the susceptible receptors. It is, in short, contrary to experience that a non-nucleated cell should exhibit the highest forms of biophoric activity, and as such must be regarded the power of multiplying its specific receptors and to this extent of undergoing growth. This does not prevent us from accepting Ehrlich's view that the red corpuscles are provided

[1] Compt. rend. Acad. des Sciences, 134: 1902: No. 24.

[2] Hofmeister's Beitr., 2: 1902.

[3] Loc. cit., 569.

with relatively abundant receptors of weak combining powers, so that they readily give up to the more avid receptors of cells proper, substances which have entered into combination with them, and act as the great common carriers of the economy.

The observations of Wright, also, upon opsonins, abundantly confirmed as they have been by numerous observers, and slighted but not contradicted by Lævaditi,[1] indicate that the phagocytes while playing an all-important part in the destruction of bacteria possess an adjuvant in the surrounding fluid. Where this adjuvant is developed we do not as yet know; the fact cited by Lævaditi that in the absence of the serum, leukocytes suspended in an inert fluid can, very slowly, take up bacteria, suggests that the opsonins also may be developed by the leukocytes, but certainly does not prove that these form the only or the main source.

Conclusions.—A careful balancing of all the facts appears, therefore, to lead to the following conclusions:

1. Phagocytosis proper (*i. e.*, the ingestion and digestion of bacteria) is a great factor in the destruction of microbes entering the system.

2. By accustomance and adaptation to the products of bacterial growth and to other toxins, both on the part of the leukocytes and other potential phagocytes in a local area of infection, and of the mother cells of those leukocytes in the bone-marrow and elsewhere, the phagocytic capacity may be markedly increased, and in this way a continued immunity be materially aided.

3. The cells which Metchnikoff regards as phagocytes and potential phagocytes, while they are those most commonly invoked to neutralize bacteria and bacterial and other toxins, are not the only cells of the organism possessing these powers.

4. With the exception of the red corpuscles (which are not cells proper), the rule would appear to be that those cells which take up microbes and microbic and other toxins are the cells which provide the antibodies.

5. Antibodies, whether present in the normal organism or developed in response to the introduction of particulate or dissolved toxins, are the products of cell activity, and their presence in the blood is a secondary process, either a true secretion (in this resembling glandular secretion proper) or to some extent, where there is cell destruction, the result of that cytolysis and of the freeing of substances previously bound in the cells.

6. Produced within the cells these antibodies can act within the cell and then bring about a condition undistinguishable from ordinary intracellular digestion, though their strikingly specific powers suggest thus that intracellular digestion, instead of being a simple single process, is one that varies to an almost infinite extent, according to the nature of the substance entering the cell.

7. They can act also outside the cell, and in this case clearly neutralize the toxin by entering into combination with it.

[1] Ann. Pasteur, 1905.

8. Whether, therefore, we regard and study the processes associated with the development of immunity as occurring within the cell or apart from it, eventually we arrive at a common underlying chemical and physical groundwork for all the phenomena, and as we approach this point, although differences exist in respect to details, fundamentally the phagocytosis and the side-chain theories are not contradictory; they merely view the one set of phenomena from different aspects.

THE SIDE-CHAIN THEORY OF IMMUNITY.

Antibodies and the Side-chain Theory.—Rather than summing up in epitome the data acquired regarding the antibodies and their mode of action, it will be well to gather together and discuss the various data recorded in the previous chapters, and this first along the lines of Ehrlich's side-chain theory.

We have indicated the groundwork of that theory so far as it refers to simple toxins (p. 473); since then, discussing the cytolysins, we have become acquainted with a new order of phenomena, with the whole group of cases in which there is not simple union between the protoplasmic molecule of the cell, whether of the organism or the microorganism and the toxin—or the complement—but combination by means of an intermediate body or amboceptor.

Here, before going farther, it will be useful to draw up, in a tabular form, the various forms of toxins and antibodies which we have had under consideration:

Enzymes	leading to the production by organism of			antienzymes	Acting singly.
Phytotoxins	"	"	"	anti (phyto) toxins	
Bacterial exotoxins	"	"	"	antitoxins	
Proteins (animal, vegetable)	"	"	"	precipitins	
Bacterial proteins(?)	"	"	"	agglutinins	
Bacterial aggressins (?)	"	"	"	opsonins	
Animal venoms (simple)	"	"	"	antivenins	
Animal venoms (complex, requiring intermediation of complement for action	"	"	"	antihemolysins, etc.	
Foreign complements	"	"	"	anticomplements	
Foreign amboceptors	"	"	"	anti-amboceptors	
Vegetable cells (bacteria)	"	"	"	bacteriolysins	Requiring interaction of 1 amboceptor (specific), 2 complement (non-specific).
Animal cells of various orders	"	"	"	cytolysins, hemolysins, leukotoxins, hepatolysins, etc.	

Studying this table, it will be noted that we advance from (presumably) simpler to recognizably very complex substances. To quote Ehrlich and Morgenroth:[1] "If relatively simple bodies have to be assimilated

[1] Zur Theorie der Lysinwirkung. Ehrlich, Gesammt. Abhandl., 1904: 15.

by the side-chains, the presence of a single binding group is adequate, and, obviously, it is side-chains of such simple structure that attach the toxins. The conditions are, however, quite different in dealing with giant molecules (protein molecules). In this case, with fixation of the molecule for purposes of cell nourishment, only the preliminary stage is a matter of concern. Giant molecules are, as such, useless for the cell, and can only be rendered serviceable when they become dissociated and broken up into smaller parts by fermentative processes. Such dissociation would fittingly be gained if the 'seizing arm' (Fangarm) of the protoplasm, carrying simultaneously a fermentative group, brought this latter into immediate relationship with the booty that needed digestion and assimilation. We find an identical tendency for the seizing apparatus to be, at the same time, provided with digestive action in the whole series of the insectivorous plants, and this in the most varied forms. The tentacles of the Drosera, for instance, are secreting and digestive 'fang arms' in the broadest sense; they cover the object seized with a juice having powerful digestive properties.

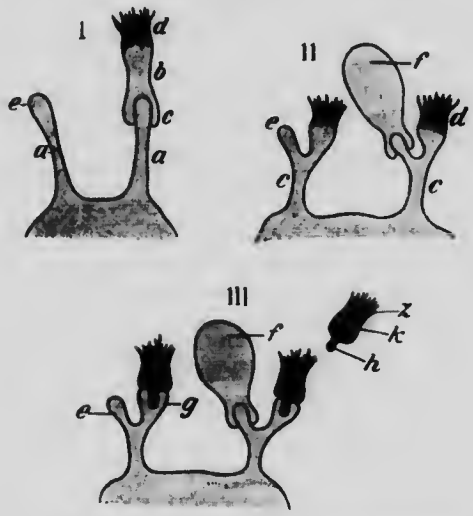
"When we note that lytic action occurs not in association with toxins, but where cell contents, whether of bacteria or blood cells, have to be absorbed, the simplest explanation is that here we are dealing with proteins of high molecular composition which are of much more complicated structure than cell secretions, for such we must regard toxins. We must conclude that to combine with these and other highly complicated bodies the cell molecule possesses side-chains of a special order, which, in addition to the seizing complex, possess another complex capable of fixing the particular ferment, and so bringing about the digestion of the seized molecule. If, through immunization, there is developed an excessive production of side-chains, then the whole of this side-chain with its two complexes will be generated and discharged into the blood as an immune body. The remarkable process whereby, as a result of introducing bacteria into the system, a matter is generated which leads to the dissolution of the bacteria receives in this way a simple and natural explanation. We deal once more with the reproduction of one of the processes of normal cell activity."

Ehrlich's Three Orders of Receptors.—Continuing along these lines, Ehrlich distinguishes three orders of receptors in the cell, whether for the assimilation of food or for seizing of toxin molecules. (1) The relatively simple toxins and ferments are anchored by a receptor of the first order (Fig. 167, I, *a*), a side-chain possessing simply a haptophorous complex *c*, to which the toxin *b* becomes anchored by its haptophore *c*. (2) For (compound) protein molecules he holds that more complex receptors are requisite. In the first place, it is evident that the cell in the process of assimilating ordinary protein food molecules by its fermentative activities dissociates them, and the same would appear to be true regarding agglutinins and precipitins. The side-chains which anchor molecules of this order must possess both a haptophore and a zymophore (corresponding to the toxophorous moiety of the simple toxin molecule). This form of receptor is indicated in Fig. 167, II, in which

c represents the haptophore, *d* the zymophore. It will be seen that this is the converse of the first case: the haptine or free molecule or side-chain *b* of Fig. 167, I, is identical in properties with the attached receptor of Fig. 167, II. (3) For the cell to act upon the yet more complicated substance of bacterial and animal cells it has to anchor not only the cell molecule, but also the complement. This type of receptor is indicated in Fig. 167, III. There the complement, *k*, is represented as possessing a haptophore *h* and a zymophorous, or more accurately zymotoxic moiety, *z*, while *f* represents the cell molecule that is acted upon.

When these receptors are produced in excess and become discharged, they are termed by Ehrlich *haptines*. They possess the same properties

FIG. 167



The three orders of side-chains according to Ehrlich.

of attachment as they do when existing as fixed side-chains of the protoplasmic molecule. Thus they are recognized haptines of three orders: those possessing a single haptophore group, those like the toxin molecule above noted with a haptophore and zymophore group (these two are both regarded as immunoceptors), and those with two haptophoric affinities, the amboceptors or immune bodies proper. Of these free receptors or haptines Ehrlich, as a result of a consideration of their properties, lays down that:

Haptines of the first order include antitoxin and anti-enzymes.

Haptines of the second order agglutinins and precipitins.

Haptines of the third order include cytolysins and bacteriolysins (amboceptors).

It is now more usual to refer to these free receptors—to bodies that

are capable of entering into combination with the cell molecules and of stimulating the formation of antibodies—as *antigens*.

It will be observed that in this scheme no note is taken of, or, at least, no stress is laid upon, the group of original attachment of the haptine or antigen to the protoplasmic molecule. Nevertheless, there must here be an unsatisfied affinity.

We cordialiy accept Ehrlich's scheme in its general bearings, and cordially admit, as must everyone who has followed the development of this department since first the theory was enunciated, that from the results obtained by working along the lines of the theory, it has more than justified itself. As by Mendeljeff's theory the chemists and physicists have been able to predict and discover new elements, so, by this theory, Ehrlich and his fellow-investigators have been able to predict with confidence the existence and properties of a series of antibodies. When such a statement can be made regarding any theory it is obvious that, if not complete, it approximates to the truth. Nevertheless, as indicated in our discussion of the toxins, in certain of its aspects—in matters which are of some importance although not fundamental—we are not quite satisfied that the theory perfectly represents the relationships between the toxins and the cell molecule. Just as we doubt whether primarily, at least, the bacterial toxins become directly anchored on to the cell molecules or biophores, so in cytolysis we doubt whether, under any circumstances, there is direct union between the biophores of the animal cell and the bacterial or animal cell introduced into the system, even when that foreign cell is ingested by a phagocyte. We doubt, that is, the correctness of Ehrlich's diagram which we have reproduced. That, it is true, is merely a diagram—a graphic simile—and, like similes in general, must not be tested too severely. It expresses, however, a relationship which we are convinced does not exist. As indicated by what occurs in ordinary gastric and tryptic digestion, as indicated also by the formation of digestive vacuoles around particles of foodstuff ingested by the phagocytic cell, the dissolution of foreign protein molecules is mediate and not immediate; it is always by free side-chains, or haptines, and it is the loss of these side-chains the condition of partial unsatisfaction thereby produced, and not the direct stimulus of direct contact and combination of the foreign matter into the protoplasmic molecule, that affords the stimulus for the production of new side-chains and so the active development of immunity.

Constantly in striving to comprehend the processes which are concerned in the destruction of bacteria and their products, the neutralization of cell products, and development of immunity, we find ourselves brought back to the fundamental fact that these constitute but special cases of the dissociation of foodstuffs, of assimilation and digestion. The processes which occur when a cell destroys an ingested microbe must be identical with those which occur when it digests any other foreign matter, and bacteriolysis in the body fluids must be brought about by procedures of the same order as occur when fibrin is digested in the gastric juice. If we admit that enzyme action is throughout opera-

tive in the one case, we must accept its operation in the other. That there may be—nay, that there are—different grades and orders of enzyme action must be freely acknowledged; the mode of action of ptyalin upon starches, which appears to be direct, is different from that of enterokinase upon proteins, which requires the intermediation of trypsin to render it complete.[1] It follows, therefore, that we must regard all these processes as examples of one or other stage of enzyme action, that we must conclude that toxins and cytolysins are enzymes, and that the data we have acquired regarding these and their mode of action reciprocally gain their explanation from what we know concerning the laws of enzyme action and advance our knowledge of these laws.

This, it may be said, is proceeding farther than many are prepared to advance at the present time. There is, indeed, a remarkable nervousness exhibited toward the proposition that toxins are ferments, which is to be explained, in the first place, as due to the fact that we do not know the composition and structure of either the one or the other, and in the second that so specialized has modern science become that we have at the present time three distinct groups, distinct in methods and distinct in aims, working at this very subject, each, with the best of good-will, recognizing with difficulty what for the other two groups are the points of fundamental importance. The chemists are interested in bringing enzyme action into line with the catalysis of inorganic matter, and at the present time the trend of their observations upon the latter is to indicate that it is of the nature of a physical contact action, and not of a true chemical combination, however temporary; they deny also that enzyme action is chemical, and, so, logically, when it is demonstrated that toxin combines with antitoxin, they are bound to deny that the toxin is an enzyme. The physiologists are torn asunder between their attempts to render physiological chemistry an exact science and to follow the guidance of the pure inorganic chemists on the one hand, and their affinities with the pathologists and bacteriologists on the other; the pathologists and bacteriologists by methods widely different from those employed by the chemists, although at the same time remarkably exact, have accumulated a vast mass of important data on enzymes, toxins, cytolysins, and so on, and their powers of combination, and as these hang together and do not harmonize with the deductions drawn by the chemists as to enzyme action from the study of inorganic compounds, they are content to group their data as a class apart and to continue gathering more facts and applying the same.[2]

[1] It is usual to express this reaction in the reverse manner. The observations of Bayliss and Starling show clearly, as opposed to Delezenne, that the activating substance is the kinase, which has properties corresponding to those of the bodies we recognize as ferments.

[2] The present confused state is well exemplified by Benjamin Moore's always suggestive, but—it seems to us not always wholly logical—recent article (Recent Advances in Physiology, edited by Leonard Hill, 1905). Moore concludes that "it is most probable that the influence of the enzyme as an energy transformer is one of a physical character; at any rate, the formation of chemical compounds must

We, on the other hand, cannot but see, in all the evidence that has been brought forward regarding enzyme action, the aptness of E. Fischer's conclusions in his studies upon fermentative glycolysis, namely, that the enzyme must be regarded as fitting into the molecule group it dissociates as does a key into a lock, and see here not the evidence of contact action, but of chemical combination, and see this same striking specific action in connection with toxins and antitoxins. We admit that the specificity is, as regards the substratum as a whole, not absolute. The same enzyme may act upon two different bodies, or two different enzymes can dissociate one substance, as, for example, both invertase from yeast and amygdalase from the bitter almond will act on the glucoside, amygdalose. But what is specific in all these cases is that for common action there must be present identical molecule groups to be acted upon. We need not adduce instances in which this is demonstrated to be the case in connection with toxins and antitoxins.

In short, the remarkable parallelism between the toxins and the enzymes, the proved existence of toxoids and zymoids, of antitoxins and anti-enzymes, of natural and experimentally acquired anti-enzymes (Bayliss), and other natural and acquired antitoxins, of complements and kinases, the evidence that a minimal amount of enzyme or toxin will, under favorable conditions in the one case convert a maximum amount of the substrate, in the other case so induce a dissociation of the substance of certain cells that death ensues, whereas under unfavorable conditions, both enzyme action and toxic action can be arrested; the arrest of action of both by the products of dissociation; the exact quantitative neutralization of enzyme by anti-enzyme, toxin by antitoxin —all these facts indicate that we are dealing with one common group of substances and with a group that act not by physical contact, but by chemical combination.[1]

be taken as unproved." At the same time, he accepts the fact that in all cases the products of reaction of an enzyme exercise a protective action against rise in temperature, *i. e.*, as Vernon has pointed out (Jour. of Physiol., 27: 1901: 288), whereas an active trypsin in nearly pure state is destroyed by a temperature of 38° C.; if protein on which it can act be present, a much higher temperature is necessary to render it inactive. There is no adequate explanation for such a phenomenon save the formation of a compound between the enzyme and either the protein or its dissociation products. And elsewhere discussing Adrian Brown's observations, which indicate that the enzyme forms a compound which persists for an appreciable time, all that he can suggest is that the "time interval of combination be regarded as constant in all cases," *i. e.*, he admits here that combination does occur. The combination of toxin with antitoxin he does not take into consideration.

[1] It is interesting to note that Moore, in his very full study of the properties of catalysers, lays down that there is a clear distinction between inorganic catalysts and organic enzymes. He lays down that, while similar in not being altered by the reaction they set up, the enzymes differ in that they require external energy in order to do their work; instead of causing energy to be given out by the chemical system, they cause the system to take up energy, and, lastly, they cause

Not knowing the structure of either class of enzymes or toxins, we must be content for the time to employ symbols to indicate the different stages of the process, after the manner introduced by Ehrlich. The molecule endowed with enzyme or toxic properties we must indicate as possessing surface (or cell complex) accurately adjustable to a corresponding surface on the fermentescible substance—Ehrlich's haptophore. We must admit with Ehrlich, also, the existence of a zymophorous or toxophorous moiety, and our study of enzyme action in general suggests how this acts. A chemical study of the substrate or fermentescible substance and the products of action demonstrates to us that enzyme action—as a general rule—proceeding in the one direction acts by hydrolysis, proceeding in the other results in the union of two molecules with the liberation of a molecule of water. A familiar example of this first process is the following:

$$C_{12}H_{22}O_{11} + H_2O = C_6H_{12}O_6 + C_6H_{12}O_6.$$
1 molecule of dextrose + H_2O = 2 molecules of glucose.

Obviously the molecule of maltose cannot be split into two equal portions: either that molecule is really a multiple formed of repetitions or polymerization of $C_{12}H_{22}O_{11}$ to some power of 2, or, if single, it becomes divided into 2 unequal portions. The simplest case of such unequal division under the action of an enzyme is:

$$C_{12}H_{22}O_{11} = \begin{cases} C_6H_{11}O_5 + OH = C_6H_{12}O_6 \\ C_6H_{11}O_6 + H \;\; = C_6H_{12}O_6 \end{cases}$$

namely, that the enzyme splits the dextrose molecule into two moieties one of which has positive, the other negative affinities, which when separated attract, the one a basic hydroxyl ion, the other an acid hydrogen ion. Our conception of the enzyme molecule must, therefore, be that it acts, whether as a base or as an acid, attracting and detaching one moiety of the fermentescible molecule. Take, for example, that it acts as an acid, then it detaches the complex $C_6H_{11}O_6$; but so soon as it accomplishes this, an H ion free in the solution, which could not act on the complete molecule, exhibits a greater affinity for the moiety than does the ferment, replaces this, and so the enzyme is free to act upon a second molecule of the substrate. Following Ehrlich's method we can express reactions of this order as in Fig. 164.

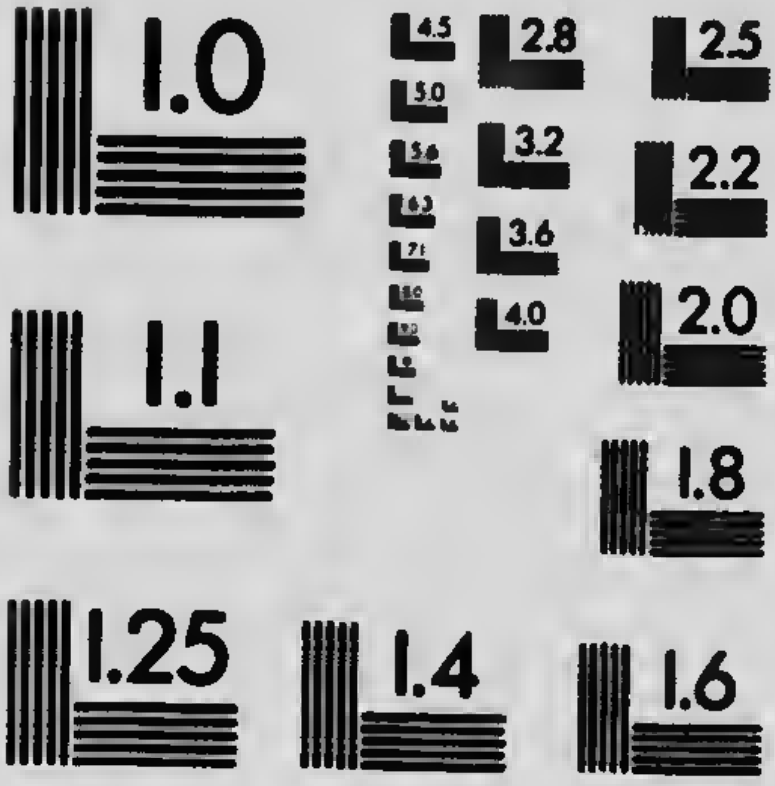
Or otherwise even in the simplest enzyme action we must recognize the cooperation of three factors: (1) the enzyme, (2) the fermentescible substance, and (3) the recipient. The existence of zymoids shows that the body or zymophorous portion of the enzyme may be so altered that whereas the haptophoric portion still is able to be attracted to and

a movement away and not toward the equilibrium point. He admits that all are not prepared to accept all these conclusions.

But it may be said the action of toxin on antitoxin is quite different from that of enzyme on its substrate. Certainly it is. It is not here that the parallelism comes in. What is of interest is the relationship *between enzyme and anti-enzyme action.*

MICROCOPY RESOLUTION TEST CHART

(ANSI and ISO TEST CHART No. 2)



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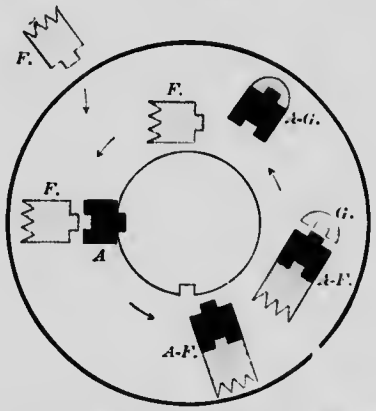
attach itself to the fermentescible molecule, the zymoid molecule as a whole is unable to split the latter; which being already satisfied cannot now be acted upon by other and active enzyme molecules.

In the more complicated enzyme action, such as has been demonstrated to occur in tryptic (proteolytic) digestion, following Bayliss and Starling we must regard the kinase, or, perhaps, more strictly the kinase plus the trypsin, as playing the part of the enzyme; the trypsin alone cannot split up the protein molecule and detach a peptone group; it has to be reinforced by the kinase, which, in its turn, cannot directly associate itself with the protein, its haptophoric group not corresponding to any of the haptophoric groups of the proteid.

The difficulty experienced—and this we would emphasize—in applying ideas gained from the study of enzymes to toxins and antitoxins is that

Fig. 168



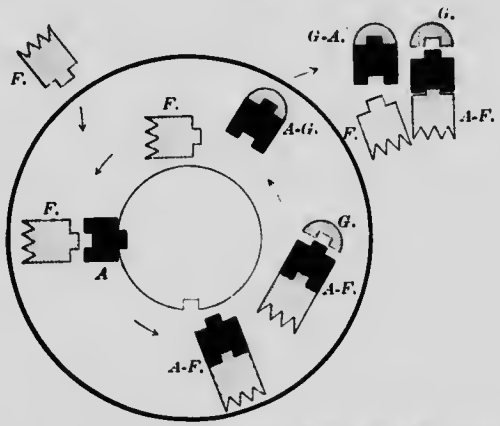
Simple enzyme action: *F*, the enzyme molecule has affinity for and detaches *A*, a side-chain of a protein molecule forming a temporary combination with it. When *A-F* is free the recipient *G* has a greater affinity for the side-chain moiety *A-F* combines with it, the enzyme molecule *F* becoming detached and ready to dissociate a second similar side-chain.

we are continually apt to confuse the latter with the fermentescible substances. *The two are distinct*, as will easily be recognized when we recall that the rennet ferment acts upon the caseinogen of milk, converting it into casein, but is completely arrested in its action by antirennin ("antilab"). In the one case the enzyme molecule acts as a carrier, as indicated in our diagram, in the other it becomes fixed and exercises no dissociative effects. Applying Ehrlich's terminology, the fermentescible and the anti-enzyme molecules possess identical haptophorons groups; the enzyme can become attached to both, but in the first place the affinities between enzyme and anti-enzyme are the greater, so that when both anti-enzyme and fermentescible molecules are present in a solution the enzyme is attracted to the former and not to the latter, and in the second place, when so attracted it is fixed and, what is more, is unable to dissociate the anti-enzyme molecule. The process of junction between fer-

ment and antiferment and between toxin and antitoxin is associative and self-limiting; that between ferment and fermentescible substances dissociative and recurrent, only arrested by the accumulation of the products of the reaction.

It is this distinction which is not clearly drawn by Professor Ehrlich,[1] and to us it appears to be of the very highest importance. If toxins are bodies of the same order as enzymes (and we have indicated that we cannot conclude otherwise), it follows that *the antitoxic side-chains developed in reaction to the presence of toxins are not identical with those dissociated by the toxins, whose dissociation leads to the symptoms of disease.* Or, otherwise, something in addition to the mere proliferation and overreplacement of the side-chains attacked by the toxin molecules is necessary to explain immunity.

FIG. 169



A-G, the side-chain combined with the recipient, when discharged from the cell into the surrounding fluid as an antitoxin molecule, is dissociated by the enzyme or toxin molecule *F*, which thus joining with *A* becomes neutralized.

We would tentatively suggest that but a slight although important modification of Professor Ehrlich's conception will meet the case. As we have noted in passing (p. 552) Professor Ehrlich in his conception of the junction of toxins and antibodies takes no note either in toxin or antibody of the group of junction with the original protoplasmic molecule. We would suggest that when dissociated, there must be in this position of the side-chains complex an unsatisfied or satisfiable affinity. If, now, we regard the toxin molecule when it gains entrance into the cell not as

[1] It is but right to state that throughout Professor Ehrlich is extremely reserved in his judgment regarding the relationship of toxins to enzymes. Wherever he approaches the subject he is most careful to leave the question an open one. As we have indicated in several places, M. Metchnikoff is very definite in his conclusions that the complements (cytases) are enzymes and that the whole process is one allied to the digestive processes.

becoming attached to the biophoric or protoplasmic molecule by means of one of the side-chains of the same, but, on the contrary, *as detaching that side-chain*, we can solve the difficulty. Namely, we can regard it as in this relationship, within the cell, acting as an enzyme, delivering over the detached side-chain to a recipient which has greater affinities for it and itself becoming free to act upon another side-chain.

It is this side-chain plus recipient which now becomes the antitoxin. In the cell itself it cannot act, the toxin having greater affinities for the still adherent similar side-chains of the protoplasmic molecules, unless the point is reached when equilibrium is established by the accumulation of products of the enzyme action, and by the overproduction and discharge of side-chains of the particular order into the cytoplasm or paraplasm. But when the excess of such side-chains plus recipients is discharged into the blood stream, then any circulating toxins, not having the greater attraction of the adherent side-chains of the cells they specifically influence, join with these antitoxins and become neutralized and are not attracted to and taken up by the cells.

Along these lines, and by considerations of this order, we most simply indicate the relationship between enzyme and enzyme-anti-enzyme action, toxic and toxin-antitoxin action. We regard the same orders of cell groups as being involved in both cases, we call in no external factor save the "recipient" which is demanded by any chemical theory of enzyme action, which recipient must be some simple but active ion present in all solutions in which the enzyme or toxin is able to act.

We might very considerably expand the considerations here brought forward, but to do so would render our treatment of this subject out of all proportion to the rest of the work. It is only necessary to point out that the same considerations can be applied to the case of cytolysis, and that in all other respects the data which have been brought forward in support of Professor Ehrlich's theory can, so far as we can see, be applied to this modification of the same.

Among the more important and authoritative works upon the subject of immunity are the various articles by the leading German workers on the subject, and by Metchnikoff, in the fourth volume of Kolle and Wassermann's "Handbuch der Pathogenen Mikroorganismen" (1904); Metchnikoff's "L'Immunité dans les Maladies Infectieuses," Paris, Masson, 1901, translated into English by Binnie, Cambridge University Press, 1905; Aschoff, "Die Seitenkettentheorie," Jena, 1901; von Dungern, "Die Antikörper," Jena, 1901; Jacobi, "Immunität," Heidelberg, 1906. In English, Ritchie has given a clear account of the different theories, Journal of Hygiene, 1:1902:215, 251, and 432, and Plimmer (of Ehrlich's antitoxin work), in the Journal of Pathology, 5:1898:189. Bolduan has published a clearly written "Immune Sera," New York, Wiley, 1907, and has translated most serviceably Ehrlich's "Collected Studies upon Immunity," New York, Wiley, 1907. Arrhenius' lectures upon "Immuno-Chemistry," delivered in San Francisco (Macmillan, 1908), have been painfully translated, and while full of important matter are scarcely to be recommended to the beginner. Another excellent account of the main phenomena of immunity is afforded (by Professor Hektoen) in a series of articles contributed to the Journal of the Am. Med. Assoc. from January to July, 1905, and republished in separate form at a very moderate price.

CHAPTER X.

SYNCOPE, SHOCK, COLLAPSE.

SYNCOPE.

With the reactions to injury must be considered a series of conditions of another order, conditions which are most often brought about by injury, which, nevertheless, just as we saw happened in the case of inflammation, may be wholly initiated by the higher nervous centres without any local tissue disturbance being at fault. These conditions are syncope, shock, and collapse. Some writers include the last two as synonymous; the symptoms are almost identical, but, following Cobbett,[1] we shall make some distinction between them. Admittedly, however, we have not a full grasp of the etiology of these states; much has still to be determined, even if, of late, material advance has been made.

Syncope, or fainting, is the slightest of the three conditions. The face suddenly becomes blanched, the pulse small, rapid, and at times almost imperceptible; a brief period of giddiness is followed by complete unconsciousness, the individual falling in a lax heap, often without time to hold on to a support or make any preparation. The condition is of relatively short duration.

In one series of cases we note nothing beyond the mechanical filling of the abdominal vessels, as when fainting supervenes upon emptying the distended bladder. Evidently closely allied to this is the syncope which at times follows the sudden change from the supine to the erect position. In another, injury to or strong stimulation of sensory nerves is the exciting cause—pain of various degrees. Numerous cases are of purely emotional origin, and that not only in the weaker sex or in those of weak health. I recall vividly a football match years ago, and the scattered dropping, like pole-axed steers, of close upon half a score of the undergraduate onlookers, consequent upon the sharp loud snap of a leg bone of one of the players and the sight of his fall helpless to the ground.

SHOCK AND COLLAPSE.

In shock and collapse we have severer states. In extreme cases death ensues, and this in the case of shock with absolute suddenness. Sir Lauder Brunton cites the case of a mock trial conducted by certain Aberdeen students upon an obnoxious janitor, who, having been led to

[1] Allbutt's System of Medicine, 3:1898:320.

the block and there struck on the neck with a wet towel, was taken up dead. In less extreme cases there is recovery, but this after hours and days, instead of minutes. There is in both conditions blanching, with rapid, feeble, and, it may be, imperceptible pulse; the eyes become sunken, the cheeks also, the cheek bones prominent (*facies hippocratica*). There is complete muscular laxity; the breathing is irregular and oppressed, the breath cold; the external temperature of the body is very noticeably lowered. The pupils are dilated; retching and vomiting are frequently prominent. The patient lies limp and regardless of his surroundings. Unlike syncope, neither in shock nor collapse is there complete unconsciousness. Upon rousing the patient, the answers, if slow and obtained with difficulty, are quite rational; but all volition is abolished. In short, there is a marked general depression of function.

Etiology.—If we attempt to classify the conditions under which this syndrome presents itself, we find the following:

1. **Operations** or wounds associated with injuries to nerves. These may be: (*a*) Peripheral, affecting the nerve terminations, as in the shock that follows extensive burns, sharp blows upon the testicle, operative exposure and irritation of the peritoneum, irritation of the periosteum, as in amputation of the thigh (it has been found that the bone substance, as such, is comparatively insensitive, the periosteum very sensitive). (*b*) In continuity, as after severance of a large nerve, such as the sciatic. (*c*) Central, as after operations upon the brain and removal of cerebral substance. According to Howell,[1] the last of these (in the dog) is the most effective in producing this train of symptoms. With regard to all these it may be noted that pain is not essential. Shock may follow operations conducted under anesthesia sufficient to abolish all sensation.[2]

2. **Pain.**—Relatively intense irritation, without gross injury to peripheral nerves, may induce, not merely syncope, but the more profound state here described. Closely allied is:

3. **Emotional Disturbance.**—To this we have already referred.

4. **Severe hemorrhage,** whether (*a*) external, or (*b*) internal into the cavities of the body, induces a similar train of symptoms, as does

5. **Loss of fluid** from the blood through (*a*) persistent vomiting (as in hyperemesis gravidarum), or (*b*) excessive diarrhœa (as in cholera).

It is these last two conditions that we distinguish as *collapse;* all the former we include under the term *shock*. The only gross clinical difference between the two is that collapse in general is of relatively gradual development, whereas shock is of rapid onset. We shall point out shortly another partial distinction.

Studying these three states, we find one feature common to all, namely, a combination of cardiovascular disturbance, with grave

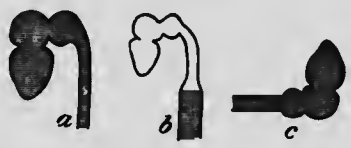
[1] Contributions to Medical Research, dedicated to Victor C. Vaughan.

[2] For full studies upon the relative liability to shock following operations upon different regions and viscera, the student is referred to Crile's "Surgical Shock," Lippincott, 1899, and "Blood Pressure in Surgery," ibid., 1903.

arrest of cerebral activity. Evidently the cardiovascular disturbance may be primary, as where fainting supervenes upon emptying the bladder, or the sudden assumption of the erect posture, or, in cases of collapse, where there is great loss of blood or of its fluid constituents. In the majority of cases, however, the indications are those of primary irritation or disturbance of the higher centres, whether direct or reflex.

The primary vascular disturbance is easily understood. We know that the vessels of the splanchnic area are capable of holding all, and more than all, the blood of the organism. The vessels of the liver alone are so distensible that they can contain all the circulating blood. That they do not is due (1) to the tone of the abdominal walls, whereby the viscera are definitely compressed, and (2) to the vascular tone, whereby, under normal conditions, the arteries more particularly, but also, as Goltz has shown, the veins, are in a state of partial contraction. Sudden removal of fluid from the abdominal cavity may so lessen the pressure upon the visceral veins that these may undergo rapid dilatation, the blood pouring into them to fill the void, and this to such an extent that, more especially when the individual is in an erect posture

FIG. 170



Schema of cardiac conditions in the "Klopfversuch" experiment on the frog: *a*, normal state of filling of inferior vena cava and heart; *b*, dilatation of splanchnic veins (erect position), heart in consequence empty; *c*, heart filled and circulation restored when the animal is placed on its back. (Sir Lauder Brunton.)

the blood is drained out of the vessels of the upper half of the body, so that little or none enters the right side of the heart. The result is not merely greatly lowered blood pressure in the radial and other arteries, but the brain is profoundly affected; the intracranial pressure is lowered, not merely by drainage away of the venous blood, but by lack of arterial blood supply, and this lack of intracranial pressure, coupled with the anæmia and lack of blood supply, is adequate to induce the unconsciousness seen in fainting. One can, indeed, produce temporary insensibility by compressing both carotids.

This is the simplest case; in other cases of syncope, brought on by nervous influences, it is evident that a similar disturbance of the circulation is brought about by nervous stimulation. We can, indeed, as in Goltz's well-known "Klopfversuch," induce reflexly this syncopal condition. It is but necessary, as Goltz showed, to tap a frog over the intestines to induce an arrest of the circulation, and, as he showed, the arrest is accompanied by an accumulation of the blood of the body in the abdominal veins. Hold the animal erect, and the exposed heart is seen to be still beating, but devoid of blood; place it on its back, or

with the head lowered, and the heart and the arteries become filled and circulation is resumed. Here I may note that the late Professor Roy and I[1] observed time and again how rapidly and extensively the arterial blood pressure could be raised by temporary compression of the abdominal area, whereby the blood becomes driven out of the abdominal veins into the right heart. It is a matter of familiar knowledge that recovery from a faint is best brought about by placing the individual in a recumbent position. It is not usual to reinforce this by steady pressure, applied to the region of the waist, although our experiments indicated that this procedure is likely to be even more effective.

As Sir Lauder Brunton[2] points out, a fuller study of the Klopfversuch indicates that, reflexly, by a tap on the abdomen, one, or both, of two effects may be produced—namely, inhibition of the splanchnic vasoconstrictor centres (whereby the abdominal veins become dilated), or stimulation of the cardiac inhibitory centre (vagus), whereby the beat of the heart is arrested. There are indications that in man either of these events may lead to syncope—and to sudden death. In deaths during operation under chloroform, which appear to come under this category,[3] it would seem that either or both of these events may be responsible; at times death is sudden, through arrest of heart action; at others, the heart continues to beat feebly for some time after the pulse has become imperceptible (vasodilatation).

What, then, is the difference between temporary syncope and more prolonged shock? In both we have indications of local splanchnic vascular dilatation and of cerebral disturbance, but the one condition is temporary, the other of long duration; the one is accompanied by complete unconsciousness, the other by depression merely of cerebral functions. It may be that we are not yet prepared to give the full answer. There are, it appears to me, sundry suggestive observations pointing to the solution of this question. We have already referred to the striking depression of all functions seen in shock. There is no perverted metabolism; the blood, it has been noted, is not toxic. But it is found that easily soluble drugs, such as alcohol, ether, strychnine (Roger), produce little effect; nay, more, they are not absorbed by the cells, and, with recovery from the state of shock, such drugs given in excess have then produced their physiological symptoms, and have even caused death. The mere act of dilatation of the vessels must favor rather than arrest the diffusion of soluble drugs; that they do

[1] On "Waist Belts and Stays," National Review, 1889.

[2] Practitioner, 11:1873:246. Collected papers on Circulation and Respiration, 1906:402.

[3] Such deaths, it has been noted by several observers, are apt to occur where, in trivial operations, the patient is not brought fully under the influence of the drug when the vagus centre is still capable of reflex irritation, but anesthesia has proceeded sufficiently far to arrest the splanchnic vasomotor constriction which normally follows severe stimulation of a sensory nerve; normally, these antagonize each other

not act would seem to indicate an actual inhibition of the tissue cells and arrest of cellular activities. Even in syncope, as first noted by John Hunter, the venous blood may become arterial in hue, but, as Sir Lauder Brunton explains, this is seen also in other cases, in which there is dilutation of the arterioles; it is not necessarily a sign of arrested cell activities in the capillary areas.

In shock, the arrest of bodily function is a most striking feature. Mere splanchnic vasodilatation and cerebral anemia may easily be recovered from; such, and such only, occur in syncope. In shock we have a more profound effect exerted, not merely on the vasomotor and cardiac centres, but upon the other centres—a condition, it would seem, largely inhibitory, arresting the function of the different organs.

It would seem that we have evidence of this nervous inhibition in the "spinal shock" of the lower warm-blooded animals. Divide the spinal cord in the dog in the lower thoracic or lumbar region and the reflexes of this area below the region of section disappear. The same is true in man, but, unlike what happens in man, gradually these reflexes in the dog again make their appearance—although the cord still remains divided. For a time the centres do not react to stimuli. We have, that is, a profound inhibition of centres other than the vasomotor, which is, in turn, recovered from. In man the spinal centres are so largely under control of those in the brain that, with central stimuli cut off, there is no assumption of automatic independent action.

Admitting this, it must also be admitted that the circulatory changes, if secondary, are the most prominent features in shock. And here it is not merely the diversion of blood into the splanchnic area, and the weak heart action that accompanies it, but, as shown by Roy and Cobbett,[1] this diversion leads to changes in the blood itself and in the tissues. By the most ingenious device of simultaneous testing of the specific gravity of the blood and tissues these observers demonstrated that in the course of shock the specific gravity of the blood becomes reduced, while that of the tissues increases. This can only be interpreted to mean that during the course of shock the volume of the blood is increased at the expense of the tissue fluids. This is in harmony with observations made by Sherrington and others upon the specific gravity of the blood following on hemorrhage—loss of blood is followed by a rapid fall in the specific gravity of that still remaining in circulation, and a similar rise in the specific gravity of the tissues. In other words, actual or relative loss of blood in a great part leads to a protective passage of body fluid into the bloodvessels, tending to preserve the circulation. This loss of fluid on the part of the tissues explains the development of the facies Hippocratica, the hollow orbits, the sinking in of the cheeks.

In collapse due to hemorrhage there is a similar reduction in the specific gravity of the remaining blood; in that due to profuse diarrhœa or vomiting, while the specific gravity of the tissues becomes raised,

[1] Allbutt's System of Medicine, loc. cit.

that of the blood becomes raised also. The loss of fluid from the tissues into the vessels is not sufficient to counterbalance the loss of fluid constituents from the blood into the intestinal tract.

Collapse thus differs from shock in mode of causation, rate of onset, and (in some cases only) in the specific gravity of the blood. If the main symptoms are identical, and if we ascribe shock to widespread cerebral depression, then a like cerebral depression must be present in collapse. This we firmly believe to be the case; only, while *in shock we regard the nervous disturbance as initiating the depression, in collapse we see that the depression of the higher centres is secondary to the continued cerebral anæmia.* We confess, however, that we are not inclined to draw too sharp a line of demarcation between these two states, while, further, we cannot but recognize that there are states in which shock and the blood changes characteristic of collapse are capable of being combined. Thus, as Crile has pointed out, one of the most sensitive tissues in the organism is the parietal peritoneum; severe handling of this in laparotomies is apt to bring on rapidly the syndrome already described. Nevertheless, Cobbett points out that prolonged opening of the abdominal cavity and exposure of the peritoneum is followed by rise in the specific gravity of the blood, there is evidently developed not merely a congestion, but a discharge of fluid from the vessels into the affected area.

Lastly, a word must be said regarding the condition of "shock with excitement," rather than depression; this, accepted as an allied form by the writers of last century, is apt to be dismissed by more recent writers as a bastard due to coincident stimulation of the cerebral centres by bacterial products. This we doubt. We have known it develop rapidly after a moderately extensive burn of the second degree affecting the front of the neck and upper part of the chest, the patient dying after six days, with symptoms of cardiac failure. A condition of almost maniacal, uncontrollable excitement supervened within an hour. The patient in this case presented a history of long-continued mental instability. We would only point out the familiar fact that sensory stimuli, which in one series of cases lead to inhibition of sundry centres, in another series of cases may produce, on the contrary, irritation of those same centres.

PART II.

THE TISSUE CHANGES.

CHAPTER XI.

THE PROGRESSIVE TISSUE CHANGES: HYPERTROPHY.

THUS far we have regarded morbid processes essentially from the aspect of their causation, discussing the changes brought about in the tissues by one or other order of disturbance. But these processes may be regarded from another point of view—one which, for an ordinary grasp of the subject, is most important—that, namely, of distinguishing and classifying these processes according to the alterations they produce in the tissues themselves. Or, briefly, while up to the present we have regarded these processes from the point of view of the irritant, from now on we shall regard these from the point of view of the tissues.

For any tissue, and for the cells of that tissue, there is a certain normal condition; within the limits of that condition we have the healthy state; outside of these limits, disease. Studying what are the factors determining this state of health, we recognize that these are two in number: (1) the nutrition of the cell, and (2) the functioning or activity of the cell. These are closely dependent the one upon the other. The more we study the more we realize this interdependence.

It is obvious, in the first place, that for the cells to remain healthy and active they must have nourishment; otherwise the destructive processes associated with life will exceed the constructive, and atrophy will ensue, and eventual death. Further, this nourishment is not a mere passive process. *Absorption is active:* the food taken in before it can be used up in the manifestation of the various forms of energy and of construction, must become part of the protoplasm of the cell.

The mere presence of a food molecule within the cell neither yields up energy nor increases the amount of living matter. It has to undergo dissociation, and some portions of the molecule, whether temporarily or more permanently, must become directly bound up with the living matter of the cell. And here while discussing nourishment, it has to be remembered that *quality* as well as *quantity* of the absorbed material has to be taken into account. Molecules of one order may supply energy to the cell complex, whether active or latent (bound up in the assimilated material); of another order, may so act upon the cell sub-

stance as to withdraw energy or inhibit molecular activities, acting as toxic agents.

As regards function, we recognize that up to a certain point the more active the cell the more extensive are the chemical changes proceeding in the protoplasm of the cell, and, with this, the more active the absorption of new material. Within certain limits, that is, increased activity becomes associated with increased assimilation. Contrariwise, diminished cellular activity demands diminished nourishment. Thus, the condition of the cell, healthy or otherwise, depends directly upon the functioning of that cell—a law applicable not only to the unit cell, but to the organism or individual as a whole.

As we have pointed out (p. 86), cell and organismal growth is intimately connected with the interaction of these two factors. Having already so fully discussed this subject of growth, we shall not enter into the matter in detail. We would, however, emphasize here the fact that a grasp of the factors influencing growth is essential for a proper understanding of the conditions we are about to discuss. That we possess a full knowledge of the factors underlying cell growth and cell shrinkage in all their aspects we do not in the least pretend to suggest; there is much that still remains to be determined. We do not know what it is that permits one cell, like the bird's ovum, to accumulate an enormous store of food material, and another, though bathed in nutritious fluid, like the bird's leukocyte, to remain small. We do not know what is the normal inhibitory force preventing a cell from developing, it may be, for months or years, or the force which suddenly stimulates that cell to undertake active growth and proliferation. At most, obscurely, we see a progressive unfolding, as it were, of environmental conditions, which modify the forces acting upon that cell from without. We are still debating, without having arrived at any sure conclusions, and without, it would seem, any likelihood of arriving at such, what are the forces which permit the regeneration of a part to proceed until the new development may reach, but does not exceed, the size of the lost organ. There are, however, certain general principles which we can recognize as being in action: that inadequate nutrition or lack of exercise of function, either of them, may lead to inanition and shrinkage of the cell unit to such a point that function is wholly arrested, and death may ensue; that excessive activity may lead to such using up of the cell substance that the absorption cannot keep pace with the disintegration, from which cause, also, cell death may ensue; that there develops an equilibrium between assimilative and functional disintegration such that the normal fully developed cell may remain for long *in statu quo;* that stimulation and functional activity somewhat above the normal, accompanied by adequate nutrition, may lead to growth, until again an equilibrium is reached (p. 93); that, also, an equilibrium tends to become established between cell mass and cell surface, nuclear mass and nuclear surface of such an order that the accumulation of living matter within cell and nucleus is beyond a certain point self-inhibitory (p. 35), or is apt to be followed by cellular and nuclear

proliferation (p. 94); that storage of energy, which is implied by growth and accumulation of cell material, and dissipation of energy, which inevitably accompanies functional activity, are opposed processes, which can only occur simultaneously within narrow limits (p. 87); that specialization of the cell through and for the performance of function in itself limits growth and proliferative capacity (p. 124); so that we find that the highly differentiated cell, as such, does not proliferate, and that the actively growing vegetative cells of the organism are either those which have never undergone specific differentiation to any degree, or, having been differentiated, have reverted to the undifferentiated, vegetative type. These are general conclusions which it is well to keep in mind. Here, as bearing directly upon the causation of pathological overgrowth, it is necessary to call attention to a controversy which dates back for its origin close upon twenty years, and which is still smouldering, upon the primary cause of that growth. We confess that we do so with some impatience. It seems to us that it is an outcome of overspecialization; that greater breadth of view, in the first place, and comparison with physiological growth in the lower and particularly the unicellular organisms would have eliminated that the position on the one side was untenable. Nevertheless, the debate has had the good result of leading to many valuable observations.

In 1889, Weigert[1] laid down, as the result of general consideration of the relationship of functional and vegetative activity, that pathological tissue growth "only occurs when, from any cause, there is disturbance of the reciprocal normal equilibrium of the tissue and tissue elements, and when the physiological restraint is removed which one tissue element exercises upon another." There cannot, that is, be a direct stimulus to growth from outside the cell; the tendency to grow is within the cell, and this is restrained by environmental conditions; these environmental conditions must be removed, the resistance diminished, and then proliferative changes show themselves. So great was Weigert's ability and authority, that this dictum was for a considerable time generally accepted, and conditions which, *prima facie*, appeared to be examples of growth due to stimulation were by hook or crook explained according to this hypothesis, even to the extent of explaining the giant cell as primarily due to defect in the cytoplasm, whereby the restraint was removed from the nucleus, so that now this proceeded to undergo direct division.

Ribbert[2] has expanded this hypothesis; he acknowledges that many factors bring about restraint of growth, not alone cell pressure, but relationship to the vessels and nerves, and differentiation for functional purposes; in short, new-growth on the part of the cell is regarded as being initiated by one and all the disturbances in function or cell relationship which disturb the equilibrium between the cells forming a tissue. He, too, it will be seen, denies that direct stimuli from without can initiate growth.

[1] Fortsch. d. Med., 1889: Nr 16.

[2] Virch. Arch., 150: 1897: 391.

But what is the cause of growth in unicellular organisms? Is it not obvious that when an amœba ingests a food particle it does so in consequence of a stimulus from without, that such stimulus precedes assimilation, and it is the assimilation that is the first step in growth and proliferation? Studying also these lower forms, animal and vegetable, we observe that physical and chemical agencies, acting from without, are capable of stimulating growth; that increased temperature renders it more rapid; that, as Jacques Loeb has shown, alteration of the surrounding medium will initiate the nuclear and proliferative changes in the ovum of lower forms of life, even in the absence of fertilization. And if thus clearly direct external stimuli can initiate growth in the lower unicellular organisms, what reasons are to be adduced against its doing so in the multicellular organisms? As a matter of fact, there are numerous instances of increased proliferative activity in the warm-blooded animal that can only be explained as brought about by direct stimulus. These have been well summed up by Lartigau and by Marchand.

How, as Marchand[1] points out, are we to explain the regeneration of the red corpuscles and the appearance of nucleated erythroblasts in the red marrow, following upon extensive hemorrhage, by the Weigert hypothesis? There has been no alteration of the surrounding cells. Or how explain the hypertrophy and hyperplasia, the overgrowth in cases of exercise and increased work—work hypertrophy? As we have already noted, and as we shall note again in discussing work hypertrophy, we are compelled to recognize that, within certain limits, increased function and the stimulus thereto is followed by growth; that, though beyond those limits cell work leads to a greater dissociation than assimilation, within those limits it favors growth. Thus, increased *strain* leads to growth. There may be, similarly, what Marchand terms a *tactile stimulus*, instancing the thickening of the epithelium upon exposed surfaces, and, as well shown by Bizzozero and Penzo's[2] experiments, *increased temperature* favors increased growth. They showed that if one ear of a young rabbit be kept at 12° to 15°, the other at 37° to 39° C., for a fortnight, the latter might become 1 cm. longer than the former, and skin, hair bulbs, and glands showed pronounced proliferation.[3] So, also, that if they caused symmetrical fractures of a metacarpal bone, warmed one extremity and cooled the other, in forty-eight hours in the region of the one fracture the periosteum showed abundant mitoses, while around the other there was none.

There are, also, the instances of *chemical stimulation*. How, for example, is the endothelial swelling and proliferation in the vessels in cases of inflammation to be accounted for by the Weigert hypothesis, or the marked swelling and proliferation of the endothelium of the lymph glands throughout the body, so abundantly demonstrated by

[1] Die Wundheilung, Leipzig, 1901: 89.

[2] Gaz. Med. di Torino, 42: 1891: 242.

[3] Sacerdotti, by similar means, obtained increased growth in length of one lower extremity as compared with the other.

Mallory in cases of typhoid and by T. McCrae in cases of burns? This we can only ascribe to the circulating toxins. We can induce similar proliferation by the inoculation of toxins. How, lastly, by this hypothesis, are we to account for the fact that free cells remain small—that the different forms of leukocytes, for example, circulating in the blood do not actually proliferate, and that when we excise a part of the brain, for example, although restraint is removed, the nerve cells show no sign of proliferation?

Many other instances might be noted at variance with this hypothesis. We are forced to admit that *there can come into action an external stimulus to active cell growth*. This, however, by no means necessarily means that tissue tension is not a factor in arresting growth, or that the interrelationship of the different components of a tissue is not of influence; only, for example, so long as the capillaries develop or dilate at the same rate as the specific cells of a gland can those cells continue to proliferate. With Ribbert, we must acknowledge that these are factors; only, over and above these restraining influences, there may be a direct stimulus which at times is sufficiently powerful to neutralize that restraint.

It follows from the above considerations that there is a relatively large number of combinations of conditions which may lead either to cell overgrowth or to cell shrinkage and degeneration. Leaving out of account those conditions in which there is equilibrium between functional activity and nutritional supply, we may have:

1. Normal functional activity of the cells, with increased nutrition.
2. Increased functional activity of the cells, with increased nutrition and assimilation.
3. Reduction in the external forces inhibiting cell growth; diminished tissue tension.
4. Normal functional activity, with reduced nutrition.
5. Normal functional activity, with perverted nutrition.
6. Increased stimulation and functional activity of the cells, with relatively insufficient nutrition (including here overstimulation of the cells).
7. Arrest of function of the cells.
8. Increase in the external forces, arresting cell growth.

These conditions, it will be seen, fall into two groups, which we may entitle the *progressive* and the *regressive* cell and tissue changes. A third group is to be noted in which we have to deal, not so obviously with changes in the living cell matter of the cell as with alteration in the paraplasmic matters stored within the cell. Such alteration, either of excess or defect, we find to be either due to, or to lead to, regressive changes in the cell substances proper; it is thus usual to include them among the regressive changes.

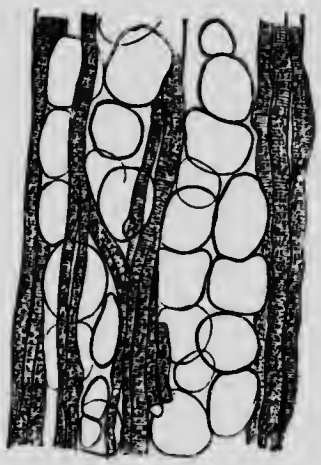
Lastly, there is the important series of cases in which we observe excessive cell overgrowth without our being able as yet to state with precision what is the primary cause. These we include, naturally, among the progressive changes, but with this admission.

Of these progressive changes we meet with several forms; these we will consider in order.

OVERGROWTH.

The overgrowth of a tissue in which the individual elements retain their physiological relationships and functions may be manifested either in an increase in the *size* of the individual elements—*hypertrophy*—or in an increase in the *number* of those elements—*hyperplasia*—or in the two combined. Yet another condition of increase in the size of organs—*pseudohypertrophy*—must here be distinguished. In this we have no overgrowth in the specific elements; but, on the contrary, an atrophy of the same, with replacement in excess by another tissue. Thus, in pseudohypertrophic paralysis, the great size of the muscles is seen to be brought about by an excessive interstitial deposit of fat-cells, with accompanying *degeneration*, and, in the main, diminution in the number and in the size of most of the muscle fibers. "Hypertrophic cirrhosis" is, in almost every respect, an unfortunate and misleading term; the condition most often indicated by this term is truly a pseudohypertrophy of the liver—or a hyperplastic cirrhosis or fibrosis of the organ.

FIG. 171



Longitudinal section through muscle of calf of leg in pseudohypertrophic paralysis. The muscle fibres exhibit atrophy, the increase in bulk is due to the excessive development of fat cells. (Orth.)

In other words, in speaking of the hypertrophy (or hyperplasia) of an organ, it is, for the sake of clearness, necessary to regard the specific elements of that organ, and refer to them only. In the liver, for example, while connective tissue is a normal constituent of this or every other organ, it is but the framework—the liver cells are the important specific constituents.

Once again we have to deal with imperfection of our pathological terms. "Hypertrophy" is employed loosely and commonly to designate all forms of overgrowth in which the elements retain their physiological relationships and functions—no matter whether there is increase in size or number of the same. Even if we overlook this, the term is in itself indefensible; its etymological meaning is "overnutrition;" thus, in itself, it is false, for overnutrition is, we now see, not the essential cause of the condition it connotes. The term is, however, so generally employed that we cannot cast it off, but must continue to employ it, regardless of its primary significance.

Such overgrowth may be either *inherited* or *acquired*. We have already considered the first group, the general or local giantisms, as

also the inherited overgrowth of individual tissues, when discussing anomalies (p. 205). The considerations then brought forward throw some light upon certain aspects of the acquired condition, which, first, we will pass in rapid review, and later discuss as regards the causes which have been in action leading to this development.

Acquired Overgrowths.—Of these the majority appear, as we shall point out, to come under the heading of functional or *work hypertrophies*, increased demands upon the tissue and increased activity, coupled with adequate nutrition, being the feature noticeable in their production; and in these we pass from examples purely physiological to those wholly pathological. Thus, at one end of the series must be placed the pregnant uterus.

1. **Physiological Hypertrophy.**—The overgrowth, both hypertrophic and hyperplastic, of the uterine musculature during pregnancy is most remarkable. The plain muscle fibers, according to Kölliker, become seven to eleven times as long and four times as broad as in the resting normal uterus. Associated with it we note: (1) Increasing distension of the cavity of the womb by the growing embryo, with pressure upon the walls; (2) greatly increased blood supply; (3) initiation of muscular contraction (from a very early period in pregnancy palpation shows that the muscle undergoes slow periodic contraction).

Other causes of distension of the uterus: fibroids, retained menses, which are unaccompanied by any pronounced increase in vascularity, result also in hypertrophy. The increased nutrition, therefore, cannot be regarded as the primary cause of overgrowth.

Next, we have a series of cases in the borderland between the physiological and the pathological: the blacksmith's arm and the excessive overdevelopment of muscle by exercise—a development which may approach the abnormal.

Here there can be no question concerning increased functional activity, coupled, we may add, with corresponding increase in nutrition, for, as is well known, coincident with mere active contraction of the muscles there is increased circulation through them.

Nor is muscle the only tissue that undergoes growth as a result of increased work. The strain brought to bear on the bones leads to increased growth of the tissue, showing itself more especially along the ridges and tuberosities of muscular attachment and muscular "pull." And, as we noted in discussing fibrosis (p. 412), the remarkable overgrowth of connective tissue following upon lymphatic obstruction, or in the walls of bloodvessels following upon increased blood pressure, increased tension (when not extreme) comes in the same category.

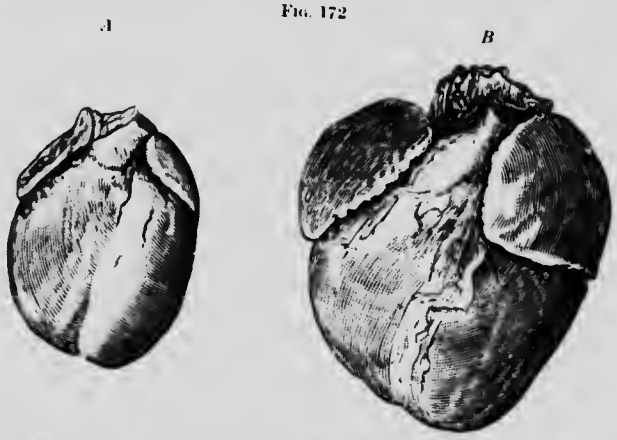
2. **Adaptive Hypertrophies.**—Allied to the above conditions, and clear examples of functional hypertrophies, are what we would term the adaptive hypertrophies. When there is obstruction to outflow, the muscular walls of hollow viscera are apt to undergo great hypertrophy.

Enlargement of the prostate, with obstruction to the passage of urine, or, again, stricture of the urethra, leads to great hypertrophy of the bladder, the individual muscle fibers being found twice as broad

as normal; this, again, when the obstruction is not extreme; where it is, hypertrophy gives place to dilatation of the viscus and thinning of the walls. In like manner, stenosis of the œsophagus induces hypertrophy of the upper œsophageal muscular coat; of the pylorus leads to hypertrophy of the stomach; narrowing of the rectum or of the bowel at any point to hypertrophy above that point. Quite the most common and characteristic example of this class is afforded by the hypertrophy of the heart which follows upon narrowing of the valvular outlets or obstruction to the arterial circulation. As Bollinger showed in the case of the Munich "beer heart," a like hypertrophy follows an increased load, *i. e.*, a larger amount of fluid to be propelled through the vessels.

The increased work leads to a very great overgrowth, both of the size and the number of the muscular elements. The organ, which, normally, in man weighs from 250 to 300 gm., may come to weigh as much as

FIG. 172



A, normal heart of rabbit; *B*, hypertrophied heart of rabbit due to repeated inoculations with small doses of adrenalin extending over several weeks. The adrenalin causes contraction of the arterioles, heightened blood pressure, and increased heart work. (From specimens by Dr. Klotz in the McGill Medical Museum. Natural size.)

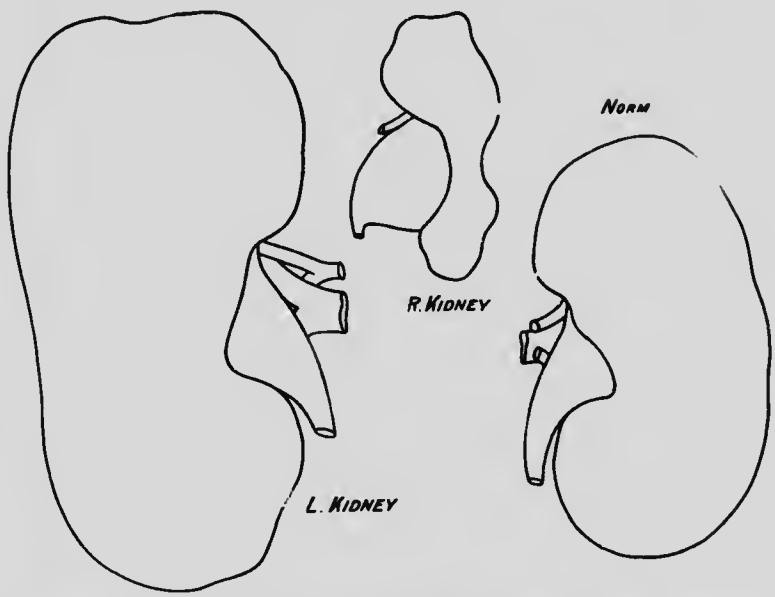
1980 gm. (Stokes' case). Here it must be noted that the hypertrophy is relatively much greater when brought about in the young individual, in whom the thickness of the right ventricle may come to equal four times the normal.

Closely allied is the overgrowth of the middle coat of the muscular arteries (as in the kidneys) in cases of increased blood pressure. In every one of these cases the increased work is of the nature of increased strain in tension acting on the individual cells of the tissue.

3. **Compensatory Overgrowth.**—Such muscular overgrowth is frequently referred to as compensatory, as, indeed, to a certain extent, it is. We prefer, however, to distinguish it as *adaptive*, and to employ the term compensatory for another series of cases, in which there is overgrowth of tissue to make up for *loss* of tissue of the same order.

Of such, many examples may be cited. If parts of several organs be removed, the cells of the remaining parts become enlarged (true hypertrophy) and undergo proliferation (hyperplasia), and, as in the thyroid, collections of cells which had been in a latent or persistent embryonic condition develop into fully formed active constituents. Thus, as Ponfick showed, if three-quarters of a rabbit's liver be removed, the remainder may hypertrophy in this way until it attains the size of the original organ. Or, again, if one of a pair of organs be (*a*) congenitally lacking in development, (*b*) destroyed by disease, or (*c*) removed experimentally or surgically, the other in a very short time shows

FIG. 173



Compensatory hypertrophy: *R. Kidney*, congenital hypoplasia; *L. Kidney*, compensatory hypertrophy (length, 14.5 cm.); *Norm.*, a normal adult kidney (length, 11.0 cm.). (Outlines made to scale from specimens in the McGill Medical Museum.)

enlargement, until it approximates toward the size and the weight of the original pair combined. And even, as has been demonstrated in the case of the thyroid and the kidney, if, after such hypertrophy of the remaining single organ, half of that be removed, the remaining quarter will still show great overgrowth. When, for example, one lung, or the kidney, through some intra-uterine disturbance, fails to undergo development, the other is found greatly enlarged; the same is true where one kidney or one testicle is the seat of destructive disease or injury to its blood supply, or where the kidney or testicle is removed by operation.

It may, indeed, be laid down that in all the paired organs of the body one member of the pair is capable of undertaking the work of both,

and in doing this undergoes hypertrophy. Indeed, in the brain there are indications that, as regards several centres, one is active and the other largely latent, so much so that through disuse it may later, if called upon to work by the destruction of the active member of the pair, be unable to respond wholly. This, however, is not the case in intra-uterine or early life, when, in addition to the hypertrophy, it would seem that hyperplasia can also occur in the nerve cells, though later this latter becomes impossible.

It may be laid down that *in all the paired organs of the body one member of the pair is capable of undertaking the work of both, and, doing increased work, undergoes hypertrophy.*

Certain limitations have to be made to this statement. One has already been indicated in the case of the brain centres. A more correct statement is that *primarily* one member of a pair has this capacity. In general, it may be laid down that, while hypertrophy occurs thus, *complete compensation* only shows itself in intra-uterine life. *The extent of the compensation is modified by the age of the tissues*, as, again, is the rate of compensation. The younger a tissue, the greater its capacity for growth; the older, the less. It is in cases of congenital and youthful valvular disease of the heart that we encounter the greatest cardial hypertrophy and hyperplasia; in cases of congenital absence of one kidney, that the other shows the greatest overgrowth. Only in these cases do we find one kidney attaining the volume and weight normal for the pair of organs. With removal or destruction late in life the compensation is much less complete, and, being slowly established, death may be brought about by disturbance of function.

Hypertrophy versus Regeneration.—A distinction must in these cases be drawn between hypertrophy and regeneration. It is not, it is true, perfect, because wherever hyperplasia occurs, there we have a regenerative process, and, in addition, a most typical regeneration often to some extent accompanies the hypertrophy where there has been loss of a portion of an organ. The feature, however, of hypertrophy is that, in an organ made up of cell complexes, the number of these complexes is not increased. There is no increase, for instance, in the *number* of liver lobules in the hypertrophying liver, or of glomeruli in the kidney undergoing compensatory hypertrophy (save in very early life); the individual complexes enlarge and become more cellular—larger liver lobules, larger glomeruli· increase, not in number, but in length, of the renal tubules. In regeneration, on the other hand, new cell complexes become budded off from the old. As might be expected, the more complicated the structure of an organ, and the greater the number of tissues entering into its composition, the less is there of orderly regeneration, the more pronounced is the hypertrophy. But even in the liver, part of which has been destroyed by removal or disease, as again in the kidney, we gain evidence of an imperfect regeneration.

4. **Vicarious Overgrowth.**—In yet another series of cases the compensation is more indirect; where one organ fails, there is overgrowth affecting organs of another order, though apparently of allied function,

these organs vicariously undertaking the work of the diseased, destroyed, or overworked tissues. One of the clearest examples of these cases has been afforded by Rogowicz and Boyce and Beadles, who have pointed out that where the thyroid gland is atrophied or removed, the pituitary gland undergoes definite enlargement. There is a certain amount of evidence of similar relationship between the thyroid and the thymus, while, according to some observers, atrophy of the pancreas is accompanied by enlargement of Brunner's glands in the duodenum. Where the spleen has been removed, the bone-marrow and certain lymph glands appear to take on some, at least, of its functions, becoming enlarged, more particularly the hemolymph glands;[1] while the enlargement of the spleen occurring in certain cases of anemia and the changes then recognizable in the same are regarded by Lœube and others as vicarious to this extent, that normally the spleen is a blood-building organ during fœtal life only; now, when the bone-marrow, the main source of red corpuscles during adult life, is inadequate to supply these in sufficient quantity, the spleen comes into activity and shows hypertrophy.

5. **Irritative Overgrowth.**—I have already dwelt upon the fact that substances which, in larger amounts and greater concentration, are toxic, leading to degeneration of the tissues or arrest of function, often, in smaller amounts, act as direct stimuli to the cells—and one of the effects of this stimulation of the cells to increased activity may be increased growth—this not, of necessity, secondary to tissue destruction, as in many inflammatory lesions, but primarily, as has been proved more especially by Wegner's observations on the increased growth of bone when minute doses of phosphorus are given,[2] and those of Ziegler and Obolonsky upon the influence of arsenic and phosphorus on the liver and kidneys.[3] It will be remembered that a study of the development of tubercles (see p. 402) proves that, under the action of bacterial toxins, there may be a similar local tissue overgrowth indeed, and that we have evidence that some, at least, of the *productive* fibrosis met with in various organs is probably of a like origin.

Mechanical stimuli, or irritation, of moderate grade may result in similar overgrowth. Years ago the late Sir James Paget pointed out that, whereas constant pressure, by cutting off the capillary blood supply of parts, leads to atrophy, recurrent intermittent pressure has the reverse effect.

6. **Nutritional Hypertrophies.**—It may, however, well be asked whether in these cases of toxic irritation leading to cell growth we are not dealing—as Virchow held—with increased nutrition, due to hyperæmia; whether the presence of the toxin in the cell does not lead to increased absorption and assimilation on its part? This may well be, but the entrance of the toxin is the primary event, and acts as the stimulant. If, however, we regard toxins, like other assimilated bodies, as

[1] For these, see more particularly Swale Vincent, Proc. Physiol. Soc., 1898: xl, and Warthin, Contrib. to Med. Research (Vaughan Festschr.), Ann Arbor, 1903: 216.

[2] Virchow's Arch., 55: 1872: 11.

[3] Ziegler's Beitrage, 2: 1888: 291.

potential foodstuffs, then we, perhaps, solve a long-standing difficulty. We refer to the following:

Mere hyperemia due to increased arterial blood passing to a part is never found to lead to hypertrophy. Or, otherwise, the mere abundant bathing of the cell with its ordinary nutritive fluid, without coincident call upon that cell to increased activity, does not cause it to grow. This fact is difficult to explain, nor do we know that we can offer an adequate explanation, there being one apparent exception that is classical. We refer to John Hunter's experiment of grafting the cock's spur on to the cock's comb, when, within a few weeks, the spur grows to a relatively enormous size. And the experiment has been confirmed by more than one modern observer. Here the point that immediately strikes one is, that the spur comes from a relatively non-vascular region and is implanted in most vascular erectile tissue. The increased hyperemia appears to be an essential factor in the overgrowth. There is this difficulty, however, that a few weeks later the spur begins to shrink and atrophy, and ultimately drops off. What relationship has this to the hyperemia? In speaking of implantation we shall meet with similar examples of preliminary overgrowth followed by atrophy. Not, by any means, all tissues exhibit the phenomenon when transplanted, nor even all embryonic actively vegetative tissues. It is not the mere hyperemia of the region of implantation, therefore, that induces the overgrowth. Some additional factor has to be invoked, and the only factor that can be suggested is that the blood, even the arterial blood, as it passes through different regions, becomes modified—here it has more oxygen, there less; here there diffuse into it, even into the smaller arteries, certain substances, there others have been absorbed from it—that, in short, the transplanted tissue receives a different pabulum from the normal, and that in some cases this in itself acts as a stimulant to active assimilation and growth. The mere diffusion of fluid into and through a cell, if the matter contained in that fluid is not taken up by the cytoplasm, does not favor growth. Assimilation is an active, we might say chemiotactic, process, depending upon the state of the cell at the time and the nature of the substance presented to the cell. Where a cell is not by nervous or other mechanisms stimulated to activity from without, and is in a state of equilibrium, it requires some abnormal constituent of the absorbed fluid to disturb that equilibrium and favor either increased building up, or increased breaking down of the cell substance.

If these views be correct, then there may be a nutritional hypertrophy, just as there may be a toxic degeneration of the cells, and John Hunter's experiment and the cell growth set up by dilute toxins fall into a common group.

In this group there are to be included also the tissue growths occurring in myxœdema, acromegaly, and osteo-arthropathy. In the first two of these we observe that there is an intimate relationship between the symptoms in general and disturbance of the internal secretions; the third in its general characters exhibits so strong a family likeness to the other two that we must associate it with them.

Myxædema is brought about by atrophic disease, arrested function, or removal of the thyroid gland, and its main symptoms appear to be brought about by absence of the internal secretion of that organ and accumulation of products in the fluids of the body which are normally neutralized by that internal secretion, for if thyroid extract be exhibited the symptoms disappear. It has been noted that in the earlier stages of the disease there is increased interstitial mucin in the subcutaneous connective tissues; later, this gives place to an hypertrophic fibrosis.

Similarly, *acromegaly*, in which there is a remarkable overgrowth of the bones of the head and extremities, has frequently been found to be associated with extensive disease of the pituitary body. That this condition is of the same order as, and allied to, myxœdema was strongly suggested by a case in the wards of my colleague, Professor James Stewart, in which tumor of the pituitary body was diagnosticated, but in which a myxœdematous condition of the hands replaced any bony enlargement. At autopsy we discovered a large endotheliomatous tumor of the pituitary.

The main feature of *osteo-arthropathy* is bony overgrowth of the extremities developing in adult life, secondary to chronic disease elsewhere. Marie, who first described the condition, regarded it as essentially secondary to chronic lung disease, and gave it the top-heavy name of "osteo-arthropathie hypertrophiante pneumonique;" cases have since been described in which the lungs have not been found involved.

Yet another class of cases is possibly to be included here. We refer to the so-called *sympathetic* overgrowths. These are largely physiological; the most marked example is the development of the breasts during pregnancy. We have no evidence that the nervous system is the exciting cause in these cases. The nerves, it is true, as in the case of muscles, may, by stimulating to increased function and dissociative activity, secondarily induce overgrowth, but in the cases under consideration the growing cells are not, so far as we can see, functionally active, and the tendency is to regard the effective stimulus as of an internal secretory nature, the increased assimilation and cell growth and proliferation being induced by products circulating in the blood. This view has recently received striking confirmation from certain experiments by Lane-Claypon and Starling,[1] in which it was shown that, by inoculating non-pregnant animals with an extract of fœtal tissues, enlargement of the mammæ is brought about.

If we regard this subject of nutritional hypertrophy from its broadest aspects, we see, as a matter of fact, that abundant nourishment has not led to the development of individuals of fullest growth. As with apples and strawberries, so with races of men, the best developed are found near the limits of tolerable existence. Not in the tropics, but in the upper temperate zone, do we find the races of men of the highest stature and best bodily development. The intestinal parasites bathed in food already partly digested are degenerates compared with the non-para-

[1] Lane-Claypon and Starling, Proc. Roy. Soc. B., 77: 1905: 505.

sitic members of the same orders. Where food is easily obtainable, that very ease reduces the need of active exercise, and want of use leads to diminished development. Activity and function in the cell, as in the individual, mean more active metabolism, better excretion of waste products, and better conditions of growth.

Passing beyond the limit in which active exercise assures good food—to within the arctic circle—we come again on small races of men. There is a certain mean between nutrition and activity of the tissues that is favorable. Abundant nutrition, with active exercise, would seem to afford the optimum conditions. We have indicated that in some cases it may be that increased nutrition, when it is of such an order as to lead to increased anabolism, may thus be the stimulus to increased activity on the part of the cell, but *in the majority of instances the reverse obtains; increased functional activity precedes and leads to overgrowth.* We would again recall what we have already emphasized, namely, that *excessive* functional activity has the very opposite result. There may be dissociation of the cell substance and liberation of energy beyond the compensatory assimilative capacity of the cell.

Simulated Hypertrophy.—Finally, we must note some cases, usually included among the hypertrophies, which externally appear to present some of the most marked examples, which, however, are not hypertrophies at all. We refer to cases in which parts persist owing to lack of attrition. The most marked examples occur in connection with the teeth of certain animals. Normally, in these animals, teeth that are opposed are undergoing constant and fairly rapid attrition, and to compensate for this there is constant growth. If, now, the opposed tooth be destroyed, the growth of that which is left proceeds without attrition, and the organ may attain enormous dimensions. Rats' teeth, for example, have been known in their growth upward from the lower jaw to curve inward into the orbit or pierce the roof of the skull.

CHAPTER XII.

REGENERATION.

Loss of substance, however produced, provided it be not excessive, and that it does not affect certain "vital areas," so causing immediate death, tends, in all living organisms, to be remedied by either regeneration of the lost tissues, or, as we have already indicated, by compensatory overgrowth of other parts and increase in their functions.

The extent to which regeneration occurs varies greatly in the different forms of life. Broadly, it may be laid down, with many exceptions, that *the simpler and lower the form, the greater and more complete the capacity for regeneration.*

The mere fact, however, that a form is low in the scale of living beings does not necessarily have associated with it the capacity for regeneration. We find some curious exceptions, in which members of allied species vary greatly in their regenerative capacity. Thus, a more accurate statement is, that among simpler forms of life we find the greater capacity for regeneration: the lower in the scale, the greater is its extent.

The illustrations of this principle are trite and familiar, the study passing back to the observations of Abbé Trembley, in 1740, upon the *Hydra viridis.* His were the first demonstrations that the power of parts to grow into the whole organism was a property of animal forms as well as of plants. He cut his hydras longitudinally into two and four parts, when each became a whole animal, some of which he preserved as long as two years; split them along one side when they grew together again, bisected the head and gained thus two-headed hydras; bisected these again, and gained many-headed hydras. Another abbé, Spallanzani, in 1768, made further advance, obtaining the regeneration of the head and tail segments of earth-worms when these had been cut off. In one experiment he obtained a new head five times in the one animal. He showed that in the salamander the tail was regenerated, even lost vertebræ being replaced, and that regeneration, as of the tadpole's tail or the limbs of the salamander, *is more complete the younger the animal.*

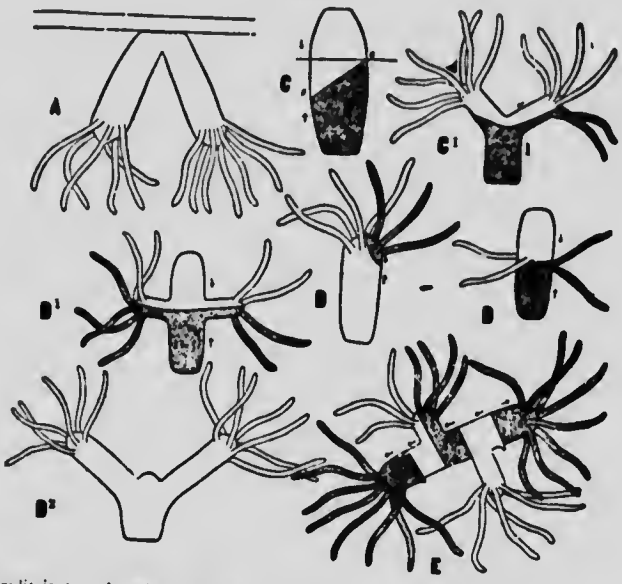
The abundant observations of late years have amply confirmed these earlier observations. Regeneration has been studied by Gruber and others in the protozoa, in which the sections containing the nucleus develop into the complete individual, while non-nucleated portions fail to regenerate,[1] in sponges, coelenterates, echinoderms, the various

[1] The observations of Gruber (Biol. Centralbl., 1904: 717, and 1905: 137) and of M. Nussbaum (Arch. f. mikr. Anat., 26: 1886: 485) are of special importance in establishing this fundamental importance of the nucleus in cell regeneration.

orders of worms, crustaceans, arthropods, vertebrates—in fact, through practically the whole animal kingdom.

It is found that the extent of growth in the normal individual is largely a function of relative position and relationship to neighboring cells. Remove the obstacle to continued growth by removing these neighboring cells, and in the hydra, for example, orally, mouth organs and tentacles develop; aborally, toward the foot, the newly proliferated cells take on the arrangement of the cells forming the foot.

FIG. 174



A, hydra split in two, hanging vertically downward; later, the halves completely separated; *B*, two posterior ends united by oral surfaces; B^1, same, it regenerated two heads, each composed of parts of both pieces; B^2, absorption of one piece leading to a later separation of halves. *C*, two posterior ends united by oblique surfaces; later, one piece partially cut off, as indicated by line; C^1, later still, two heads developed, one at *N*, the other at *M*; *D*, similar experiment in which only one head developed, at *M*; *E*, five pieces united as shown by arrows; four heads regenerated, one being composed of parts of two pieces. (King.)

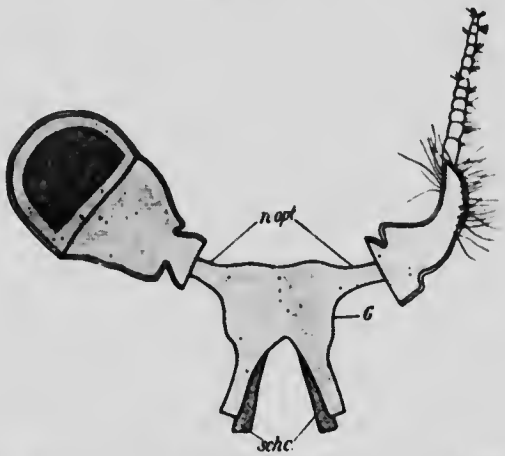
But the mere inter-relationship of the cells is not the only factor; external influences, also, determine the nature of the growth. Thus, as shown by Jacques Loeb,[1] *geotropism* may be a factor. Take a tubularian (a form allied to the hydra), cut off the head and foot ends, and invert it; place it upside down in the sand of the aquarium, and now a new head develops from what was the foot end, a new foot from the original head end. Indeed, so sensitive are these organisms to position that, if the position of the whole animal in the water be reversed, the foot end, even though uninjured, becomes converted

[1] Amer. Jour. of Physiol., 4: 1900: 60.

into a head. We dwell on these facts because certain observers, studying regeneration in higher animals only, deny this influence of external agencies to stimulate growth. The ultimate function of a cell and its capacity to proliferate are functions (1) *of its position relative to other cells*, and (2) *of the action upon it of external physical and chemical agencies.*

A very full consideration of regeneration throughout the animal kingdom is afforded in Morgan's work upon *Regeneration*,[1] which well deserves perusal. Some of the most interesting and valuable recent studies have been upon the vermes, notably upon the flat-worms (*Trematodes*), by Morgan, Flexner,[2] and others. Thus, as indicating the influence of one tissue upon the other, it has been noted that the

FIG. 175



Heteroplasia: regeneration of an antenna to replace an eye in the crustacean *Palæmonetes*. (Herbst.)

planarian head only undergoes perfect regeneration when the ventral nerve ganglion has not been destroyed. Similar observations have been made in the earth-worm. Allied to this is the remarkable phenomenon of *heteroplasia*. In certain crustaceans, for example, if one eye be removed, there develops in its place, not a new eye, but an antenna-like organ, *unless the ganglion cells connected with the eye have been left behind*, in which case an eye is redeveloped. From these facts it would appear that, *while the nerve cells do not initiate the regenerative process, they may influence the ultimate cell relationships and functions.*

Obviously, it is not the active functioning of the cells that initiates the regenerative process, for, in the earliest stages of a regenerating eye or limb of an arthropod, the new parts are, obviously, incapable of functioning.

[1] New York, Macmillan, 1905; see also his studies upon regeneration of Planarians, Arch. f. Entwickelungsmech., 7: 1898: 361

[2] Jour. of Morphol, 1898.

In the higher vertebrates and in man this capacity to reproduce lost organs and lost *parts* is wholly wanting. At most, we recognize the capacity to reproduce lost *tissues*, but this only within certain limits.

1. *If an organ be completely removed or destroyed it cannot regenerate.* Where portions have been destroyed or removed, the remaining parts may proliferate and bring about regeneration. With development, that is, the cells forming the anlagen of the different organs become so specialized that other cells cannot take their place. Remove a whole bone, and it is not replaced; leave what we have termed the cambium layer—the periosteum—and this may reproduce the lost substance.

2. *The higher and more specialized the tissue the less its capacity for regeneration.* Portions of nerve cells, nerve fibers, may grow again after destruction, but not the whole neuron. Muscular reproduction is very imperfect, as is that of most glands. When we consider that the regeneration of an organ means that not one but several tissues must undergo coördinate development, the higher specific cells of the organ, the connective-tissue framework, the vessels, and the nerves all assuming particular relationships, it becomes marvellous that so elaborate a part as the limb of a crustacean can be reproduced, and not difficult to realize that, in man, organs like the liver, while they may hypertrophy, do not regenerate. It is only simple glands, like the salivary glands and, to some extent, the thyroid, that actively regenerate, and that by a process of budding from the preëxisting ducts, and even then the regeneration is imperfect, and as the new-formed connective tissue contracts, the new acini are apt to atrophy.

Morgan, in his Harvey lecture, New York, 1906, comes to the same conclusion, as an explanation of the lack of regeneration of parts in the higher animals. The tendency on the part of the newly formed connective tissue to contract, and so induce atrophy of other cells, is, in our opinion, the main hindrance to adequate regeneration.

In the liver, after removal of a part, the surrounding bile ducts may give off cell processes, but, again, the new connective tissue arrests development into acini proper. The only cases in the liver in which true regeneration occurs are those of acute atrophy, with complete destruction of the specific cells. In these the framework is retained, and here, from the remaining bile ducts, regeneration may occur—regeneration, that is, of the old lobules (Ribbert). In the kidney, as pointed out by Galeotti and Santa,[1] true regeneration occurs in very young animals, the organ showing an increased number of glomeruli (and, therefore, of tubules); in older animals, there is purely hypertrophy. We here have the working of Spallanzani's law, that regeneration is more complete in the younger individual. In the skin, the hairs, sweat and sudoriferous glands do not regenerate, though in mucous membranes there is more or less imperfect reproduction of the follicles. Even with the lowest form of tissue—connective tissue—as we have already noted (p. 391), the regenerated areas are apt to be of imperfect development.

[1] Ziegler's Beitr., 31; 1902; 121.

3. So, also, in a given tissue, *where the cells of one order exhibit different degrees of specialization and differentiation, it is the less differentiated cells which most easily regenerate;* in glands, for example, the neck and duct cells more than the actively secreting cells.

4. Lastly, to express what has already been indicated, in a somewhat different form, where an organ contains two or more tissues of different proliferative capacities, in the regenerative process the more actively proliferative arrests the growth of the less active tissue, and leads to imperfect reproduction of the lost part. Of all tissues, the ordinary connective tissue has the greatest proliferative capacity, and, in the processes of healing, we observe that this overwhelms the other regenerating tissues.

In the study of regeneration we frequently observe that the more specialized tissues are not without the power of regeneration. Muscle cells, for example, at the cut end of a muscle show what are clearly the first stages of regeneration; but the process is a slow one, and too often before it is nearly complete the developing cells atrophy, as a consequence, it would seem, of the disturbance of nutrition and pressure exerted by the already developed fibroblasts and fully formed connective tissue.

REGENERATION OF THE VARIOUS TISSUES IN MAN.

Connective Tissue.—White Fibrous Connective Tissue.—It is unnecessary here to repeat in detail the successive stages of observations and opinions based thereon whereby we have attained to our present state of—it must be confessed—some uncertainty regarding the development of new connective tissue, interesting though that history is. This may be admitted, that connective tissue falls into line with other tissues, and is, in the main, if not entirely, produced by proliferation from preëxisting connective tissue. Ziegler, who was, for a time, the great upholder of the view that leukocytes are the main source of new connective tissue, was also, with his pupils, the main influence in controverting that view. Nevertheless, during the last few years the pendulum has shown a tendency to swing back. Metchnikoff has pointed out that in lower vertebrates wandering cells can be seen to assume the characters of fibroblasts within the tissues; and Maximow's[1] very full studies upon what he terms "polyblasts" would indicate that one of the fates of these wandering cells is to come to rest in the newly forming tissue and assume all the characters of a connective tissue. These polyblasts he regards as lymphocytes, modified by sojourn in the tissues. The recent observations of Schridde[2] throw doubt upon these conclusions. By the employment of a stain which differentiates the cell granulation in sections, Schridde points out that, while it is true that in form these cells are identical with the fibroblasts, their granulation remains distinct, and, as a consequence, they do

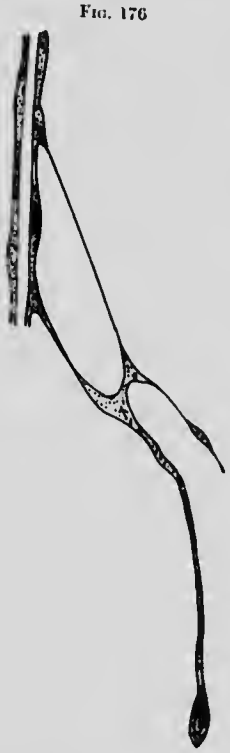
[1] Ziegler's Beitr., Supplemental Heft 5, 1902.

[2] Münchener med. Woch., 1906, Nr. 4.

not become identical, while it is justifiable to assume that their properties remain different.

This much may be stated with definiteness, that *the polymorphonuclear leukocytes*, the commonest of the infiltrating leukocytes, *never become converted into connective tissue;* also, that *the main mass of fibroblasts are derivatives from the preëxisting connective-tissue cells.* As regards cells of the lymphocytic and endothelial type, opinion remains divided. We ourselves are inclined to see an extremely close relationship between the vascular and lymphatic endothelium and the connective tissue, and cannot recognize any distinguishing marks between the cells and their processes, given off as buds from the new capillary loops, and the fibroblasts and their processes, with which they enter into connection. We would, indeed, include such endothelial derivations along with the connective-tissue derivatives. But this view is not generally accepted.

Fig. 176



Formative cells, or fibroblasts in direct connection with the endothelial processes. (Ziegler.)

The undoubted authority of His has led most pathologists to accept his conclusions that the vascular endothelium is a special derivative of the mesenchyma, derived from an order of cells that is distinct from the connective tissues. But, granting that this is so, they are but later developments from the common mesoderm, from which connective tissue, and mesenchyma, are derived. They are closely related. And we have the observations of practically all recent students of the organization of thrombus (Waldeyer, Cornil and Ranvier, Thiersch, Baumgarten, Raab, Riedel, etc.) that there the new connective tissue is almost, if not entirely, derived from the endothelial cells. We do not see how this testimony can be refuted, and, if the process occurs in one region, we fail to see why it should be denied in another. Nevertheless, Thoma[1] and Henking are the only ones who have boldly laid down that endothelial proliferation precedes fibroblastic development, and is the main origin of the fibroblasts, though not a few others tend toward this conclusion.

To the view of Leo Loeb[2] and others, that epithelial cells may assume a fibroblastic type, we shall revert in discussing metaplasia (p. 586).

[1] Ziegler's Beitr., 10: 1891: 434.

[2] Johns Hopkins Hosp. Bull., 9: 1898: 157.

It is unnecessary to repeat here the various stages whereby the vegetative young connective-tissue cell, oval and stout, becomes successively stellate, then spindle-shaped, then surrounded by fine fibrils, and eventually but the skeleton, as it were, of a cell, with long, thin, greatly compressed nucleus and scarce any body substance (see p. 391); or to discuss the relationship of the primary mucinous matrix to the eventual connective fibrils.[1] We would only emphasize that throughout the body it is this tissue which is most active in regenerating, replacing in the process tissues of higher development.

Elastic Connective Tissue.—This is not only able to exhibit overgrowth, but may be definitely regenerated, appearing in areas of new tissue. Thus it may appear in abundance in areas of new connective tissue; in the intima of the arteries, for example, and in interstitial new tissue, or in some cases of cirrhosis of the liver. No distinction has as yet been made out between the cells connected with its development and the fibroblasts and connective-tissue cells proper; indeed, the nature of its development is still unsettled.

According to Loisel[2] (1897) the elastic fibers of the ligamentum nuchæ originate within the cell, either as a peripheral sheath, or as a fine process at either end. In regeneration Enderlen[3] and Jores[4] note that they develop from preëxisting fibers, according to the latter as fine granules lying in series in the spaces between connective-tissue fibrils and cells, or in other cases as fibers which at first do not take on the specific elastic-tissue stain (Weigert's orcein). Development is slow, and for long a cicatrix may show no elastic tissue save at its edges.

Fatty Tissue.—It is doubtful whether we can truly speak of the regeneration of fatty tissue, for it is still an open question whether fatty tissue exists as a distinct entity, or whether it is to be regarded as a local modification of connective tissue. We are inclined to regard it as the latter. There are, however, certain regions in which, in the adult, fat is constantly present under normal conditions, *e. g.*, the subcutaneous tissue, the appendices epiploicæ, and the auriculoventricular grooves.

There is still some uncertainty regarding the normal process of development of the fat cell. The generally accepted view is that certain somewhat large endothelioid cells in the immediate neighborhood of capillaries undergo multiplication, and in their relatively abundant cytoplasm fat gradually becomes stored in the form of larger and larger droplets, until, by fusion of the same, the cell becomes distended by a homogeneous spherule of fat, the protoplasm coming to form a mere peripheral ring, being collected in rather greater amount around the nucleus, the cell assuming thus a signet-ring shape. The view of Grawitz[5] and his pupils, that the fat cell arises from the fusion of several cells, whose nuclei, with one exception, fade into those of "slumber

[1] For this see Appendix B.

[2] Quoted by M. Heidenhain, Plasma und Zelle, Pt. 1: 1907: 37.

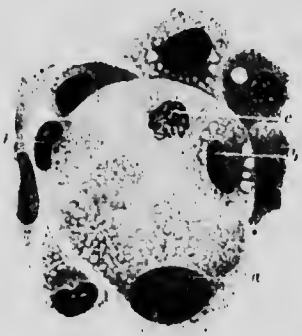
[3] Zeitsch. f. Chir., 45: 1897: 453.

[4] Ziegler's Beitr., 27: 1900: 381.

[5] See more particularly Schmidt, H., Virch. Arch., 128: 1892: 58.

cells," is generally discredited. For ourselves, we cannot accept the slumber-cell theory. We are impressed, however, with the fact that the development by fusion of several cells has not been refuted, and, recalling how constantly degeneration is a reflection of development, the fact that the degenerating fat cell affords multiple cells is, in our opinion, very significant. In the degenerating muscle fiber, which is generally accepted as being developed from a cell-complex, we get a very similar appearance. We have repeatedly noted the appearance of characteristic polygonal cells, with transparent bodies and fine vacuoles, in cases of inflammation and in degenerating areas of lipomas—occupying the space of a previous fat cell, which remains clearly indicated by its persistent membrane—cells which are wholly unlike any surrounding leukocytes, and most modern observers (Crajewicz, Flemming, Cornil and Ranvier, Marchand) agree that these are derived from the original fat cell. Sometimes, in a like position, a multinucleated mass is found, while Marchand figures definite mitotic figures in the cells. Eventually the membrane is absorbed, or gives way and the cells may appear irregularly distributed.

Fig. 177



Degeneration of a fat cell in an area of inflammation. At *a* can be seen the main nucleus of the fat cell; at *b* and *c* other nuclei with surrounding cytoplasm (regarded by Maximow as degenerated polyblasts). The homogeneous fat globule has disappeared from the cell, but fine fatty droplets are present in the cytoplasm. (Maximow.)

In cases of inflammation passing on to healing in a wound (as of the abdominal wall) in which cicatrization is already well developed, cell masses like those above described may still be seen lying within a more or less perfect membrane of the old fat cell. We are apt to regard these as still in the process of degeneration, but it appears to be as permissible to suppose that here the reverse process is gradually developing with fusion and loss of nuclei until a single large vacuolated cell is left.

It is, most difficult to arrive at a conclusion regarding the appearances seen, for, as noted, some of the cells are free, and these may show indications of increased size. In inclining in part to the Grawitz view, we wish to indicate that we cannot consider the matter definitely settled, nor that we are satisfied that it is correct.

In the appendices epiploicæ and in the atrophying thymus there appears to be an inverse relationship between the development and increase in the fatty tissue and the stroma of lymphoid tissue (each appendix epiploica contains a minute lymph nodule). This has been noted by more than one observer, but the nature of the relationship has not been surely determined.

Cartilage.—As noted by all observers, the regeneration of cartilage is a very slow process, so slow in some cases that certain observers have denied its occurrence, but it is well established that two distinct processes are possible: (1) perichondrial regeneration, and (2) regeneration from the cartilage proper.

1. In the former the perichondrium is detached, swollen, and inflamed, the space between it and the injured cartilage filled with fibrin. The inner aspect of the perichondrium becomes intensely cellular, and gradually these cells replace the fibrin, projecting into the area of injury and loss of substance. The cells, like those of the inner aspect of the perichondrium, at first closely resemble ordinary connective-tissue corpuscles and spindle cells. Those that are oldest and farthest from the perichondrium become rounded or polygonal, and are seen to lie in a transparent matrix; they have the characters of young cartilage cells. More commonly, however, the matrix is not transparent, but fibrillar. If, for example, a cut has been made into the costal cartilage of a young animal, resulting in a wedge-shaped wound, this becomes filled with a wedge-shaped, fibrillar mass, and, on making sections, the fibrils are found to originate from the injured aspect of the cartilage, or to be attached there in bundles which cross the wound. Here and there between the bundles are cartilage cells, at first without definite capsule, later enclosed and multiple, lying in a clear space; later again, judging from the statements of several observers, the fibrils disappear or become transparent, and a hyaline, completely formed cartilage results.

2. The process of regeneration from the cartilage proper is, in general, imperfect. To a slight extent it may be found accompanying the process just noted. In the immediate neighborhood of the wound the matrix undergoes softening, the "capsules" surrounding individual cartilage cells become larger, the cells divide, so that clusters of daughter cells replace single cells. There is, thus, proliferation—and often softening of the matrix, and, after more or less proliferation of the specific cells, each would seem to govern the formation of a new surrounding matrix, either hyaline or more or less fibrillar. According to Tizzoni,[1] the fibrillar modification may extend into the uninjured surrounding, and previously hyaline, cartilage. It was clearly stages in this process that Redfern[2] described in that remarkable series of experiments which constitutes the first full microscopic study of the process of inflammation and repair.

Bone.—We have noted in the preceding section that the cells in the earliest stages of perichondrial proliferation are undistinguishable from fibroblasts. Cartilage must, indeed, be regarded as but a modified form of connective tissue, and the same applies to bone. The characters of periosteum very closely resemble those of perichondrium. Cartilage may, we need scarce remark, become converted into bone, and, what is more, under certain conditions periosteum may give origin to fibrous tissue—to a fibrous, instead of an osseous, union between

[1] Arch. per le sci. med., 2; 1878; 27.

[2] Monthly Journal of Medical Science, March, 1850; September, 1851.

the fractured ends of a long bone. Therefore, although we distinguish two forms of bone, according to the mode of normal development, the chondriform and the membraniform, the one passing through a cartilaginous fore-stage, the other not, it must be realized that in both we are dealing with modified connective tissue, and be prepared to find that in regeneration no distinction is to be drawn between the two, as, also, that in its essence, regeneration from the medulla is of the same order as from the periosteum.

Periosteal Regeneration.—It used to be held that when once periosteum becomes stripped from the bone that inevitably undergoes necrosis. We now realize that this is by no means necessary. Periosteum can regenerate, and Marchand and others have published cases in which an area, deprived of its periosteum has become eventually covered with a new layer. Only when there is suppuration and infiltration of the outer table of the bone by the suppurative microorganisms, and destruction of the bone cells, does necrosis become inevitable. According to Marchand's description, the new periosteum is firmly attached to the bone and separated from the overlying connective tissue; the old periosteum at its edge shows thickening, and its fibers, instead of being arranged longitudinally in the direction of the long axis of the bone, exhibit a radial development, suggesting definitely that growth, in the main, has been inward from the periphery. There may be a definite osteoblastic layer on its inner surface.

Osseous Regeneration.—Bone is constantly undergoing regeneration. One has but to study a longitudinal section of a long bone, such as the femur, to be convinced that the lamellæ are laid down along the lines of strain. The adaptation, indeed—the economical use of a minimum of material to support a maximum load as indicated, in the first place, by the tubular nature of the bone; in the second, by the arrangement of the lamellæ—is most wonderful. But at different periods of life the load to be borne and the direction of the strain varies, and the old lamellæ become absorbed and replaced by new; or, more correctly, can be seen to be undergoing absorption along one aspect while new material is deposited upon the other, so that the position of an individual lamella becomes shifted. Howship's lacunæ, in normal bone, are areas in which the osteoclasts are thus absorbing the old bone, and a microscopic section of such normal bone exhibits layers of bone, evidently of different ages.

Such regeneration is wholly apart from the periosteum, though, at the same time, in the process of growth there is steady addition to the amount of bone, with increase in diameter, due to periosteal activity. As thus, normally, there is both internal and medullary, as well as periosteal regeneration, so, after injury and fracture, both play a part in the regenerative process.

Regeneration of Membraniform Bone.—In the following description we follow Marchand,[1] and the statements apply both to what is seen

[1] Die Wundheilung, Leipzig, 1901. The fullest recent work upon the regeneration of tissues.

in the medullary spaces of an implanted portion of one of the bones of the skull and in the medullary spaces of a long bone after injury. The first change to be observed is the development of a mass of young spindle cells, identical with ordinary fibroblasts. These, which become the eventual osteoblasts, give origin, first, to fibrillæ in increasing amount. In the meshes of the fibrillary network the cells are seen as irregular, angular, and rounded or elongated bodies, now free in the spaces of the network, now lying on the walls. At this period they have no processes. The nuclei are large, rounded, and with large nucleolus. The cells are not distinguishable from the layer of osteoblasts beneath the periosteum.

Next, the fibrillary substance becomes more homogeneous, previous to its forming the new bone substance, and the cells above described become included, and, shrinking and becoming stellate, form the bone corpuscles; whereas, the free osteoblasts and these cells in their earlier stages exhibit mitosis, as bone corpuscles this is wholly wanting. The successive stages from the osteoblast to the bone corpuscle are difficult to follow, but the successive processes closely resemble those observed in the development of hyaline cartilage from perichondrium; there is the same preliminary fibrillation, but, whereas, in that this eventually becomes homogeneous, here there is not so much an impregnation as an intimate organic binding of the calcareous salts into the matrix.

Regeneration of Chondriform Bone.—Where there is a preliminary laying down of cartilage either of two processes may be noted: (1) The cartilage is at first relatively non-vascular. Now, vascular loops make their way into the cartilage, which becomes absorbed before them, and upon the cartilaginous remains, again, through the agency of osteoblasts, layers of young bone are deposited; or (2) the cartilage cells become converted into bone cells, and the surrounding matrix becomes converted into osseous matter. The two processes may occur simultaneously. The latter is often well marked in the conversion of cartilaginous into bony callus.

Regeneration of the Medulla.—There have been many recent studies upon the regeneration of the bone-marrow, of which the more notable are those of Enderlen[1] and Haasler.[2] The appearances vary largely, according to the age and condition of the individual, whether we deal with the red marrow of youth and certain anemic conditions, white fatty marrow, or the latter gelatinous fatty atrophy. These marrow cells form the specific constituents of the marrow, but with them, it is unnecessary to say, are abundant vessels, connective tissue, and cells of osteoblastic type. According to the different observers, these can readily be distinguished. According to Enderlen, the degenerative changes in the marrow cells, which show themselves during the first twenty-four hours after injury and hemorrhage, give place within forty-eight hours to active mitosis and proliferation, while similar

[1] Deutsch. Zeitsch. f. Chirurg., 52: 1899: 293.

[2] Arch. f. klin. Chirurg., 50: 1895: 75.

proliferation occurs in the connective tissues around the capillaries at the margin of the injured areas, and fibroblasts make their way into the hemorrhagic area. In seventy-two hours there is definite formation of new capillaries; on the fourth day a network of new fibrillar tissue has invaded the area of injury, and in the network are new marrow cells, with, in addition, foreign-body giant cells around splinters of the injured bone; and gradually the young marrow cells, which at first had been rare, become abundant, more particularly at the periphery. Here, on the sixth day, hematoblasts can be distinguished, and, more deeply, developing fat cells. Certain cells with giant and often lobulated nuclei (distinct from the multinucleated osteoclasts) are evidently modified myelocytes (marrow cells).

Beyond the proliferation of the vessels it is deserving of note that in these cases of injury of the marrow there is little evidence of reactive inflammation; there is, for example, no migration of polynuclear leukocytes into the injured area.

FIG. 178

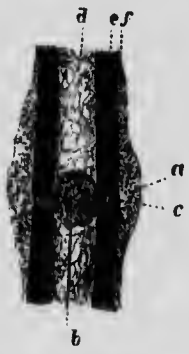


Diagram of early stage of regeneration of bone. *e*, *c*, repair of fracture of a long bone; *a*, external callus; *b*, medullary callus; *c*, region of fracture; *d*, medulla; *e*, shaft; *f*, periosteum. (Perls.)

The Healing of Fractures.—This subject is so fully treated in works upon surgery that it is unnecessary to recall here but the outlines of the process.

1. The variation in the process of healing depends primarily upon two factors: (*a*) the apposition of the fragments; (*b*) the nutrition of both fragments. The more perfect the apposition, and the more perfectly apposition is maintained, the less is the amount of exudate and subsequent callus, and the more rapid the knitting together; the greater the amount of riding of one fragment on the other, the greater is the irritation, exudation, and callus; while, further, if one fragment be without due blood supply, the reaction on its part is imperfect, and union is delayed or completely arrested.

2. Both periosteum and medulla take part in the process. To this we have already referred.

3. The formation of the callus exhibits the following stages:

(*a*) First, hemorrhage and some exudation from the surrounding vessels, with coagulation.

(*b*) Invasion of the coagulum by cells—polymorphonuclear from the surrounding tissues, fibroblastic from the periosteum and marrow.

(*c*) Organization of the clot from periosteum and marrow, with absorption of the fibrin and replacement by tissue.

(*d*) Conversion of the cells derived from the periosteum into carti-

lage cells and formation of a cartilaginous marrow. This is not a necessary stage, but is seen wherever the callus is extensive.

(*e*) Conversion of the cartilaginous into osteoid callus, i. *e.*, modification of the cartilage cells into bone corpuscles. Here two stages are described by some authors: (1) A vascularization of the cartilage from the periosteum and marrow, with conversion of the cartilage into bone cells, without, at first, any deposit or combination of calcareous salts in the matrix. This soft tissue is regarded as *osteoid* tissue proper. When, later, the salts become deposited, but the tissue has still not the perfect features of bone, some still speak of this as osteoid tissue, others as *osseous* or *bony* tissue, as distinct from perfect bone. The distinction is unnecessary. (2) Absorption of the imperfect bone originally deposited, whether through fibrillar or cartilaginous development, and replacement by lamellar bone, the lamellæ being laid down along the lines of strain.

This absorption is a very gradual process, extending over years where there is extensive callus or grave displacement. The medullary cavity is, in general, completely closed by new bony growth; this in time becomes absorbed, the ends of overriding fragments become rounded off; and, eventually, whereas at first there had been an excess of imperfect bone, there remains only sufficient properly formed bone to secure perfect solidity of the part.

Lymphadenoid Tissue.—It is, perhaps, difficult to speak of regeneration affecting a tissue, which, as regards its specific element, the lymphocytes, is always, normally, regenerating. There are indications, however, that these are not of the same origin as the framework, and that the lymphocytes and the framework, along with the large endothelial cells (macrophages) of the lymph spaces are of different origin. The observations of Gulland show that the lymph cells wander into certain areas, and these, in the connective-tissue framework, form germ centres, and it would seem established that in the embryo the system of lymph spaces is developed before any leukocytes show themselves in the blood.

Beard, confirming an older observation of Kölliker, finds that the earliest leukocytes originate in the thymus by a remarkable conversion of the *epiblastic* cells of the follicles; and his observations have been corroborated by others. What form of leukocyte originates thus is left undetermined—a matter of some importance when we regard the lymphocytes and the polymorphonuclears as wholly distinct types. More recent observers find leukocytes in the blood before there is any sign of change in the thymus.

Under certain conditions new lymph glands develop in various situations, in the subperitoneal tissue, the liver, etc., where, normally, these are unrecognizable. It is possible that lymphadenoid tissue is "latent" in these positions. Such latent or potential tissue is present in the sheaths of veins, though here, again, we note that the lymphocytes are capable of migrating from the lumen into the perivascular lymph spaces. The generally accepted view is that this latter process

is the usual course, namely, that lymphocytes come to rest in these positions, and then, proliferating, lead to a modification of the inclosing tissue.

When a lymph gland is injured, according to Ribbert, proliferative changes, with new-growth, are to be observed, affecting all the elements of the follicle—reticulum, endothelium of lymph spaces, bloodvessels, and germ centres—in the immediate neighborhood of the injury.

Leukocytes.—We have noted that the lymphocytes undergo active development in the lymph nodules, which contain accumulations of "mother cells," the germ centres. As regards the leukocytes proper (of some authorities), namely, the polymorphonuclear leukocytes (including the eosinophiles), these, in postnatal life, and under normal conditions, are developed (along with the erythrocytes) more particularly in the bone-marrow, where there can be no question that they originate directly from the myelocytes (Ehrlich). The opinion enunciated by Gulland and Uskoff, that they are an older mature form of the lymphocyte, would not seem to be tenable. In pathological conditions the spleen, the liver, and other organs may exhibit myelocytes and be, therefore, a seat of formation. Mitotic forms have been observed in the normal blood, but very rarely; more abundantly in pathological conditions (*e. g.*, leukemia).

It must be noted that the sudden exhibition of an increased number of leukocytes in the blood is not a necessary indication of regeneration, but may be merely evidence of attraction of the cells out of the bone-marrow, lymph glands, etc. To such wandering out is to be ascribed the physiological leukocytosis that follows a meal. At the same time it must be remembered that there is a constant normal destruction of leukocytes and constant new development.

Blood-vascular Tissue.—During the stage of growth three methods of vascular formation have been distinguished: (1) A remarkable process of cell cavitation, certain cells (of the vascular area in the chick, for example) becoming hollowed out, and during the process giving rise to blood corpuscles in their interior, the cavities of apposed cells fusing in series, so as to form tubes, which eventually become connected with vessels containing circulating blood. (2) A process of canalization, the blood making its way between rows of cells, which cells become converted into the endothelial lining of the capillary channels thus formed. It is now regarded as doubtful whether this method of formation occurs in the developing organism. (3) A process of budding. Certain cells of the endothelium of capillaries already formed give off buds or long protoplasmic processes, at first non-nucleated; the process from one capillary fuses with that from another, and the solid strand thus formed becomes hollowed out, thus giving passage to the blood from one capillary to the other, while eventually, by mitosis, nuclei pass into the walls of the tube, which becomes converted into a capillary with endothelial walls.

Thoma, who has made peculiarly full and painstaking observations upon vessel formation, wholly denies the existence of the first process.

He holds that all new vascular formation is truly *inter-* and not *intra-*cellular. In the vascular area of the chick he describes the mesoblastic cells as becoming arranged in strands; rounded spaces appear between the cells, these spaces become filled with clear substance, probably fluid, open into one another, and thus form the first capillaries, the surrounding cells primarily polygonal, becoming gradually transformed into pavement endothelium. Following upon this stage, further new capillaries are formed by the third or budding process. It will be seen that he regarded the canalization as primary and independent of any blood pressure.[1]

In regeneration, the first of the processes above described has never been observed. The nearest approach to the second is seen in the somewhat rare cases of complete dissecting aneurysm.

In this condition, owing to disease of the inner wall of the aorta, sudden exertion and sudden rise of blood pressure lead to rupture of the intima, and now the blood forces its way between the fibers of the middle coat. If nothing further happens, then the blood thus leaving the vessel coagulates, forming a solid clot; at times, however, dissecting a passage for itself, it reënters the aorta or one of its branches at some point lower down. As a result, the blood expelled from the heart finds its way down the natural, as well as down the dissected, passage, and the aorta appears to be doubled. Where the current is free but little coagulation occurs along the walls of the artificial passage, and, if death occurs a week or more after the rupture, what coagulum is formed is found to be covered by a distinct endothelial coat.

In granulation tissue, whether superficial or internal, the third process is that encountered. This we have already described (p. 388).

Red Corpuscles.—After great loss of blood, and in profound anemias, the red marrow of the bones becomes markedly increased in amount, and the spleen is frequently found enlarged. In the red marrow, as Neumann first pointed out, there are normally present nucleated cells having hemoglobin in their cell substance. In anemia, and after loss of blood, coincident with the increase in red marrow, nucleated red corpuscles are to be detected in the circulating blood. Further, increased mitosis of these *hematoblasts* is to be observed in the bone-marrow. This is an indication that there is an increased production and discharge of hemoglobin-containing cells from the bone-marrow. As Howell has more especially pointed out (in this confirming Bizzozero and Salvioli), similar hematoblasts are recognizable in the spleen under similar conditions.

We therefore conclude that the red bone-marrow and the spleen are preëminently the seats of regeneration of red corpuscles. The hemolymph glands of the abdominal area, organs intermediate in histological structure between the lymph glands and the spleen, which have of late been studied by Swale Vincent, Warthin, and others, would seem also to be concerned in this production.

[1] Thoma, Pathology, English edition. Translated by A. Bruce, 1: 1896: 474.

It is when we come to determine the origin of these hematoblasts, and, again, the method whereby the nucleated hematoblast gives rise to the non-nucleated red corpuscles, that doubts arise. We are not certain how far hematoblasts arise from preëxisting hematoblasts, or from less differentiated "mother cells." Löwit, indeed, has described certain small, colorless, nucleated cells in the bone-marrow—"erythroblasts"—which he regards as the precursors of the hematoblasts, and upon *a priori* grounds, arguing from what occurs in the embryo, where connective tissue mesoblastic cells give rise to the nucleated hematoblasts, this may well be the case; while, again, it is not impossible that the endothelial cells of certain areas may, by division, give off, as in the embryo, such hematoblasts. According to Bizzozero, the hematoblasts are not in the lymph spaces, but actually within the capillaries of the bone-marrow.

It is now coming to be held that the non-nucleated red corpuscle arises from the hematoblast, not by a process of budding (the hemoglobin containing moiety of the cell substance dividing off from the perfect cell, which then is capable of elaborating more hemoglobin-containing cell substance, and giving rise to a second, or a series of red corpuscles), but as noted by Macallum a process of discharge of material from the nucleus which undergoes eventual disintegration.

Epithelia.—There is no known exception to the rule that, in regeneration, epithelial elements develop from preëxisting epithelium. The apparent exceptions, *i. e.*, where an island of new epithelium begins to develop in the middle of an area of granulating tissue, are, judging from transplantation experiments, explicable by accidental transplantation of living epithelial cells on to the granulating surface, or, in some cases, by the persistence of epithelial elements upon the eroded surface—the deeper parts of hair follicles, or skin glands, which, proliferating, take on simpler epithelial characters.

A rather remarkable example of this persistence has been met with in connection with the lens, which, it need scarce be said, is of epithelial origin. Occasionally it has been noted that, after complete extirpation of this organ in cataract operation, a new lens has developed. Experiments upon the rabbit[1] show that, where this occurs in mammals, [illegible] of the posterior ligament or capsule have been left behind, [illegible] section with which is the "cambium" layer, from which thro[illegible] new lens cells have been developed. It is from this, after a [illegible] the main mass of the organ, that regeneration takes place. In certain of the lower animals the new lens has a different origin; to this reference will be made in discussing metaplasia (p. 592).

An apparent exception to this statement has been noted by Saxer[2] and others in certain gliomata. Here there is a tendency to the formation of cysts containing serous fluid, and in some cases these cysts,

[1] Vide R. Randolph, Welch Festschrift (Johns Hopkins Hosp. Repts. 10): 1900 237, who gives full references to earlier literature.

[2] Ziegler's Beitr., 38: 1904.

which are clearly secondary developments, are found to possess a more or less regular lining of fairly columnar cells; they gain, that is, an epithelium which evidently is derived from the glial cell of the body of the tumor. While this is clearly the case, we gravely doubt if this can be spoken of as a true epithelium. It must be remembered that the neuroglia is itself of epiblastic origin, so that, were a true epithelium found, it would not be an example of conversion of cells of one order into those of a wholly different type. But specimens which we have seen, and Saxer's figures, show that no basement membrane is formed; the lining cells pass imperceptibly without demarcation into the underlying cellular tissue.

Along with the vascular endothelium and endothelia in general, the epithelia of the body stand preëminent in their capacity for *complete* regeneration, and, what is more, offer particularly favorable conditions for a study of the process, which thus has been investigated by a large number of observers.[1]

Fig. 170

"Pseudoepithelium," or secondary epithelium without basement membrane lining a cyst in a glioma, formed by modification of the superficial layer of glioma cells. (Saxer.)

Here we may rapidly note the data which may be regarded as well established. Within two hours of the removal or destruction of epidermis, whether of the outer skin, the tongue, or of mucous membrane, in warm-blooded animals, as also in amphibians, the cells of the deeper layers, and even columnar epithelium, exhibit translation. Keratinized cells are degenerated and inert, but prickle cells and those of the lower layers are seen to alter their shape, to become pyriform, and, gliding one over the other, while still retaining connection, there is thus early exhibited a tendency for the uninjured cells to close over the defect. Within twenty-four hours the epithelium surrounding a wound is distinctly thinned, composed of fewer layers, while, at its edge, a single layer of flattened cells covers

[1] See, more especially, Mayzel (who first established that epithelium arises from preexisting epithelium), Sitzber. der Warschauer ärztl. Gesell. (April, 1874): Ref. Virch.-Hirsch Jahresber.' I, 3, and Arbeiten a. d. Lab. d. Med. Fac., Warschaw, pt. 4; Ref. Virch.-Hirsch Jahresber., 1878; W. Flemming (on Mitoses), Arch. f. mikr. Anat., 19: 1880: 347; and ibid., 24: 1885; S. Garten (On the Arrangement of the Intercellular Bridges in Regeneration), Arch. f. Anat. u. Physiol., Physiol. Abth., 1895: 401; Leo Loeb (on the migration movements of epithelial cells), Bull. Johns Hopkins Hosp., 9: 1898: 157; Ranvier (Regeneration of Conjunctiva), Compt. rend. Acad. de Sci., 123: 1896: 1228; Spuler (Regeneration of Hairs), Verhandl. Anat., Gesell., 1899: 17.

over the wound. Direct division of the cells is frequently noted, so that many cells contain two nuclei.

Cellular masses may be seen extending between the layers of the fibrinous scab which by now covers the wound, but more especially they extend along the surface of the injured tissue and into depressions on that surface. Occasionally, it would seem, small collections of these cells may, by movement, become detached, and form islands of growth on a granulating surface. Within forty-eight hours mitoses may be observed in the Malpighian layer of the surrounding less altered epidermis and prickle-cell layer, as also in those cells which have spread over the surface. Briefly, by this combination of translation and cell multiplication the denuded surface tends to be covered, at first, by a single or irregular layer of flattened cells encroaching from the edge of the wound.

At first these are relatively loosely attached to the underlying surface and granulation tissue, but at a comparatively early date the formation of *a basement membrane* is observable, apparently by the fusion of fibrils passing from the underlying connective tissue, upon which the overlying cells become sessile. The exact relationship to this basement [illegible]ne is still undetermined. At first there is free passage out of [illegible]es between the cells and their communicating bridges, and a [illegible]extensive phagocytosis has also been observed, the young epithelial cells evidently utilizing the leukocytes as one source of nutrition. Later, both these processes become restricted; the proliferation leads to the formation of several cell layers, of which the outer layer, at first, shows irregular keratinization (Unna), without an underlying granular layer. Eventually, a granular layer shows itself, and a complete simple epidermis becomes developed, with all the normal layers, from the Malpighian upward.

Hairs, sweat and sebaceous glands are not reproduced, unless the original injury had not been deep enough to destroy the deeper lying portions of their structure, in which case they may develop anew. In this case it is interesting to note, as regards the glands, that there is a definite down-growth of solid processes of the overlying epithelium to meet them, which is difficult to explain save in the theory of reciprocal attraction between cells of like nature.

In cases of chronic ulcerations, tuberculous and syphilitic, we observe at the edges of the ulcer a marked tendency for the epithelium to grow downward into the underlying tissue in the form of processes. These may become snared off, and develop into epithelial pearls; or, if thin, may become infiltrated by, or themselves infiltrate, the surrounding tissue, in which case isolated epithelial cells, or small clusters of such, with no exact demarcation, are encountered in the dermis. Where this is the case it is oftttimes practically impossible to determine whether we are dealing with mere chronic inflammation or with the earlier stage of epithelioma. As a matter of fact, chronic inflammation may be succeeded by definite epithelioma, and this not merely of surface tissues; but where fistulous tracts occur leading down to bone, for

example, owing to this spreading property of epithelium, the epidermal cells may spread down the fistula into the bony cavity, and there be a cause of apparently primary cancer of bone. Of *hairs*, it may be repeated that they only regenerate when the root beds have not been destroyed. Where, as in certain parasitic inflammations and anemic conditions of the scalp, there is destruction or death of the root-bed, permanent baldness is the result.

The same is, in general true of the *nails*. The nail-bed passes further back than is generally imagined, and this would seem to explain how it is that after removal of a terminal phalanx an imperfect nail occasionally shows itself at the end of the finger. In forming the flap, a portion of the nail-bed has been retained. There are, however, several cases on record in which this explanation is not adequate—in which, after removal of two phalanges, an apology for a nail ultimately develops at the end of the remaining part. We have to accept, it appears to us—however unwillingly—that environmental conditions may stimulate a metaplasia of the ordinary skin into nail-producing matrix.

Regeneration of Mucous Membrane.—The same general process described for the epidermis is found to apply in connection with the mucous membranes. At the edge of a wound even the fully formed columnar cells lose their cilia, become more cubical, and ultimately rounded and flattened, and undergo a translation over the exposed surface, with relatively considerable rapidity. Later, proliferating, they form again a columnar epithelium identical in its characters with the normal. Unlike what occurs upon skin surfaces, the simple gland follicles become reproduced, the reproduction being hastened if the lower parts of the primary follicles have not been entirely destroyed.

Such regeneration of mucous membrane takes place in the uterus, to some extent, after every menstrual period, and very extensively at the placental attachment after pregnancy and delivery.

There has been some discussion as to the cells from which this puerperal regeneration originates. Certain giant cells are to be met with in the upper layers of the muscularis which disappear later, and some observers have regarded them as latent remains of the mucous glands. Aschoff doubts that this is their origin, and points out that throughout pregnancy, below the placental site, recognizable remains of the mucous glands are to be made out. It is more natural to accept these as the site of origin of the new mucosa.

Endothelia.—In the regeneration of endothelium there is observed the same tendency toward translation and proliferation by both direct and indirect nuclear division, so as to cover a denuded surface, as is seen in the case of epithelia, and the surface may be covered with extreme rapidity. Such endothelium may form a covering not only over the tissue proper of the part, but over fibrin, as, again, over new-growths which, as is sometimes seen in the peritoneum, have clearly originated by surface transplantation. The generally accepted view is that such endothelium arises from preëxisting superficial endothelial cells, and provisionally, until this is surely determined, this is the safer

view to accept. But, as already noted, the relationship of endothelial cells to fibroblasts and connective-tissue cells has not been wholly settled, and if, as Baumgarten maintains, and claims he has demonstrated, this vascular endothelium can, by proliferation, give rise to underlying fibrous tissue, the reverse process must also be regarded as possible.

Regeneration of the Glandular Tissue.—It is impossible to read the more recent studies upon the results of wounds or excisions of glandular organs without being impressed by the singularly small amount of regeneration that is found in most cases. In saying this, as we shall point out in our remarks on hypertrophy, a distinction must be drawn between that condition and regeneration proper. But the development of new glandular tubules, or acini, is wholly wanting, or slight and of little or no functional value until we study the simplest glands, such as the Lieberkühnian follicles of the intestines, the uterine glands, or the salivary glands. These may undergo extensive regeneration, though, in the case of salivary glands, the newly budded-off outgrowths from the ducts, which develop into acini proper, are apt to be surrounded by a new connective-tissue growth which is not normal, and subsequently, with contraction of the same, to undergo more or less atrophy.

Liver.—According to Podwyssozky,[1] the changes here vary according to the animal employed. In guinea-pigs and rabbits, there may be a certain amount of the regeneration following upon excision of a part. Already, two days after the injury, the epithelium of the bile ducts in the neighborhood exhibits mitoses, and processes are formed of new bile ducts, forming a network in the newly developed cicatricial connective tissue, while some of them at their termination develop into liver cells, the result is very incomplete, and the regeneration bears no proportion in the amount excised. In cats and rats, the liver cells show active proliferation, but in many this stops short of cellular multiplication, and cells with double nuclei result. The process here is one of hypertrophy and enlargement of the preëxisting lobules, without regeneration in the true sense of the term.

Kidney.—In this organ the fairly numerous studies that have now been made in man, after injury or operative excision, afford no evidence of regeneration, although in certain of the lower animals, more particularly from the medullary collecting tubules, new tubules may make their way into the region of the wound; but, in the adult animal at least, these have no glomerulus formed at their upper end, are small, imperfect, and cannot function.

There is evidence, however, that in quite young animals, not so much in an injured kidney, as accompanying the hypertrophy of the opposite kidney, new glomeruli and tubules are capable of arising, for the number of these is found greater than in the normal kidney, and certain cell accumulations have been detected in the growing organ,

[1] Ziegler's Beitr., 1: 1886

more particularly in the outermost portion of the cortex, which are now accepted as latent glomerular anlagen.

Thyroid.—In the thyroid, also, Wölfler[1] drew attention some years ago to similar cell masses, which he likewise regarded as latent anlagen, and, after partial destruction of the organ, he recognized active growth in these with development into the typical follicles. We have recognized Wölfler's clusters in several cases of thyroid disease. Whether they are persistent anlagen, or reversions through atrophy, it is difficult to say, but transitions may be recognized from these cell masses to others having a small lumen, and so to typical follicles. Where, as by Halsted and others, portions of the thyroid have been removed, the regeneration, which is here not inconsiderable, is by a process of budding and separation of new follicles from the old.

Pancreas.—The observations here are practically unanimous that no regeneration takes place.

Spleen.—Here, also, the balance of evidence is to the effect that, while there may be hypertrophy, and compensatory (or vicarious) hypertrophy of the hemolymph glands,[2] which may take on the characters of splenic tissue, at the edge of a wound in the spleen no true regeneration occurs.

Testicle.—Griffini[3] found that there might in the frog be regeneration of the tubules by budding and growth from the ducts, though Maximow,[4] who, in part, confirms the observation, denies that this is a perfect regeneration. In higher animals, although there may be a marked overgrowth of the characteristic interstitial cells, the tubules do not regenerate.

Ovary.—It is generally accepted that this organ also is incapable of regeneration. Pugn[illegible] observation, that after removal of one-half of the rabbit's o[illegible] wound becomes covered by germinal epithelium, which thei[illegible] origin to abundant ova, has not been confirmed.

Muscle.—Plain Muscle Fibers.—After injury in their neighborhood, as shown by observations upon the stomach wall, muscularis mucosæ, and uterus, these may, in from two to five days, exhibit abundant mitoses, and in the newt (Stilling and Pfitzner[6]) there may be formation of new fibers as a result; but in the rabbit (Ritsche[7]) it is followed by no proper new formation of fibers; the cicatrix in the uterus and elsewhere is formed entirely of connective tissue.

Striated Muscle.—The regeneration of striated muscle after injury is a slow and most often an incomplete process, for where there has been any extensive laceration and separation of the fibers, these, in the first place, contract apart, and, in the second, we find the rule

[1] Die Entwickelung und den Bau der Kropfes, Berlin, 1883.

[2] See Dock and Warthin, Am. Jour. Med. Sci., 1904, and for full literature, Weidenreich, Arch. f. Mikros. Anat., 1905.

[3] Arch. per le sci. med., 5: 1887: 11.

[4] Ziegler's Beitr., 26: 1899: 2.

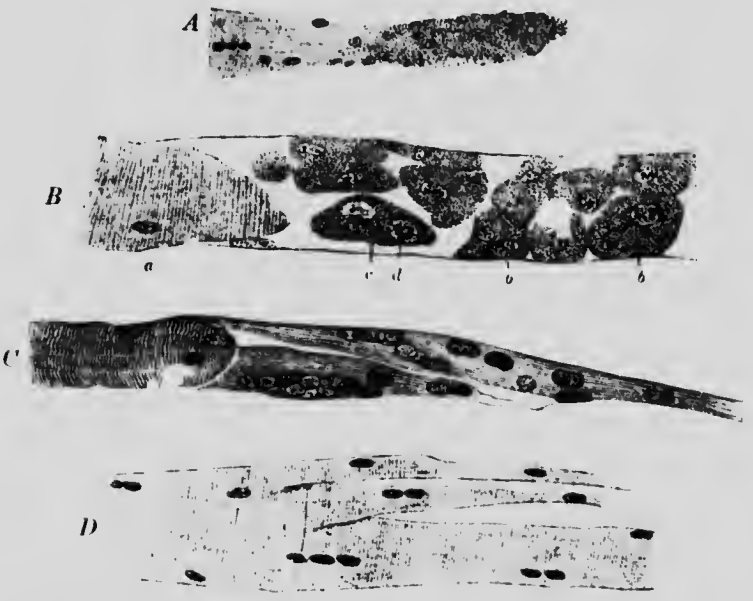
[5] Compt. rend. Soc. de Biol., 1900.

[6] Arch. f. mikr. Anat., 28: 1886

[7] Virch. Arch., 109: 1887: 507.

in operation already noted, namely, that the more rapidly regenerating connective-tissue elements usurp the place and hinder the development of the higher tissue. Thus, most often a fibrous cicatrix unites the two ends of a wounded muscle. But this is not always the case. Where a wound or cut has been, in the main, longitudinal, or where the cut edges can be kept apposed, there may, in a few months, be found very little indication of fibrous cicatrix. Or where, as happens in connection with Zenker's degeneration of muscle in typhoid, and may occur

FIG. 180



Successive stages in the regeneration of voluntary muscle: *A*, formation of bud of cytoplasm with loss of striation and multiplication of muscle nuclei; *B*, the nuclei acquire cytoplasmic territories and cells, uninucleate and multinucleate, separate from the bud (sarcoblasts); *a*, unaltered end of muscle fibre; *b*, sarcoblasts; *c*, multinucleate sarcoblasts, one nucleus at *d*, showing mitosis; *C*, early stage of new muscle fibre, multinucleate and exhibiting longitudinal striation, becoming fused with the original fibre; *D*, regeneration complete but irregular, the original fibre being continued into three processes. (After Volkmann.)

in contusions, the substance of the fiber is gravely injured without the sarcolemma sheath being destroyed, there the regeneration may be complete. The series of changes in the two orders of cases exhibits certain differences. Needless to say, the two may be combined to a greater or less extent. 1. The latter series of cases offers the simpler picture, *i. e.*, where the sarcolemma remains intact. Here, first the separated fragments of the muscle substance proper contract into broad, swollen masses. All the muscle nuclei are not destroyed, and it is from them and the undifferentiated zone of protoplasm around

them that the regeneration proceeds. They multiply with relative rapidity, and become abundant, each surrounded by an increasing zone of cytoplasm, and forming masses or clumps from which separate individual mononucleated cells, or multinuclear. As they grow in size they cause erosion in the now homogeneous glassy masses of the original striated matter, or make their way between these and the sarcolemma. It is obvious that they absorb this old material, employing it as a foodstuff, until little of it is left. In the meantime some of these new cells become elongated and obscurely spindle-shaped, irregular in size, others still remaining small and polygonal. These larger forms exhibit, first, a longitudinal fibrillation; later, the nucleus or nuclei becomes lateral, and away from it, or them, the first signs of transverse striation show themselves. With this the old sarcolemma sheath becomes absorbed, and the new muscle elements, of very irregular size, lie free. Some (the smaller cells) migrate or disappear, just as in the tadpole's tail Metchnikoff showed that like elements from the degenerating muscle could become wandering cells; the others gain a sarcolemma from the surrounding connective tissue, though the stages of this process are not clearly understood. The nuclei are now prominently lateral, and the breadth of the fibers markedly increased, although still smaller than the normal. It will be seen that in this process, when uncomplicated, small-celled infiltration and fibroblastic overgrowth play no part.

2. When the muscle fibers are ruptured, as by a cut or laceration, the abundant capillary network is also ruptured, and hemorrhages, fibrin formation, inflammation, and fibroblastic regeneration complicate the picture. As regards the ruptured fibers themselves, again the separated portions contract into clumps, which largely lose their striation. Within twenty-four hours the muscle nuclei show a remarkably active direct division, giving rise to chains, sometimes of thirty to forty members, and these collect more particularly in the homogeneous unstriated clumped end of the fiber. Sometimes collections of the nuclei in a homogeneous protoplasm form lateral buds at the side of the injured fiber. More often they are terminal, and the fiber may divide into two or more parts, each terminating in one of these nucleated clumps or buds. The process, it will be seen, is a modification of that described above, and here, also, at times, individual nuclei, with surrounding cytoplasm, or multinucleated masses, separate themselves off, though, owing to the accompanying leukocytosis, the nature of the cells seen cannot always surely be made out.

The buds elongate, extending between the fibrils of new connective tissue derived from the growing intermuscular tissue, and in favorable cases, and in the course of weeks, the number of nuclei becomes reduced, longitudinal fibration and transverse striation show themselves, and the new-formed extension of the fiber becomes indistinguishable from the old, save that its direction may be irregular. More often the would-be fiber is strangled by the cicatricial tissue, and,

after development up to a certain point, atrophy and absorption occur.[1]

Nerves.—In discussing the regeneration of nervous tissue, three component parts have to be considered: the neuroglia, the neurons, or nerve cells, and the nerve fibers, or peripheral portions of the neurons. In addition, it has to be kept in mind that there is yet another element, both in the central nervous system and the peripheral nerves, namely, ordinary connective tissue, not only of the pia mater and of the endoneurium and perineurium, but also within the substance of the brain and cord accompanying the vessels, and this plays an important, and, as usual, a disturbing, part in arresting regeneration of the specific elements proper.

Neuroglia.—The glial cells originate, like the nerve cells proper, from the lining of the medullary groove, and form, it must be remembered, a connective tissue of epiblastic origin. In the early stages it is impossible to differentiate between the glial and the eventual nerve cells, and it would appear possible that, after atrophy of certain cells of the cord in the growing human fœtus, either latent neuroblasts or glial cells can undergo development and replace the atrophied cells.[2] In the amphibia, where the terminal portion of the spinal cord has been removed, there is a partial regeneration of the nervous elements, proceeding from the epithelial cells lining the central canal, and giving rise to glial cells, along with other cells provided with fibers, and so of the neuron type, though imperfect.[3] In the adult there is no sign of this transformation. But there is abundant evidence that these glial cells in the human adult retain their proliferative capacity. Not only can they form tumors (see later), but in wounds of the brain and cord they exhibit abundant mitoses and subsequent proliferation. Their proliferative capacity is, however, hindered by the greater activity of the fibroblasts, and eventually, in a wound, they form a relatively narrow, dense zone, within or underlying the connective-tissue cicatrix.

Nerve Cells.—*Where the whole neuron or its cell body undergoes destruction, there is no regeneration in man or the higher animals.* This must be regarded as definitely settled. At most, mitoses have been observed in the neurons following injury, but, as Sanarelli[4] points out, these are imperfect, nor is there any indication that they lead to subsequent cell division and proliferation. Certain observers (*e. g.*, Klebs) have described new-growths—true neuromata—containing nerve cells, and from this have concluded that presence of the latter indicated abnormal proliferation of neurons. This conclusion is regarded as most doubtful; such neurons are either inclusions in the tumors (Solokoff),

[1] The more important papers on this subject are by Zenker, Regeneration des quergestreiftes Muskelgewebes, Leipzig, 1864; Waldeyer, Virch. Arch., 34: 1865: 473, E. Neumann, Arch. f. mikr. Anat., 4: 1868: 323; R. Volkmann, Ziegler's Beitr., 12: 1892: 233; Stendel, Diss. Tubingen, 1887; Askanasy, Virch. Arch., 125: 1891: 520, Nauwerck, Ueber Muskelregeneration, Jena, 1890.

[2] Adami, Jacobi Festschrift, 1900. [3] See Caporaso, Ziegler's Beitr., 5: 1889: 67

[4] Accad. dei Lincei Ser., 4: 7: 1890 (Ref. Centralbl. f. Path., 2: 1891: 429).

or are of the nature of cell rests, portions of nerve tissue isolated during the course of development and incapable of coördinated function.

There is no regeneration of gray matter of the brain or of the cord. The same is true, also, of the sympathetic or spinal ganglia.[1]

Peripheral Nerves: Nerve Fibers.—It cannot be said that as yet the relationship of the different structures which constitute the nerve fibrils in regard to the development of the same is definitely established, and, this being so, our explanations of the processes seen to occur in the undoubted regeneration of the same lack finality. The essential portion of such a fiber, that establishing the communication between the nerve body and the peripheral organ or other neuron, is the axis cylinder. The older, well-established view is that this is a direct outgrowth and portion of the neuron. But, from more recent embryological studies, the view has gained credence and is gaining ground that it is formed by relays—that the cell of the sheath of Schwann practically governs the development of successive sections, and many authorities see in the facts of regeneration a considerable amount of support for this view.[2] Fortunately, this may be laid down with precision, that *any new development of an axis cylinder always originates from a pre-existing axis cylinder, and, what is more, from such axis cylinder in organic connection with a neuron.* Solution of continuity of a nerve fiber or of its axis cylinder leads to degeneration distalward of the distal portions separated from the cell body, and of the proximal and still connected portions upward as far as the next node of Ranvier, or, in some cases, a node or two higher.

There are not a few debatable points regarding this Wallerian degeneration and its extent that are of great importance; they are, however, not immediately germane to our present inquiry, and we must forbear to dwell upon them. Such, for example, are the questions of arrest of degeneration in the peripheral section of a cut nerve, by maintaining the tone of the muscle to which it runs, the question of the existence of peripheral nerve cells, and peripheral regeneration.[3]

Regeneration occurs, provided (1) that the shock (as in tearing out whole nerves) has not been too severe and the destruction has not led to complete arrest of function of the nerve cell; (2) that the organ or part innervated has not been destroyed or does not become atrophied and degenerated in consequence of the severance of its nerve supply; and (3) that the path of the regenerating fibers does not become blocked by cicatricial tissue.

In regard to the second of these conditions it is to be noted (and the same applies to the third) that regeneration of an imperfect order may show itself in these cases; it may commence, but is unable to effect

[1] Monte and Fieschi, Arch. ital. de Biol., 24: 1895: 401; Tirelli, ibid., 23: 1895: 301.

[2] Galeotti and Levi, Ziegler's Beitr., 17: 1895; Kennedy, Phil. Trans. Royal Society; B. 1877: 188; Wieting (under Marchand), Ziegler's Beitr., 23: 1899: 42.

[3] Upheld by Bethe, Allgem. Anat. u. Physiol. d. Nervensystems, Leipzig, 1903, and by Stewart and Ballance, The Healing of Nerves, London, Macmillan, 1901.

any satisfactory result. This is well seen in the amputation neuroma, so called, in which the axis-cylinder processes grow out from the end of the severed nerve, but become wound and twisted in all directions in the connective-tissue overgrowth of the perineurium and endoneurium, a nodular mass resulting. We call attention to the degeneration of the organ innervated in consequence of certain important observations of our colleague, Dr. Shirres,[1] that if, by massage and electrical stimulation, the healthy conditions of the muscles which are supplied by the severed nerves be preserved, even in the spinal cord there are indications that the axis-cylinder processes are capable of some regeneration, a result which previous observers have failed to attain—apparently because this preservation of the innervated parts has not been sought after—and so have denied its possibility. Forsmann[2] would seem to have approached this point in his recognition, as the results of many experiments of a form of "chemiotropism," or positive neurotropism, attracting the newly formed axis cylinders downward to join the distal portion of the nerve. Apparently, that is, the condition of the muscle has some influence upon the distal, severed portion of the nerve in connection with it.

With reference to the third condition, as we noted in connection with muscle, so here, regeneration is most complete when there is not complete section, but only contusion and destruction of the axis cylinder by any means, without rupture of the sheaths of Schwann.

There is, indeed, an interesting parallelism between the muscle and the medullated nerve fiber in this, that both are compound structures provided with a sheath (the sarcolemma and neurilemma respectively) which is of connective-tissue origin, closely applied to which in normal development are the specific muscle nuclei in the one case, the nuclei controlling the myelin sheath in the other.

Considering this simpler case first, the stages in connection with regeneration are the following:

The first result of injury in the course of a fiber is traumatic degeneration. This is apt to show itself first in the medulla, the myelin dividing up into irregular masses and globules; it is followed by fibrillation, imperfect staining, and disintegration of the axis cylinder. The fragments of the myelin sheath become smaller and more numerous, and by the second day these conditions are very pronounced, the disintegrated axis cylinder becoming wholly unrecognizable.

But by the second or third day there is already noticeable a distinct proliferation of the nuclei of the sheath of Schwann. They multiply by direct division, no longer lie immediately beneath the neurilemma, but pass between the myelin globules, and, like the future sarcoblastic nuclei under similar conditions, it is to be observed that they gain a surrounding cytoplasm, increasing in amount. Mitoses, with further multiplication, may become evident on the third and fourth day, and, as with the hyaline, degenerated muscle masses, so here, the myelin

[1] Montreal Med. Jour., 34; 1905: 239.

[2] Ziegler's Beitr., 24; 1898; 56.

droplets diminish as these cells grow and enlarge. Of these remarkable cells, while some degenerate and disappear, others become elongated and spindle-shaped. As to their further development, there is still some debate. It is generally admitted that they give origin to the new sheath of Schwann and to myelin. It is in regard to their connection with the new axis cylinder that there is difference of opinion, as above noted. We see that the new axis cylinder originates from the central end of the damaged nerve, not necessarily from the last node of Ranvier; some of the fine young processes may be traced to an origin higher up the nerve. We see, also, that where there has been merely crushing, without destruction of the sheath, the axis cylinders, often multiple, or, more correctly, with fine aberrant fibrillæ, proceed down the old sheath surrounded by the myelin cells, and, doing this, pass eventually beyond the region of injury into the distal undamaged part of the nerve.

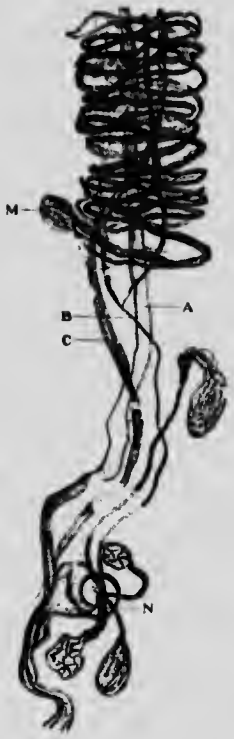
Recent studies, more particularly those of Marinesco,[1] throw light upon the positive neurotropism of Forsmann above mentioned. It is seen that the end of regenerating axis cylinder is not filiform, but formed of a nodular mass of protoplasm possessing a most remarkable power of apparently pseudopodial motion. Following the development of the axones in removed portions of the primitive nerve tube of the larval frog, Ross Harrison, of Johns Hopkins, has shown that this nodular mass creeps forward, in this way lengthening the axone behind it, and this at the rate of about 1 micromillimeter in two minutes. The regenerating axone creeps thus across the area of destruction and along the lines of the old sheaths of Schwann until it enters the nerve bundle beyond. Not all necessarily reach this; some become diverted and arrested in the damaged area, but eventually a certain number of the swollen ends can, by appropriate staining methods, be detected in the distal nerve bundle. Presumably these fuse with the still intact axones of this distal portion: the exact mode of fusion has not been followed.

Regeneration after Section or Rupture.—Unlike what occurs in the divided muscle fiber, there is, so far as we can see, no marked difference in the behavior of the myelin nuclei (or nuclei of the sheath of Schwann) when the nerve fibers have been divided from what occurs when they remain intact, save this, that they wander out of the sheath, and, wandering in various directions, the axis cylinder processes also are apt to curve and be distributed very irregularly, some wandering directly backward instead of forward. Whether, under these conditions, complete *functional* regeneration occurs, depends upon whether any considerable proportion of the new fibers find their way to the tract of the distal portion of the nerve, and is governed largely by two conditions, namely, (1) the distance apart of the two ends of the severed nerve, and (2) the extent of the cicatricial formation between these two ends.

For complete restoration of function many months may be necessary,

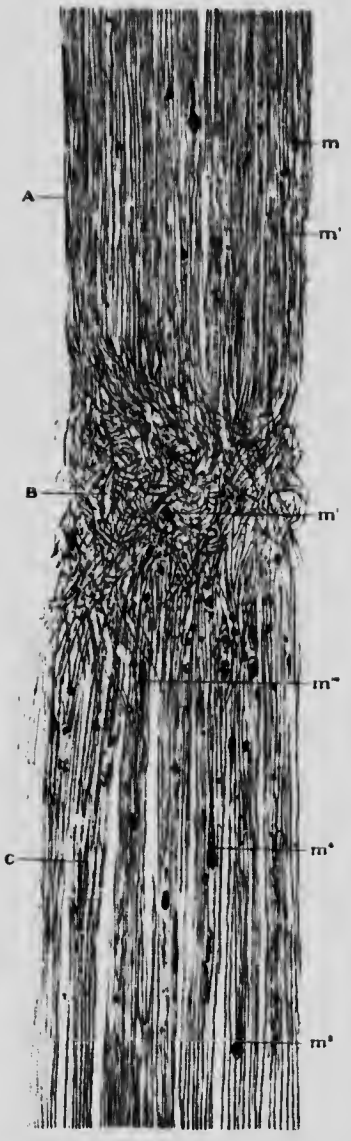
[1] Marinesco and Minea, Revista Stiintelor Med., Bucharest, 1905, No. 5. For a fuller description of recent studies see Halliburton, Science Progress, 2; 1908; 413.

Fig. 181



Regenerating nerve fibres. These are of varying thickness (*A*, *B*, *C*), and each is provided with a terminal swelling. The figure also shows the marked tendency on the part of a certain proportion of the regenerating fibres to take a spiral course (*M*). (Marinesco.)

Fig. 182



Longitudinal section of nerve from dog twenty-one days after division: *A*, central end. *B*, cicatrix of union in which the nerves take a very irregular course. Many regenerating fibres with club-like ends; *m'''*, *m*,⁴ *m* have already penetrated into *C*, the peripheral end of the divided nerve. Some, like *m''*, have become so diverted in the cicatrix as to be turning directly backward. Others, *m'* and *m''*, growing from above, have not yet reached the cicatrix. (Marinesco.)

and experiments show that the wider apart are the two ends of the nerve the longer is the time necessary (*ceteris paribus*). Beyond a certain distance no results are obtainable. Vaulair, in the dog, had negative results when a length of 4 cm. of the vagus was excised, though where a tubular-bone suture, or canal, was placed between the two ends, Huber obtained regeneration after excision of 6 cm. of the ulnar nerve of a dog (see also Tiedemann's results below). Regeneration, indeed, is materially aided by affording a path along which the new fibers are directed, whether a hollow bone (Vaulair), a small artery from some other animal (Bünger), a bundle of catgut threads (Assaky, Gluck, etc.), a lappet or slip from the nerve bundle itself turned over to join the severed ends (Létiévant), a length of nerve from another animal, etc. Where suppurative inflammation and leukocytic infiltration occur, it will readily be understood that there is subsequent dense cicatrization, forming a barrier preventing union. There are, however, some exceptional cases on record in which, eventually, regeneration has taken place. Of these, one of the most remarkable is that of Tiedemann, in which, after excision of from 10 to 12 cm. from the brachial plexus of a dog, almost suddenly, at the end of two years, there was complete restoration of functions in the limb. In fact, many of the negative observations upon this subject of regeneration by one or other means of favoring the passage of the fibrils downward appear to have allowed too short an interval before making the record.[1]

[1] Other important papers on this subject of the regeneration of peripheral nerves are: Howell and Huber, Jour. of Phys., 13 and 14: 1892, 1893; Huber, Jour. of Morphol., 11: 1895: 629 (a classical study of the subject); Stroebe, Ziegler's Beitr., 13: 160, and Centralbl. f. Pathol., 6: 1898 (a useful review of this literature); Vaulair, Arch. de Biol., 3: 1882: 379, and Arch. de Physiol., 8: 1886; Willard (nerve suturing), Internat. Med. Mag., April, 1894; Assaky, Arch. gén. de méd., 1886.

CHAPTER XIII.

GRAFTING OR TRANSPLANTATION.

It is possible, within limits to be presently laid down, to transplant certain tissues or portions of the same, and for these to preserve their vitality and perform their functions in their new situations, and this not only (1) in connection with tissues removed from one portion to another of the same individual, but (2) with tissues removed from another individual of the same species, and even (3) with tissues removed from an individual of another species.

Terminology.—Here, as there is a tendency to use terms somewhat loosely, it may be well to lay down that under *implantation* we include all processes of inserting solid matter into the tissues of a living animal, whether living or dead tissue, or inert material of animal origin, whereas *transplantation*, or grafting, refers only to the one order of cases of insertion of living tissue. Such transplantation is spoken of as *autoplastic* when it is sought to graft tissue from the same individual; *heteroplastic*, where the tissues of another animal are employed. *Replantation*, the replacement of an organ or tissue after removal (*e. g.*, tooth, end of nose, etc.), explains itself.

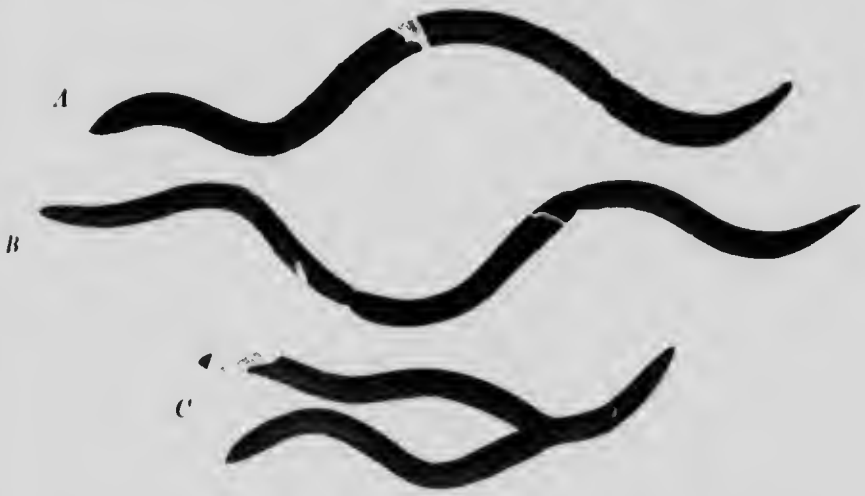
Such grafting is a common operation in gardening and arboriculture, and there it has been known for centuries that not only is it possible to mate and gain perfect organic autoplastic or heteroplastic union, but that successful grafts can be made upon a stock of wholly different species. It generally is found that the more nearly allied the species, the greater the measure of success attained. Nevertheless, the growth of the parasitic mistletoe upon the apple and other trees shows how widely apart may be stock and graft.

That such transplantation is possible in man has been known in the East for centuries and introduced thence to Italy and European civilization, and has been regarded as one of the marvels of surgery. Of late years, the scope and frequency of the process has been much widened. It has, however, to be admitted that the result has been—save in rare exceptions in connection with transplantation of skin and autoplastic grafting of thyroid and ovary—to create a profound distrust; the limits of successful operations are found to be singularly narrow, and while at first the results appear admirable, within a few short months the patient is found in the *status quo ante*, as a result of resorption of the transplanted tissues. Ignorance of the laws bearing upon the subject has led to the performance of operations as absurd as they are indefensible—as, for instance, the attempted grafting of the eyes of the lower animals into the human orbit. It will be well here to point out

what has been determined, and to show what surely can be deduced from many studies made during the last few years.

There is now no doubt, more especially from the observations of Joest[1] upon earth-worms and of Born[2] upon amphibian larvæ, that in lower animals transplantation is possible to an extraordinary extent.

FIG. 183



Heteroplastic transplantation in the earth-worm. *A*, of tail end of another individual of the same species (Allolobophora terr.); *B*, intercalation of mid-body region of another individual; *C*, lateral grafting of anterior half of another individual. (Joest.)

Thus, the latter was able to join together larvæ, or parts of larvæ, of different species, and, taking individuals of one species and cutting out portions of their bodies, he could replace these with like portions of the bodies of other individuals, and found that, if parts were accurately

FIG. 184

Transplantation in an oblique plane between two distinct species of earth worm Lumbricus rubellus and A. terrestris. (Joest.)

applied, corresponding parts of such organs, as the heart, the intestine, and nerves, would fuse neatly together, and that growth continued with functional unity.

When, however, we come to study warm-blooded animals, we find that the capacity no longer obtains to anything like the same extent.

[1] Arch. f. Entwickelungsmechanik, 5: 1897: 119.

[2] Ibid., 4: 1896.

Ribbert,[1] Lubarsch,[2] and many others, have conducted full and most careful studies upon the effects of transplantation of very many tissues, with eventually little more than negative results. Transplanting various portions of various glands of the animals of the laboratory into regions well supplied with blood—into the liver (Lubarsch) or the abdominal lymph glands (Ribbert)—it is found that for a time there is complete healing in, and complete union, eventually absorption and disappearance of the transplanted tissue, takes place, a fibrous cicatrix alone remaining.

There has, it is true, been evidence of primary growth; thus, the ducts of glands, especially, have shown mitosis and active proliferation, and the appearance of the tissue has shown what we elsewhere speak of as reversion, or reversionary degeneration, the cells assuming a simpler, more embryonic type, and with this the parts which, developmentally, are found to exhibit most active growth now show the same properties. In bone transplanted into a lymph gland, also, the periosteum may remain active, and there may even be new development of either cartilage or bone. But within a few weeks or months all the specific cells of the transplanted tissue atrophy and disappear. This has been the experience with such tissues as liver, kidney, and testis.

What at first appear to be satisfactory results are gained by grafting embryonic tissues into the fully grown animal. Knowing the active vegetative capacities of the embryonic cells, this is readily understandable. Such observations have been carried out more particularly by Ribbert,[3] Birch-Hirschfeld,[4] and Feré.[5] The latter observer, planting portions of forty-eight-hour chick embryos under the skin of young chickens, gained, rarely, progressive growth, the growth persisting and being recognizable in one case for five months, in another for thirty-three months. In one case, by the end of two months, small black feathers appeared on the graft, in another, simple epithelium. As a rule, the "tumors" were composed of mesodermal elements, vessels, plain muscular tissues, etc., with, in one case, cartilage. But in the greater majority of the cases, by the end of two months, the grafts began to diminish and undergo absorption. The same was true in Ribbert and Birch-Hirschfeld's cases, carried out more particularly with pieces of rabbit embryos. In these there was found a greater persistence of cartilage than of other tissues, and this at times formed masses of considerable size, which, however, eventually underwent regressive changes and atrophy. This growth of perichondrium and cartilage has been noted by several observers.

[1] Arch. f. Entwickelungsmechanik, 6; 1898; 131, etc.

[2] Zur Lehre d. Geschwülste, Wiesbaden, 1899. The observations of Paul Bert, De la Greffe animale, Paris, 1863, call for mention; they were performed on the rat, and were very extensive and more successful than those of later observers.

[3] Loc. cit.

[4] Ziegler's Beitr., 26; 1899; 132.

[5] Compt. rend. de la Soc. de Biol., 1895 and 1897 (several papers); also Arch. d'anat microscop., 1; 1897; 193 and 417.

Hunter's famous experiment[1] upon transplanting the cock's spur into the cock's comb shows, in general, the same phenomena. There is a primary, most active growth, and the spur with its bony centre may attain the length of some inches. Such spurs have been reported as still being present at the end of two years. More often, after a few weeks or months, they undergo atrophy and fall off.

Thyroid.—More satisfactory results follow transplantation of the thyroid. Von Eiselberg[2] first transplanted one-half of the cat's thyroid into the animal's abdominal wall, and when this was healed and appeared to have united, he transplanted the other half into the abdominal wall or cavity. The animals so treated bore the operation well and showed no symptoms, but so soon as the transplanted portions were removed they rapidly died with the symptoms of tetany which follow extirpation of this gland in the cat. Munk,[3] Enderlen,[4] and Sultan[5] have confirmed these observations, and have proved that both in the cat and the dog the central parts of the lobes undergo necrosis, the peripheral follicles remaining unaffected, while as granulation tissue, derived from surrounding parts, passes in between these into the central necrotic area, there is an actual growth of the thyroid-gland tissue, in the shape of solid cell processes or buds given off from the persisting follicular epithelium. These become separated off, and eventually, with secretion of colloid, may gain a lumen and become quite typical. Lubarsch[6] transplanted thyroid tissue into the kidney, found the new growth imperfect, and eventually, within six months, becoming atrophied and absorbed. Transplanting into the abdominal cavity, other observers have gained more successful results. Thus Enderlen, grafting the dog's thyroid into its abdominal cavity, found that, at the end of five and a half months, the tissue there was of the normal type, and Christiani,[7] making autoplastic grafts of the cat's thyroid into the abdomen, found the graft throughout glandular, very vascular, and the follicles full of colloid at the end of two years; and was justified thus in concluding that the organ can function in its new position during the whole course of the animal's existence.

Mammary Glands.—Ribbert's observations indicate that the *mammary glands* of young individuals, if grafted subcutaneously, are capable of growing permanently in this new position. Taking a guinea-pig a few days old, he grafted the mammary glands below the ears; the skin did not heal over them completely, and when, five months later, the animal became pregnant, the glands underwent enlargement and secreted milk, while at the same time new mammary glands showed themselves in the normal position, apparently from regeneration of portions left behind.

Ovaries.—There remain to be mentioned those more important instances in which, in the higher animals, transplantation would seem to

[1] This experiment, however, it must be noted, was the repetition of an experiment by Aldrovandi in the sixteenth century, confirmed by Worm in 1685 and by Duhamel in 1746.

[2] Wiener klin. Woch., 1892: 5.

[3] Virch. Arch., 150: 1897: 271.

[4] Mitth. a. d. Grenzgeb., etc., 3: 1898.

[5] Centralbl. f. Path., 9: 1898.

[6] Loc. cit., p. 251.

[7] Arch. de Physiol., 7: 1895: 65.

be attended by continued growth and vitality of the transplanted tissue, namely, the transplantation of the ovaries and of the skin and of the periosteum.

As pointed out by Knauer[1] and by Grigorieff,[2] if both ovaries of a rabbit be transplanted to other regions of the peritoneum, it is found that while the central portions of these organs necrose, the other portions remain normal, exhibiting normal Graafian follicles and successive corpora lutea—and the follicles still produce ova. Three of Grigorieff's animals became pregnant after the operation, and Knauer notes the birth of young sixteen months after the transplantation. The transplantation would, therefore, seem to be perfectly successful, although further experiments are necessary to determine the exact length of time during which the ovaries continue to perform these functions. Like observations were conducted, some years earlier, in the human female by R. T. Morris,[3] in one case, in a girl, aged twenty years, who had never menstruated. Menstruation followed the grafting of part of the ovary of another woman into the uterine wall; in another, after the removal of both ovaries and tubes, he grafted a portion of one of the removed ovaries upon the stump of the right tube. Pregnancy followed later, ending in abortion at the end of the third month.

Skin Grafting.—The facts in connection with transplantation of the skin are so well known that here we need but summarize the results obtained:

(*a*) The deepest layer of the epidermis—the Malpighian layer—most surely undergoes proliferation when skin is transplanted; thus, for successful operation, the grafts must pass down well into the papillary layer of the cutis. It is true that, as MacLeod has pointed, out these deeper cells can be obtained by blistering and employing the blister serum, but the surest results are obtained by Thiersch's or by Krause's methods, in which the papillary layer or even a large portion of the cutis is removed with the graft.

(*b*) In all cases the greater part of the graft dies, but as the vessels of the underlying granulation tissue make their way through the cutis and reach the under surface of the grafted epidermis, the cells of the Malpighian layer exhibit mitosis (generally about the third day) and now undergo active multiplication, spreading out in centrifugal manner. As pointed out by Loeb,[4] these new cells have amœboid properties.

(*c*) In this way, the denuded area becomes gradually covered with a new epithelium, which, however, is unprovided with hair follicles or sweat glands; the more differentiated portions of the skin are not reproduced.

In some cases, at least, this new transplanted epithelium is quite permanent, although Loeb's interesting results, obtained by transplanting pigmented skin (in guinea-pigs) into unpigmented areas, and *vice versa*, would show that unpigmented skin so transplanted gradually becomes

[1] Centralbl. f. Gynäk., 22: 1898: 201.
[2] Ibid., 21: 1897: 663.
[3] New York Med. Jour., 62: 1895: 436.
[4] Medicine, Chicago, March, 1898.

pigmented; that there is a definite migration of pigment cells into the surrounding epidermis; that in albinos pigmented grafts become, eventually, colorless; and they raise a doubt as to whether, after all, there may not be a gradual replacement of the graft, piecemeal, by cells derived from the epithelium of the "host," and whether the continued vitality of the graft is not more apparent rather than real.

Certain remarkable results have been obtained by Allen[1] and others, by the employment of the skin of frogs and other animals for the purposes of grafting. For a time much attention was called to experiments and the surgical employment of grafts of this nature. We may sum up the results of a fuller study by stating that *in no case is the skin of another species found to be successfully grafted in man;* in all cases the cells undergo necrosis. At the same time, there are indications that the existence of epithelial cells on the healthy surface of a wound, even when not those of the same species, have a stimulating effect upon the epithelium of the host, causing it to spread more rapidly over the denuded surface. It is difficult to explain the observations to this effect, save on the basis of the existence of a *homotropism*, an attraction of cells to others of like order, to the possible existence of which we have more than once referred (*e. g.*, p. 574).

Mucous Membranes.—Here it may be added that mucous membranes show a like capacity for transplantation. Thus, several observers have, with greater or less cosmetic success, grafted the mucous membranes of the lips and mouth upon the conjunctiva and eyelids.

Teeth and Bone.—The grafting of teeth and bone are frequently cited as examples of successful transplantation. In reality, they belong to a different order of phenomena, being examples of implantation.

It appears to have been known for some centuries, in India, that after removal of a relatively sound tooth, a similar tooth removed from another man and placed in its socket becomes perfectly united and healed in, and in the time of the Roman Empire there are indications that something was known of the implantation of artificial teeth formed of bone, while, following upon Ambroise Paré, the employment of freshly drawn teeth from one individual to replace those of another seems to have been somewhat frequently practised in France and England, until the conveyance of syphilis, in several instances, threw the procedure into discredit.

Here it need only be noted that equally good results are gained, whether an entirely fresh and healthy, newly drawn tooth is employed, a tooth that has had its pulp removed, one that has been thoroughly sterilized so as to kill off any living cells, or one that has been out of the body for years. There is not, that is to say, organic union in the strict sense. Vessels, and even nerves, may penetrate into the pulp cavity, and osteoblasts also passing in, it may eventually become filled with bone and so become firmly fixed; but in all cases—even those in which the recently drawn tooth retains active alveolar periosteum, which can become grafted on

[1] Lancet, London, 1884: ii: 875.

to the alveolar periosteum of the jaw, and so cause firm fixation of the cement substances—the tooth proper is an inert substanee whose scanty cells do not persist. And, while in some cases the implantation is sueeessful, in a considerable proportion the roots become absorbed, and the tooth loosens and eventually falls out.

We observe very largely the same order of events in connection with *bone*. The implantation of dead, sterilized bone, or particles of such, whether of man or the rabbit, or even, following Senn's method, of decaleified bones, gives every bit as good results—in some respects, better results—than does living or recently removed bone of the individual grafted upon. Employing this latter, the bone corpuscles examined a few days later are found dead and non-staining. Such bone, in fact, forms, like any other porous material, a framework into whieh may penetrate the cells and vessels from the surrounding periosteum and living tissues. It acts, in short, very mueh as does the fibrin and blood-e ot found in a wound under natural eonditions, with the additional advantage that it is rigid and so is more likely to preserve the natural contour of the part.

Periosteum.—With *periosteum*, as again with *perichondrium*, the case is very different. The autoplastic transplantation of both is most suceessful and most often the heteroplastie (*i. e.*, from one individual to another of the same species), although here the younger the animal that affords the graft, the greater the measure of success. Saltykoff's[1] observations indicate that in the days following the operation the greater number of the periosteal cells undergo necrosis; a certain proportion of them, in the inner osteoblastic or cambium layer, remains alive, and by the third day shows ..itoses; in five days the proliferation of these cells is abundant and they form into rows of osteoblasts, which give rise to new bone. It is the inner layer of the periosteum that is aetive in this bone formation. There may be a preliminary formation of hyaline cartilage followed by the development of the bone. In general, it is to be noted that transplantation into the bloodvessels (Cohnheim and Maas[2]) or into the soft tissues does not lead to sueh perfect results as when the transplantation occurs over old bone or in an area of previous bone. In the first of these cases there is eventual absorption, in the last the formation of apparently normal bone, even to the development of a medullary eavity.

With regard to bone-marrow the results of different observers have been eontradictory, but by the autoplastie grafting of red marrow under the skin Bruns[3] gained the formation of eartilage, osteoid tissue, and, after twenty-two to twenty-four days, of true bone, results which were confirmed by Kölliker[4] as regards transplantation into the anterior chamber of the eye and the abdominal cavity.

Carrel's Experiments.—The above was the state of our knowledge on this subjeet until within the last two years, when eertain remarkable

[1] Arch. f. Entwickelmech., 9: 1900.
[2] Arch. f. klin. Chir., 26.
[3] Virch. Arch., 70: 1877: 161.
[4] Centralbl. f. Chirurg., 1881: 577.

observations of Carrel[1] have greatly altered our point of view. With great surgical ingenuity, Carrel has developed the method of vascular anastomosis and union, and of the accurate adaptation of nerves, ducts (like the ureter), etc.; and by this method he has proved convincingly that, *provided the circulation be restored fully*, not merely can arteries and other vessels from one animal be transferred into another, remaining functional and apparently healthy for long weeks, but that this may even happen when the graft is taken from an animal of a different species; further, that organs of very considerable size, such as the kidney, may be transplanted from one animal to another of the same species and exhibit evidences of normal function.[2] His latest achievement has been to transplant the whole limb from one animal into another, with indications of at least temporary success. Time has not yet been afforded to determine what are the limits of the vitality of tissues so transplanted into another host, but sufficient has been done to show that if the nourishment of the graft through its vessels be secured, a success is obtainable which is far greater than that hitherto accomplished by more haphazard methods.

Conclusions.—We reach, therefore, the following conclusions:

1. In lower animals (as in plants), transplantation and grafting is possible to a remarkable extent, but in the higher warm-blooded animals, it is possible to but a very limited extent, unless there be gained an accurate adaptation and anastomosis of the nutrient vessels.

2. In the latter, without such anastomosis, there may be temporary success, the grafted part gaining complete union and showing cell multiplication; but, with relatively few exceptions (epidermis, mucous membranes, periosteum, perichondrium, thyroid, and ovaries), the cells of the graft sooner or later undergo atrophy and absorption.

3. Autoplastic grafting is more successful than heteroplastic, and this, again, than grafting with tissues of a different species. In vertebrates the latter is only possible where immediate vascular anastomosis is brought about between the vessels of the host and of the graft.

4. The more vascular the site of transplantation, the greater the likelihood of obtaining (temporary) union.

5. The younger and more actively proliferating the tissue composing the graft, the greater the likelihood.

6. The more the graft is in position to satisfy the needs of the organism and to actively function, the longer, in general, would its cells appear to retain their vitality, *e.g.*, portions of liver grafted into other organs when the liver as a whole is still functioning, rapidly degenerate; the thyroid or *both* ovaries removed from their natural site and transplanted elsewhere retain their functions. The skin transplanted on to a superficies forms a perfect graft.[3]

[1] Proc. Soc. Exp. Med., 4: 1907, Carrel and Guthrie, Science, 22: 1905: 473 and 23: 1906: 394. [2] Jour. of Exp. Med., 10: 1908: 98.

[3] Quite the most thorough study of this subject of transplantation and implantation will be found in the work to which we have already more than once referred, Marchand's Die Wundheilung. The literature is there given very fully.

CHAPTER XIV.

METAPLASIA AND HETEROMORPHOSIS.

METAPLASIA.

If an eye that through traumatism has been rendered functionless be removed some years later, it is, in general, found that from the choroid coat there has developed a layer or deposit of true bone. In one case, studied in our laboratory at the Royal Victoria Hospital, by Dr. Mathewson, not only the choroid, but also the lens was definitely implicated in this bony formation. To account for this remarkable development in a region where, normally, bone is wholly wanting, two theories may be adduced: (1) that in the process of formation of the eye, a few cells destined to form bone become accidentally carried into the eye, along with the invaginating membranes, and remain latent and inactive so long as the organ performs its functions, but when by accident it becomes functionless then the altered conditions are such as to favor the active growth of the cells and the eventual formation of true bone; (2) that the bone formation is due to modified function and nutrition of certain choroidal (connective tissue) cells. Normally, in the uninjured eye, the choroidal cells have definite duties, and their activity appears to bear a direct relationship to the light-receiving function of the eye. When either the anterior or posterior chamber of the eye is injured, the functional activity of these cells is arrested; the vascularity of the choroid undergoes modification, and now certain of the choroidal cells become modified in their action and form bone; (3) the third theory, that of Ribbert, of conveyance of bone-forming cells to the part by the blood, we will discuss later (p. 591).

The first of these theories must, I think, be discredited. If we came across this choroidal bone formation only exceptionally, it might well be urged, but the eventual formation of this bone in the useless eye is the rule, not the exception. Holding to this theory, we should have to hold that the inclusion of aberrant tissue or "mother cells" in the developing eye—and in other developing organs—is a matter of constant occurrence. As we shall proceed to show later, while we must admit the occurrence of these "cell-rests," and admit that they are not uncommon, we cannot believe that cell-rests of osteoblasts are practically constant in the coats of the eye. We have absolutely no ground for such an assumption. In studying normal tissues under the microscope, it is only very exceptionally that we encounter appearances which we can ascribe to the persistence of cell inclusions. In other words, *metaplasia*, or the production of specialized tissues from cells, which normally produce

tissues of other orders, affords a more satisfactory explanation of the appearances above described than does the theory of *cell-rests*.

We are apt to forget that metaplasia is a constant physiological process. The conversion of cartilage into bone (p. 557) is a typical example of metaplasia, as again is the conversion of ordinary connective-tissue corpuscles into fat cells.

But, physiologically and pathologically, we are forced to recognize that there are certain narrow limits bounding such metaplasia, at least after birth. *Epithelial (epiblastic and hypoblastic) tissues can only be converted into other forms of epithelial tissue, one form of mesoblastic into another form of mesoblastic.* Epithelium and gland cells, for example, never become converted into bone or cartilage, or *vice versa*, while, again, it may be laid down that among epiblastic and hypoblastic tissues, on the one hand, and mesoblastic tissues, on the other, there is no new

FIG. 185

Island of squamous epithelium in cervix uteri of newborn infant (? developmental metaplasia or inclusion). (R. Meyer.)

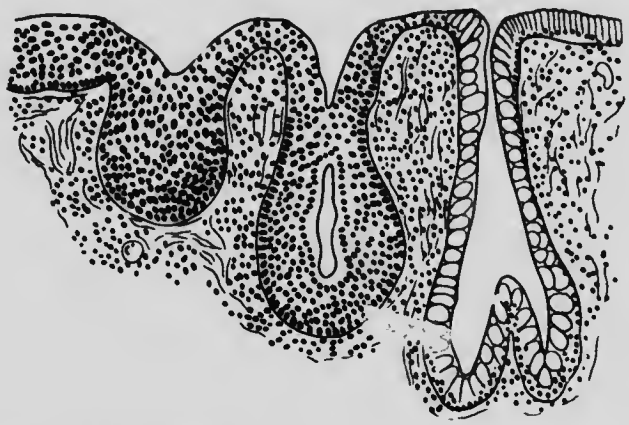
development or metaplasia of the most highly specialized tissues from less specialized tissues; a simple epithelium cannot in the vertebrate give rise to the more complex glandular tissue, or to nerve cells; in regeneration of epithelium there is no new formation of hair roots or cutaneous glands. The cells of white fibrous connective tissue have not been seen to form striated or even non-striated muscle. Within these relatively narrow limits numerous examples of pathological metaplasia present themselves.

Epithelial.—The mucous membrane of the uterus is a columnar epithelium; if the organ be everted so that it projects from the vagina, forming a pear-shaped mass, exposed to the air, the mucosa covering it becomes eventually smooth and dry, and now, upon examination, in place of the columnar there is found a stratified squamous epithelium, of which the outer layers may show very definite keratinous or horny change, as in the true skin. Similarly, as the result of chronic irritation,

the columnar, ciliated epithelium which covers the greater part of the larynx may here and there show thickening, and, on microscopic examination, these thickenings are found to be formed of a squamous epithelium of many layers of flattened cells. In the gall-bladder also similar transformation of the columnar mucosa has been observed following chronic catarrh.

A reverse change is occasionally encountered in the bladder. This organ is lined by a distinct, if somewhat loose, pavement epithelium in several layers. As a result of chronic inflammation, overgrowth of a papillomatous type may be initiated, when in place of the squamous epithelium there is developed an epithelium of the columnar type. This is often noted in cases of ectopia vesicæ, and here even simple glandular crypts may show themselves.

FIG. 186



Metaplasia from a case of ectopia of the bladder; the ordinary squamous epithelium becomes replaced by a columnar epithelium. (After Enderlen.)

Mesoblastic.—The most marked examples are afforded by the metaplastic formation of *bone*. This may be:

1. From cartilage, as in the ossification of the laryngeal and tracheal cartilages in advancing age, in which it is to be noted that, as in all these true metaplasias, there is merely conversion of one tissue into another—replacement and not new-growth. There may, however, be some admixture of replacement and growth. Occasionally the smaller bronchi are found converted into rigid bony tubes. It is a question here whether we have to deal with metaplasia of the small cartilaginous plates in the bronchial walls alone, with subsequent slight growth and fusion, or with metaplasia affecting both the cartilage and the intervening connective tissue. The replacement of cartilage by bone in callus after fracture is an example of the same process.

2. Osseous metaplasia of connective tissue. In the lungs we may

encounter small irregular spiculated masses of true bone, best explained as originating in this manner, while relatively large plates of true bone are to be met with in old pleural and pericardial adhesions, where the inflammation has been prolonged and the formation of new tissue excessive. Both bone and cartilage are occasionally met with in the arterial wall in arteriosclerosis, as also in the fibroid valve of chronic endocarditis. Professor J. J. MacKenzie[1] and W. Harvey,[2] of Toronto, and others have noted the liability for bone to form in the walls of arteries of rabbits that have been experimentally injured.

3. Osseous metaplasia of tendons. Occasionally the tendons of origin or insertion of a muscle are found replaced by true bone, forming large bony prominences. This may be the first stage of a remarkable

FIG. 187

Osseous metaplasia in the wall of a bronchus (so-called "osteoma"): *a*, mucosa; *b*, submucosa; *c*, mucous glands; *d*, cartilage; *e*, connective tissue; *f*, *f*, masses of bone in submucosa; *g*, fat-cells. (Dennig.)

and rare condition, to which the mistaken designation of *myositis ossificans* has been given.

There is no certain evidence that we have to deal with an inflammatory process, nor is it certain that the muscle fibers are primarily involved. In this condition, in the course of years, the muscle tendons and the bodies of one set of muscles after the other become replaced by bone, until at last the patient is unable to move his limbs, or to rotate the head or bend the back bone. Further and fuller studies are needed into the essential nature of this very remarkable condition.

Cartilage.—The most marked example of cartilaginous metaplasia (except forms that are observed in connective tissue tumors) is seen in

[1] Brit. Med. Assoc., Toronto, 1906.

[2] Journ. of Med. Res., N. S., 12: 1907: 25. For cartilage similarly produced see Trachtenberg, Centralbl. f. Path., 17: 1906: 614.

the development of the provisional callus of long bones after fracture (see p. 559). In connection with new-growths derived from the connective tissues (osteomas, fibromas, sarcomas, lipomas, myomas), islands of cartilage are frequently observable. In mixed tumors of certain organs, such as the parotid and testis, it is usual to ascribe this cartilaginous formation to the existence of cell-rests. A consideration of cartilage development in general leads us to consider that we have no adequate ground for separating these from other cases of metaplasia. The development of cartilaginous tumors, not uncommon in the mammary gland of the bitch (and very rare in that of the human being), must equally, we think, be regarded as originating from a primary metaplasia of the connective tissue of this gland. This, however, is not the prevalent view.

Fibrous Tissue.—As might be expected, we meet with frequent examples of the conversion of more specialized mesoblastic tissues into the simpler fibrous connective tissue type. As Thoma well points out, one of the clearest examples is met with as the result of immobilization of a joint by surrounding adhesions, etc., when the cartilages covering the opposed surfaces disappear, being replaced by connective and mucoid tissue. There is, it is true, a primary neoplastic development of vessels in the part, but the appearance of the fibrous and mucous tissue must be regarded not as a degenerative change (for inactivity of the joint would lead to atrophy), but as directly due to change of function. Immobility of the joint does away with the condition which necessitated joint and cartilage, and slowly a new-formed tissue develops.

Another very frequent example of fibrous metaplasia may possibly occur in what are the commonest of tumors—the so-called uterine fibroids. The frequent difficulty in distinguishing between the pure myoma or non-striated muscle neoplasm and the pure fibroma may be explained by regarding the majority of these "fibroids" as originally muscle tumors, which, in the course of growth, become gradually changed into fibrous tissue—not by an overgrowth of the connective-tissue framework (although this may occur coincidently), but as a direct conversion or metaplasia of the muscle fibers into connective tissue. We suggest this with very considerable diffidence, for again it is not the prevalent view, which is that the muscle undergoes atrophy and replacement.

Mucoid Tissue.—It is doubtful whether we should speak of the development of mucoid tissue in adult life as other than a degeneration, or, at least, a retrogressive change. For mucoid tissue developmentally is always found as an intermediate stage in the growth of some other tissue. All the connective tissues may be said to pass through a mucoid stage in their evolution, the intracellular substance or matrix being for a time mucinous. Where, therefore, as happens more especially in bony, cartilaginous, fatty, and fibroid tumors, we find cases of mucoid change or growth, I am inclined to classify this as a retrogressive, rather than a metaplastic, change. How such retrogressive change may be associated with active growth, we shall point out in discussing neoplasia.

Such metaplasia is in all cases to be regarded as an adaptation on the part of the cells to altered environment, not of necessity and primarily to altered function. One can, for example, recognize no change of function in the laryngeal and other cartilages with advancing life, but can recognize alterations in nutrition leading to absorption here and there, entrance of bloodvessels and *conversion into bone*, just as much as, to employ an instance afforded by Lubarsch[1] is the conversion of spherical unicellular organisms, like the micrococcus prodigiosus, into bacillary or even spirillar forms under the influence of acid added to the medium of growth; and in the lower multicellular forms of animal life the modification thus brought about may affect not merely the cells and groups of cells, but entire organs, when instead of metaplasia we speak of *heteroplasia*. To this we have already referred (p. 551) and quoted the example of the regeneration of an antenna in place of an eye noted by Herbst[2] in the *palinurus* and other crabs (Fig. 171). Another remarkable example, noted first by Spallanzani in the eighteenth century, and confirmed by Morgan, is that occasionally the earth-worm, whose head end has been removed, regenerates not a head, but a tail. Very similar in character are the cases to which Loeb first applied the term *heteromorphosis*. The hydra, the tubularia, and the anemone *Cerianthus* all possess a simple digestive *cul-de-sac*, the mouth opening into a digestive pouch. If in any of these an opening be made through the body wall into the digestive sac, so that fluid so soon as it flows through the mouth flows out through this opening, it is found that the opening, in a short time becomes provided with a ring of tentacles and comes to resemble and function as a true mouth.

The cells here through primary alteration in environment are capable of taking an altered function—and so it is in the more restricted condition of metaplasia. To deny or to minimize metaplasia almost to the vanishing point, as is the tendency of certain pathologists at the present day, appears unwarranted; on the other hand, we are not prepared to proceed to the other extreme and recognize that in the developed individual the cells of hypoblastic and epiblastic origin can take on mesoblastic functions.

One of the strongest opponents of the frequent occurrence of metaplasia is Ribbert.[3] He admits the existence of physiological metaplasia, but criticises, with scarce an exception, the examples here brought forward. Metaplasia, he holds, is an "extraordinarily much rarer occurrence" than is usually held. Where in phthisis bulbi, or in the vessel walls or lungs, or in sites of old calcification there occurs development of bone, what happens, according to him, is the appearance of a richly cellular tissue which either is directly converted into bone owing to the development between the cells of a homogeneous ground substance, which undergoes further modification (as may occur in callus), or rows of osteoblasts are to be seen as in normal ossification. But, says Ribbert,

[1] Allgemeine Pathologie, Wiesbaden, 1905: 53.

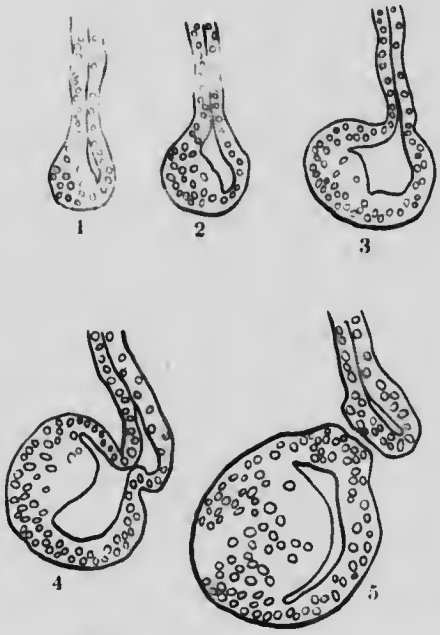
[2] Arch. f. Entwickelungsmech., 9: 1899: 260 and 13: 1902: 436.

[3] Geschwulstlehre, Bonn, 1904: 5

this is no metaplasia. These cells and the marrow cells, which subsequently form, *may* have been derived from the blood and indirectly thus from the marrow of bones elsewhere.

This possibility has to be admitted, but is it the greater probability? We think not. How does bone arise first in the fœtus? From mesoblastic cells; and even in the periosteum of the adult the future bone corpuscles pass through a stage in which they are indistinguishable from fibroblasts, and in delayed union they may actually be converted into connective-tissue corpuscles.

FIG. 188



Stages in the metaplastic regeneration or formation of a new lens from the iris, in the larval Newt: 1, edge of iris becoming swollen; 2, 3, 4, progressive overgrowth of the edge; 5, separation of the hypertrophied mass of cells to form the lens. (Fischel.)

It is the environment and relationship to the vessels and other influences acting upon them that lead certain mesenchyme cells in the first place to become osteoblasts and marrow cells. No satisfactory reason exists for denying that this may be in action later, just as all through life osteoblasts which have never functioned as such hitherto become converted into bone corpuscles. Similarly, he would explain the replacement of columnar by squamous epithelium as most often due to the existence of included islands of squamous epithelium, which now under altered conditions overgrow the more highly differentiated form. This, however, does not explain the reverse condition seen in ectopic bladders.

where columnar epithelium makes its appearance. He admits that the development of a many-layered epithelium of squamous type may replace a single columnar duct epithelium, under conditions in which this explanation cannot hold, as in the extensive alteration which he has himself figured as occurring in the submaxillary duct of the rabbit, after ligature of the same. This he explains as an "innate tendency" on the part of this epithelium, a derivative of the squamous epithelium of the mouth, to form squamous epithelium, a tendency which under ordinary conditions has not the opportunity to show itself and admits the same for like changes in the urinary passages under altered states. *So he concludes that only tissues that, while externally different, possess, nevertheless, the same histogenetic capacities can undergo metaplasia one into the other.* But this is what all pathologists will admit. The histogenetic capacities of a cell are brought out by its surroundings; all we would urge is that they are not so narrow as Ribbert would make them out to be.

One of the most remarkable examples of metaplastic regeneration has been studied by G. Wolff[1] and Fischel.[2] The lens in vertebrates is formed by an invagination of the *surface* epithelium of the head into the primary optic vesicle, which in its turn is formed by a similar invagination from the forebrain. The inner wall of this primary vesicle forms eventually the retina and iris. If, now, in the larval newt or salamander the lens be extirpated, in a short time a new lens is developed *from the iris*. Further observations have shown that the retina itself can produce lens-like bodies, and that if the old lens be not removed but simply pushed to one side, the iris will form a new one. There can be no more remarkable example of cells of one tissue taking on the functions and properties of another. But it must be kept clearly in mind that both the normal lens and the iris, even if of widely different origin, are both epiblastic. The case comes clearly within the limits noted by us, that epiblast can produce epiblast; mesoblast, mesoblast. The same is true in Saxer's case of the development of an epithelium lining the cysts in gliomas (p. 565). While, as we have noted, we do not regard this as a proper epithelium, the cells in question, like the glia cells, are of epiblastic origin. In regenerating planarian worms, as Flexner[3] has pointed out, epithelium can even give rise to distinct nervous elements. Brauer[4] has shown that the same occurs in the larval frog.

The cases we are not prepared at present to accept are such as those placed on record by Leo Loeb, and confirmed, we may add, by other observers, in which in the course of epithelial regeneration certain epithelial cells have been noted to pass into the underlying tissues and assume the appearance of fibroblasts. While we admit that the process occurs, we would urge that the fate of these cells has still to be determined.

[1] Biol. Centralbl., 14; 1894.

[2] Abhandl. d. Deutsch. pathol. Gesell., 1902. For a discussion of the cases see Schwalbe, Morphol. der Missbildungen, Jena, 1906, pp. 87–88.

[3] Jour. Morphology, Boston, 1898.

[4] Jahresber. d. Anat. u. Entwick., 1903 and 1904.

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As shown by Schridde, the mere fact that a cell of the plasma-cell type comes to simulate in size and shape the connective-tissue corpuscle of connective tissue does not make it into a connective-tissue corpuscle. It has still to be shown that the fibroblast-like cells of epithelial origin function as fibroblasts and become fully formed connective-tissue cells. While it is true that in the past too great a stress has been laid upon the tendency of epiblast and hypoblast to form what we have termed lining membrane or lepidic tissues, and too little attention to the fact that each of the primary cell layers can form tissues of both orders (matters to which we shall revert in discussing neoplasia[1]), the pulp of higher tissue derived from the epiblast (*e. g.*, the neuroglia) exhibits constant differences from the mesoblastic connective tissue, and for the present, we must continue to lay down that *while there may be conversion of one epiblastic or hypoblastic tissue into another epiblastic or hypoblastic tissue, and of one mesoblastic form of cell into another mesoblastic form, this conversion is of a limited extent; metaplasia of mesoblastic tissue into epiblastic or hypoblastic and vice versa does not occur.*

In discussing neoplasia we shall point out the possibility that cells of epiblastic origin may undergo *anaplasia* (or *kataplasia*) and revert to the lower type common to both epiblast and mesoblast. This, however, is not metaplasia.

[1] See p. 644.

CHAPTER XV.

THE NEOPLASMS: TERATOMATA AND TERATOBLASTOMATA.

WHATEVER branch of biological science we make the subject of our study, the more deeply we enter into it, the more do we realize that classification, which is the goal and outcome of our knowledge—so far as it concerns the knowledge in itself—is not the sorting of data into sharply defined departments; such departments do not exist. Rather, it is the arrangement of our data in progressive order in such a way that we most satisfactorily give a comprehension of their relationships and the place they occupy in one harmonious scheme. The classes of living objects and of vital phenomena are not distinct; classes as such have no absolute existence; they pass imperceptibly one into the other by many transitional forms. While this is so, classification is nevertheless necessary. To measure the grade we have to set up posts at convenient intervals; to grasp the progression of forms we have to select types here and there at suitable points, group the forms most nearly allied around these, and so constitute classes. Nowhere do these considerations gain a better illustration than in this study of the different forms of neoplasms.

Terminology.—We speak familiarly, and rightly, of any unusual swelling recognizable in any part of the organism as a tumor, for "swelling" is the root-meaning of that term. Under this heading we may include (1) examples of dislocation of parts, (2) abnormal collections of fluid or gas, whether sharply encapsulated, as in cysts, or, though localized, more diffuse, as in inflammatory and hemorrhagic conditions, and along with these, (3) actual tissue growths, whether (*a*) physiological (as in the case of the pregnant uterus), or (*b*) hypertrophic, or (*c*) due to localized abnormal growths of part of a tissue or organ, or within an organ. Save for gross descriptive purposes, unless preceded by a qualifying adjective, the term tumor has no value. If, therefore, we wish to classify and distinguish from other forms of tumor a series of solid overgrowths which are included under none of the conditions hitherto studied, namely, the class which Thoma has, we think, appropriately termed the *autonomous tumors* (*i. e.*, those which are or which possess a law unto themselves) we have to select some more definite term, and for some years it has been usual to speak of *neoplasms* (literally new-growths) and of *neoplasia*, the process of new-growth. But, as Klebs justly points out, these terms are applicable also to conditions of regeneration, hyperplasia, and all forms of new or renewed growths of tissues. Conventionally, however, when we speak of neoplasms we only take into consideration the autonomous tumors we are now about to discuss. Where accuracy of description is required we distinguish two distinct

orders of these neoplasms proper, the *teratomas* and the *blastomas*, and, as I[1] have pointed out, it is serviceable to recognize a third intermediate order, the *teratoblastomas*. What we understand by these terms will be made clear in the following pages.

The termination *oma* following the Greek root for tissue of one or other nature, or even of some descriptive adjective, conventionally indicates an overgrowth of the types about to be considered.

Here, again, owing to the evolution of our science, exceptions are to be noted. Before it became possible to make clear distinctions between the different forms of neoplasia, the termination *oma* was employed indifferently to indicate swellings of any order. We thus still refer to subcutaneous collections of blood as *hematomas*,[2] and use it when referring to specific inflammatory overgrowths—*tuberculoma*, *syphiloma*, *condyloma*, etc. These conditions are, however, not autonomous, and we no longer include them under the neoplasms proper.

It is this autonomy, this growth independent of function and of either present or future needs of the organism in which they occur and from which they gain their nourishment, independent also of obvious stimulation from without, that distinguishes the neoplasms proper from all other forms of tissue growth. And it is this also that renders it difficult to define them in terms applicable to other vital processes. In seeking for such a definition the natural course to follow would be to consider processes apparently most nearly allied, and carefully to analyze the points of likeness and of difference. Now such processes exist; there are overgrowths the result of inflammation, and others of the nature of congenital hypertrophies, in which it is almost if not wholly impossible to state where the division comes between inflammatory disturbances or hypertrophy on the one hand, and blastomatosis on the other. But these we shall consider later, when discussing the blastomas, for it is in connection with that order of tumors that these difficulties arise. In order to present as clear a picture as possible, we shall at first consider autonomous neoplasia in general, define that, and then take into consideration the different orders and their relationships.

Definition.—Too often have theories as to the causation of these autonomous neoplasms entered into the definitions. Thus, Colnheim defined them as "circumscribed atypical productions of tissue from a matrix of superabundant or erratic deposit of embryonic elements." Here we have introduced the untenable theory that all autonomous neoplasms arise from embryonic tissue which has remained latent. We are still uncertain as to the causation of these growths, and so etiology must not enter into our definition. Thus, Ziegler's definition is more

[1] Adami, Montreal Med. Jour., July, 1908.

[2] When words so formed were new and foreign, it was correct to employ the Greek form of plural, and to speak of sarcomata, osteomata, etc. But these words have now become so familiar a part of every-day language that they may be regarded as naturalized and given the ordinary English plural. We shall use the two forms of plural indifferently.

satisfactory: "A tumor is a new formation of tissue possessing an atypical structure, not exercising any function of service to the body, and presenting no typical limit of growth." The use and limitations of the term "atypical structure" require here a little explanation, add to which, the pure teratomas to be presently described do present a limit of growth; and so we prefer C. P. White's statement that "*a tumor proper is a mass of cells, tissues or organs resembling those normally present, but arranged atypically. It grows at the expense of the organism without at the same time subserving any useful function.*" Von Rindfleisch characterizes them as a "localized degenerative excess of growth;" *i. e.*, the very excess of growth is regarded as in itself a degeneration: Birch-Hirschfeld, as originating spontaneously, becoming separate from the physiological tissues in their physiological and functional relationships, as developing from the cells of the body, and possessing progressive growth: Ribbert, as "self-confined, dependent upon the organism for their nourishment, but otherwise largely, if not quite independent, corresponding more or less but never absolutely with the tissues of the natural body, and presenting no definite limit to their growth." Lubarsch's definition is closely allied: "Under tumor proper we have to understand those growths of apparently independent origin which histologically correspond in structure more or less completely with the matrix from which they originate, but in form are atypical; which further, in spite of their organic connection with that matrix, and in subjection apparently to laws of their own, pursue an independent existence which is not, or only exceptionally, of advantage to the organism as a whole."

How next can we classify the growths possessing these characters? As indicated by the definition we have selected, these neoplasms are composed of cells, tissues, or organs resembling those normally present in the body; in fact, we cannot but conclude that they have a like origin. It would seem to follow, therefore, that classification is possible according to the type of cellular tissue present, just as we are able to classify the cells and tissues of the normal organism. But before proceeding to do this, it is well to take into account the variation noted in the definition (White's), namely, that some of the tumors are composed of cells of one particular type, others show a tendency toward arrangement of those cells in definite order with intervening stroma, such as we can see in normal tissues; a third group shows cells derived evidently from more than one type of tissue—the mixed tumors; a fourth shows even greater variation in the type of cells with tendency to the development and presence not merely of irregular cell collections, but of such fully formed organs as brain, teeth, masses of bone, skin, sebaceous and other glands.

We will consider these last first.

TERATOMAS.

All monstrosities are *terata*, and such terata we have discussed in an earlier period of this work, pointing out the successive grades, from the dichorial and monochorial twins, through the symmetrical double

monster to the asymmetrical parasitic monster, such as we see in the fœtal inclusion. The study of that series has demonstrated that we there dealt with, in the simplest cases (the dichorial twins), the development of two ova side by side in the uterus, in the next with the formation of two separate (twin) individuals from a common ovum, until, reaching the fœtal inclusion, we find that, of two individuals so developing from a common ovum, one, the feebler, became during early embryonic development infolded into the other and that it gains its blood supply from that other stronger fœtus, becoming ingrafted into it. Now such a fœtal inclusion, an imperfect grafted individual we may regard as our type of teratoma. It is not an independent individual; it is incomplete; it is nourished from its host; but it *has begun existence as a separate individual*, its tissues have developed from an independent primitive streak. Even if, as in our earlier chapter we pointed out, both parasite and host originated primarily from a single ovum by a single act of fertilization nevertheless, at an early period, that single ovum came to exhibit two independent centres of growth, and it is the autonomous growth of one of these that has given rise to the mass of tissues constituting the parasite.

If, then, we take this as our type, we may define the teratoma as *an autonomous growth, the product of the continued development within one individual of another individual of the same species.* We place an emphasis upon the "continued development" in order to exclude the normal fœtus, which possesses only a temporary development of this order, and then through its placenta, which penetrates into the maternal tissues.

There are several different types of tumor which fulfil this definition, but before describing them it will be well for the purposes of orderly classification if we consider what cells in the organism in its different stages are capable of giving origin to all the orders of cells which constitute the individual. Our first inclination is to lay down that the fertilized ovum alone can do this; a little consideration shows that the potentiality is more extensive. Every *totipotent cell*, to employ the terminology of the embryologist Barfurth, must be regarded as capable of giving origin to an individual, every cell, that is, possessing the power of giving origin to cells of every order.

Of such totipotent cells, in addition to the fertilized ovum, we recognize the following:

I. The primordial blastomeres. We know from abundant experiments that these, even among the vertebrates (the frog, Roux, Morgan), can be broken apart and each give origin to a complete dwarfed individual.

II. The primitive germinal area cells.

III. The "growing point" cells of the germinal area (p. 216), which give origin to the successive mother cells for the various tissues. The powers of these cells, it is true, is more restricted; they are not, like the blastomeres, yolk-containing, and can only give origin to the embryo so long as they are in connection with the body of the ovum.

IV. The germinal blastomeres. These from the very earliest period of segmentation of the ovum appear to be set apart, becoming eventually lodged in the generative glands, and there give origin to the eventual ova or spermatozoa. There is a succession of generations from the primordial germinal blastomere down to the mother cells of the ova and spermatozoa, all retaining and conveying onward totipotential characters. Here we do not include the ova and spermatozoa as such, the results of a reduction process affecting the mother ge·a cells (see p. 131).

V. The mature ova and spermatozoa after fertilization.

1. As already noted (p. 207), separation of the primordial blastomeres can only be regarded as giving rise to dichorial twins, not to teratomas.

2. Monochorial twins would seem to originate at a rather later date, and then not so much from a single primitive blastomere (although this cannot be wholly excluded) as from an early division or dichotomy of the cells set apart to form the germinal area, cells which, it is true, are totipotential. From this same order of cells we must regard the individuals as originating which become the eventual *fœtal inclusions*.

3. Excess production of growing point cells affords the most satisfactory explanation, as already noted (p. 218), of those remarkable forms of teratoma, *Epignathus* (at the superior pole) and *Congenital Sacral Teratoma* (at the inferior). They may be regarded as examples of polar or serial deduplication.

4. The germinal blastomeres. (*a*) It has been noted by several embryologists who have followed the germinal blastomeres from the earliest stages of development, that these undergoing multiplication do not necessarily, in every individual, all find their way into the ovary or testis. Certain of them may come to be included in other organs and regions—in the cranium, the gill clefts, thoracic cavity, etc. To the later development of these misplaced germinal blastomeres have been ascribed the *embryomas* showing themselves in different regions. (*b*) But if this be so, a similar origin from germinal blastomeres, or more clearly from the mother cells capable of giving origin to ova or spermatozoa, most satisfactorily explains the much more common development in the ovaries and testes of complicated tumors containing tissues derived from all three cell layers (epiblast, mesoblast, and hypoblast), the *ovarian* and *testicular embryomas* (terms less confusing than the older ovarian and testicular "*dermoids*").

These, then, we regard as the teratomas.

Elsewhere,[1] we have proposed that they should be classified into:

1. Twin teratomas (when host and parasite are of equal age).

2. Filial teratomas (in which the teratoma is the product of one of the germ cells of the host); and have subdivided this into:

(*a*) Parthenogenetic, from germ cells multiplying without previous fertilization, and

(*b*) Gamogenetic, the product of growth of a fertilized germ cell.

Further consideration has made us a little doubtful as to the expediency of this classification; while we believe that the conception of twin

[1] The Classification of Tumors, Jour. of Path., 1: 1902: 233.

and filial teratomas is a useful one, we would replace the term germ cell by totipotent cell, to include growths of the epignathus type. So, also, we have noted that using the term "parthenogenetic," it has been assumed that what we meant was that teratomas of this order (ovarian and testicular embryomas) originate from the mature ova or spermatozoa. This is not our belief. Lastly, while formerly we were inclined to classify placental moles and that remarkable form of growth, the chorio-epithelioma malignum, both derived from cells of the fertilized ovum, among the teratomas proper—a position for which much may be said—we are now of the opinion that as such growths do not represent the individual, but only the aberrant growth of one set of cells belonging to the individual, it is better to discuss them as a class a part—of *Teratogenous blastomas.*

Here the classification of Wilms[1] deserves attention:

1. Developments of two anlagen on one germinal vesicle with partial fusion: *Double monsters.*

(*a*) With equal growth: *Duplicia symmetros.*

(*b*) With early arrest (lagging behind) of growth of one: *Duplicia asymmetros.*

(*c*) With parasitic inclusion: *Fœtal inclusion.*

2. Developments from one anlage on the germinal vesicle producing excess blastomeres which become included in the growing individual.

(*a*) The included blastomere undergoes development at a very early age, the growth being relatively elaborate: *inclusions recognizable at birth.*

(*b*) The included blastomere lies latent within the organism for some period, and starts active growth only at a later period (often in the fully developed individual) as a result of some altered conditions (Gelegenheitsursache): most cases of *abdominal inclusions, embryomas* of the genital glands, and *embryoid* (*mixed*) *tumors.*[2]

Accepting for the time being the view that the tumors of class 2 are derived from aberrant blastomeres, it is difficult to suggest a term which will succinctly indicate them. Wilms first labelled them embryomas, in the belief that they were derived, parthenogenetically, from fully formed germ cells, and were, in short, of the same rank as the embryo. Similarly we have classed them as filial teratomas. If for "blastomeres" we employ, as suggested, the term "totipotent cells," then Wilms' classification and that here adopted become practically identical.

Fœtal Inclusions.—The inclusions may be complete or incomplete and projecting (Fig. 92). Our conception of such as a weaker and smaller embryo carried into the body of the more fully developed embryo, during the process of closure of the great anterior fissure,[3] makes it

[1] Wilms, Die Mischgeschwülste, Leipzig, Georgi, 1899: 250. This is the locus classicus for the forms here under consideration, and is a masterpiece of clarity. *Si sic omnes!*

[2] This, as Wilms states, does not pretend to be a full classification of the double monsters.

[3] The existence and early development of the amnion surrounding the embryo on its lateral and dorsal aspects prevents such inclusion anywhere save at this fissure.

essential that those embryomas only can be regarded as fœtal inclusions which are in relationship to that fissure, *i. e.*, whose situation is (1) median, (2) ventral, (3) thoracic or abdominal. We cannot, that is, conceive inclusion as occurring in any other region. Teratomas, for example, having a retroperitoneal and more dorsal abdominal position, posterior mediastinal, or cranial cannot be explained on this supposition.

Epignathus and Congenital Sacral Teratomas.—For a description of the mode of origin of these forms see p. 218.

Schwalbe distinguishes four groups:

1. There is inserted into the roof of the mouth of the one fœtus the umbilical cord of a second, which can be more or less well developed (very rare and cases poorly described).

In Baart de la Faille's case there was a large epignathus of the type of group 3, attached to which were the umbilical cords of two acephalic acardiac fœtuses, indications, that is, of three terata. This case in itself makes it impossible to regard the monstrosities of this type as of bigeminal origin with inclusion, and would seem to favor the theory of liberation of totipotential cells from the superior growing point. We are not, however, prepared to make definite pronouncement regarding the mode of origin of this very remarkable and rare order of monstrosity.

2. A mass of tissue presenting definitely formed organs (lower extremities, sexual organs, etc.) projects out of the mouth of the host.

3. A mass of tissue having its root at the base of the skull in the midpharyngeal region projects out of the mouth of the host, but this presents no definite organs, only an irregular mass of tissues—skin, connective tissue, cysts formed by epithelium both of epiblastic and hypoblastic type, cartilage, etc. This is the common form.

4. A larger or smaller tumor of the palate or oral cavity composed of a mixture of tissues of simpler type than the above (not from all three cell layers).

The indications are that not all of these are of median origin and attachment, and that they come under the teratoblastomas to be described later, rather than the epignathi proper. We must recall the difficulty in classification already referred to (p. 595). It is evident that in the same growing point region at a later period aberrant multipotential, rather than totipotential cells may be produced, giving rise to a less complicated form of tumor.

Sporadic Embryomas.—As above indicated, we occasionally encounter teratomatous growths of the same type as, but not conforming in position to, the preceding forms, bearing no relationship to the fissures or the poles of the body, nor again to the generative glands, and these we can only, *per exclusionem*, regard as due to the independent development of aberrant germinal blastomeres, blastomeres which, instead of finding their way into ovary or testis, have become displaced and arrested in one or other region of the developing organism. Such blastomeres may take on growth and the production of a mass of various tissues (epiblastic, mesoblastic, and hypoblastic) either during fœtal life or, lying latent, only during postnatal existence. In this way we

best explain the organoid tumors of the deep thoracic and abdominal regions of the cranium (independent of the sella turcica), neck (often in close association with the thyroid), anterior mediastinum (often associated with and apparently originating in the thymus), etc.

The careful study of these various teratomas made during the last few years has shown conclusively that by far the greater number contain tissues derived from all three germinal layers, although characteristically these do not present themselves in the proportions seen in the normal individual; one or other (notably nervous tissue) may be present in marked excess, and there is wanting in a very striking manner the orderly relationship of these tissues one to another: they are "jumbled" together. With this two orders of tumor may be distinguished, which employing the terminology employed for the blastomas, we may speak of as the *typical* and the *atypical*. Among the sporadic teratomas the former is the rarer class: in it the tissues are of the adult, fully formed type, and growth is characteristically limited. The indications are that development has been *pari passu* with that of the host. The latter is the more frequent class; while they may show themselves in early life, more often they are just noted at, or after puberty, and they grow with relative rapidity, and, what is more, tend to afford metastatic new-growths on distant organs, also composed of a mixture of cell elements. The cells are of imperfectly differentiated type, hence they are known as *embryonal* teratomas. We have here orders comparable with the benign and malignant blastomas to be presently studied. In other cases one or other of the component tissues of a typical teratoma may take on excessive growth, affording metastases of the one cell type. This formation of a "tumor in tumore" we shall take up later. (See p. 612.)

Ovarian Teratomas.—But quite the commonest seat of teratomas is in the ovary. Here similarly we encounter two forms: (1) the large-cystic teratoma, or ovarian dermoid, and (2) the solid or small-cysted teratoma. The former is much the commoner. It presents itself as a cyst occupying the situation of an ovary, which may attain the size of an orange, a child's head, or larger; the contents are characteristically fatty debris with long hairs. It is lined by squamous epithelium provided with sebaceous and sudoriparous glands, and often bony masses are to be detected in the walls. Examination generally reveals what Rokitansky described as the "insular protuberance," a region which we now recognize as the representative of the head. From it arises the tuft of long hairs, and around a depression to one side there projects one or several teeth, frequently embedded in an amorphous bone which may be taken to represent a jaw. Serial sections demonstrate that into this depression opens a tube, which proximally has the characters of a trachea, distally takes on the structure of the digestive canal with muscular sheaths. Sections through the protuberance exhibit the presence of five layers: (1) The skin and subcutis; (2) central nervous system elements (glial cells, neurons, occasionally pigment cells), and the meninges; (3) entodermal tissues (tracheobronchial, gastro-intestinal);

(4) sympathetic nerve cells and their processes; and (5) the remains of the ovarian cortex.

While recognized most commonly in adult life, operation or post-mortem may reveal the presence of the form of tumor in the young child, and it is to be noted that the cells of the various tissues are as fully formed as are those of the host; we deal with a *typical* teratoma. Very rarely—only four cases are on record (Axel Key, Repin, Askanazy, and Shattock)—some proportion and relationship of parts is preserved, with development of extremities and genital parts, so that a definite fœtus may be inferred.

The solid ovarian teratoma is distinctly uncommon. It has all the characters of the atypical sporadic teratoma already described.

FIG. 189

Interior view of an ovarian teratoma ("dermoid cyst"), showing Rokitansky's island bearing *c*, hairs with *d*, teeth surrounding. (Schwalbe.)

Testicular Teratomas.—Here the relative frequency is reversed: the solid small-cysted form is the usual type, whereas examples of a large solitary epithelial cyst or dermoid are few in number. To this solid form would seem to belong the greater number of the malignant-mixed tumors of the testicle of relatively late but rapid development that used to be regarded as chondro-sarcoma or sarcoma carcinomatodes. Study of all parts of such a tumor in general reveals elements derived from all three germ layers, although in contradistinction to the ovarian growths the ectodermal elements are in a minority. This, with the one exception of the chorio-epithelium, to be referred to later (p. 611).

THEORIES OF ORIGIN OF OVARIAN AND TESTICULAR TERATOMAS.

Needless to say there have been very numerous theories regarding the origin of these tumors: (1) That they are due to inclusions in the ovary or testis of portions of all three layers during the course of growth. Against this the frequent bilateral nature of the growth was seen to militate. (2) That they are the product of fertilized polar bodies (Marchand). But no less than five separate embryomas have been noted in the one ovary (Wilms), and the ovum in preparation for fertilization only casts out three polar bodies. (3) That they are due to parthenogenesis, a mature germ cell, ovum, or spermatozoon, under certain unknown conditions, taking upon itself to start growing and segmenting without throwing off the polar bodies, and without fertilization. This very lack of normal stimulus, and the abnormal site in which growths occur, is held to explain the aberrant nature of that growth. Parthenogenesis, we know, is common among the lower forms of life, and even the virgin chick has been known to lay eggs which may exhibit an apology for a germinal area, and rarely, later stages of aberrant development. The grounds taken by Bonnet,[1] denying the possibility of such parthenogenetic development, do not appear to us absolutely convincing. What, however, is strongly against such a theory is that experimentally we know that for a cell to proliferate, the nucleus must be surrounded by a certain not inconsiderable quantity of cytoplasm. The spermatozoon, as such, exhibits much less than what we regard as that minimum, and nothing of the nature of yolk to support the growth during the early stages of segmentation. It is against all we know regarding the conditions favoring cell multiplication that the adult spermatozoon should give rise to an embryo, or an embryoma. And if the testicular embryoma cannot thus be a parthenogenetic development, the identical ovarian growth is unlikely to be of that nature. (4) That they are due to the aberrant development of cells of the theca interna of the Graaffian follicle. For this suggestion absolutely no evidence of any weight has been advanced.

There remain, so far as we can see, only two other possibilities: (5) That they are derived not from ova or spermatozoa matured for fertilization, which have undergone the reduction process, but from oocytes or spermatocytes, or even the forerunners of the same; this we may term the modified parthenogenetic or germ cell theory; or (6) that they spring from dislocated blastomeres. This last is the theory at present in vogue. It supposes that in the early embryonic stage certain blastomeres capable of producing all three cell layers become dislocated, and so arrested in their proliferative activity, and carried into the anlage of the future ovary or testis, when sooner or later they may take on growth.

Bonnet, who first propounded this theory, based it upon the facts to which we have already referred, that in many of the lower animals, the early segmenting ovum can have its cells shaken or otherwise broken

[1] Ergebnisse der Anatomie und Entwickelungsgesch., 9: 1899.

apart, when each is capable of developing into a complete if small individual, and that the segmentation and mitosis in mammalian eggs is known to be most irregular.

We confess that this theory does not appeal to us. The very fact which Wilms, who supports it, urges, in another connection, that he has found five separate embryomas in one ovary, would suggest altogether too extensive a dislocation and carriage of the not too numerous blastomeres into one particular locality to be within the bounds of probability. We, ourselves, must accept the *germ cell* theory, and this, for several considerations. We know that these germ cells from the first are dedicated to eventual reproduction, or, to be exact, to the development of cells which shall reproduce all the tissues seen in the parent. We know, as pointed out by Beard and other zoologists, that there is an actual dislocation of many of these cells in the process of development. The total number of *germinal* blastomeres (already specialized and recognizable at a significantly early stage in the segmenting ovum) does not find its way into the ovum or testis. Here, in short, we have the cells which will fulfil all the needs of the case.

These germinal blastomeres, as distinct from Bonnet's primitive blastomeres of any order, we know may be carried to various parts of the developing organism. This carriage and deposition afford an adequate explanation for the development of three-layered teratomas in the abdominal and thoracic cavities and in other regions, teratomas of the same type as these in the ovary and testis. The sporadic teratomata outside the ovary and testis obtain their simplest explanation in an origin from such aberrant germinal blastomeres. Within these organs it does not seem to be necessary to postulate, however, that the embryomas arise from germinal blastomeres that have lain intact *ab initio*. The function of the germinal blastomere is to give rise to cells having like properties, and thus we note that it is probable that any cell along the direct line between the primitive germinal blastomere and the mature and *reduced* ovum or spermatozoon (these last being excepted) may potentially give origin to an embryoma.

What is the cause of such cell taking on aberrant growth will be discussed when we come to deal with the theories of neoplasia (p. 768).[1]

TERATOBLASTOMAS.

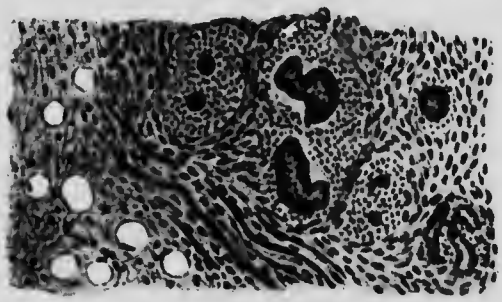
This is the proper place to consider another order of growths, growths which are not true embryomas, because all three germinal layers are not represented by the tissues found present. Under this heading we include the most striking examples of what are known as the "mixed tumors."

[1] The most masterly survey of the present status of our knowledge regarding teratomas is afforded by Askanazy (Verhandl. Deutsch. Pathol. Gesellschaft, 1907), 11: 1908: 39. With his conclusions I find myself largely in agreement. The succeeding article by Borst gives valuable bibliographical references.

Certain of these "Mischgeschwülste" are of another type, but the most characteristic examples come under this head.

1. **Renal Teratoblastomas.**—The type example of this form of growth is found in certain remarkable tumors of the kidney present, it may be, at birth, or developing during infancy or early childhood. We deal with relatively large localized growths of the body or the pelvis of this organ; soft and sarcoma-like, with great tendency to internal hemorrhages and necrosis. This on section shows a more or less spindle-celled, sarcoma-like matrix, but in it we encounter epithelial elements of the nature of gland tubules recalling, but different from, the typical renal tubules, fat and cartilage cells, plain muscle fibers, striated muscle fibers, fibrous and elastic tissue, all in no apparent order. The tumors have been recorded under very different names—adenosarcoma, carcinoma, sarcomatodes, rhabdomyoma, spindle-celled sarcoma, according to the tissue most in evidence.

Fig. 190



Section of a "mixed tumor" of the kidney, showing gland tubules with surrounding sarcoma-like cells of the plain muscle type, fat cells, etc. (Ribbert.)

They are to be explained as follows (Wilms): The mesoderm of the kidney, or primitive kidney ("Urniere," or Wolffian body) region, gives rise, first, to the *myotome* (primitive segment), later gives off the *nephrotome*, or matrix for the future kidney tissues. From the myotome is given off also the *sclerotome*, whence develop the mesenchymatous elements of this region of the body (striated muscle, vertebra, etc.). A tumor containing all these tissues—namely, kidney tissue proper, striated muscle, and different connective tissues—can only have originated from cells themselves capable of originating all these forms. Or otherwise to explain this particular form we are forced to the conclusion that in the course of development of this region certain of the primitive mesoderm cells, potentially capable of originating both sclerotome and nephrotome, are carried in a latent condition into the area of the future kidney, and growing later, give rise to all the tissues in question. Such is a one-layered embryoma, *i. e.*, all the contained tissues are of mesoblastic origin.

Muus, from Marchand's laboratory at Marburg, in one such tumor, from a child aged eighteen months, found definite epidermal inclusions

exhibiting strata mucosum et granulosum, and stratum corneum. For the explanation of such we must pass back to a still earlier date, to the inclusion of an epiblastic cell over the future kidney region, a cell capable of giving rise to both epiblastic and mesoblastic structures, and must regard this as a two-layered or dyphillic embryonn.[1]

2. **Mixed Tumors of the Parotid.**—The mixed tumors of the parotid are apt to be even more complicated, for here, not rarely but frequently, extensive epithelial overgrowth is present, both squamous epithelium (Hirschberg points out that many of the larger scattered cells regarded as endothelial, or even connective-tissue cells, are of epithelial nature and origin), cubical, and cylindrical epithelium. Adult goblet cells, elastic fibers, cartilage, mucoid interstitial tissue, osteoid tissue, and even true bone and spindle-celled, actively growing connective tissue, may all be present in these tumors.

3. **Submaxillary Gland.**—More rarely similar mixed growths are found in connection with the *submaxillary gland*.

The cells which originate such tumors we must ascribe to a developmental period when they were capable of giving rise to both squamous epithelium (of the mouth) and parotid glandular tissue, that is, to a period before the mouth proper had become differentiated. So also for the mesenchymatous elements, the cells of origin must have been capable of producing connective tissue, cartilage, and bone. There is greater power of transformation (metaplasia) between connective-tissue elements; nevertheless, proceeding on the same lines as we followed in connection with the kidney tumors, we must conclude that cells of the primitive epiblast have become displaced at a period when they had not as yet undergone differentiation, and have thrown off the mesenchymatous elements, so that, passing into the parotid area, they there eventually give origin to all these forms of tissue.

4. **Of the Vagina** (in children).—Such exhibit round and spindle-celled sarcoma elements and striated muscle fibers; due, it would seem, to misplaced mesoderm of the inferior region of the body, misplaced during the growth of the Wolffian duct, which in the female, as Gärtner's duct, is present in early fœtal life opening into the vaginal area.

5. **Of the Cervix Uteri.**—Similar sarcomatous elements with plain and striped muscle, and sometimes cartilage, may be found in mixed tumors of the cervix. These occur later in life. Wilms suggests for them also displacement along the course of Gärtner's duct, traces of which may also be found in the cervix.

6. **Mammary Glands.**—Cystofibrosarcomatous growths within parts, squamous epithelial tissues present in this region may be ascribed a like origin.

7. **Lacrimal Glands, Cheeks, and Gums.**—Here also are rarely found mixed tumors allied to the parotid and submaxillary tumors.

In conclusion, we would repeat the axiom laid down by Wilms, that

[1] While most of the primitive mesoblastic cells are derived from the hypoblast some are given off from the epiblast.

"the mixed tumors always correspond wholly in structure with the normal processes of differentiation, occurring in the particular region of the body in which they originate."

TERATOGENOUS BLASTOMAS.

Placental Moles and Chorio-epithelioma Malignum.—The developing ovum consists of two parts, the fœtus and its membranes, including the fœtal placenta—an organ developed primarily from the chorionic villi, which, at first wholly epiblastic, come, with the development of the allantois, to gain a vascular and mesodermal core. As first demonstrated by Peters,[1] in his study of a singularly early human embryo, and since repeatedly confirmed, long before the development of the placenta the outer cell layers of the chorion show active erosive properties, for already his ovum was practically buried in the uterine mucosa. The outer layer of the villi has, in fact, intensely active phagocytic properties, and as the placenta forms, by its rapid growth and erosive powers, the villi penetrate through the mucous membrane into the underlying venous sinuses, where, by selective absorption, they gain nourishment for themselves and the fœtal organs.

Under normal conditions, with the maturation of the fœtus, these villi withdraw; their outer layer of fused cells, the syncytium, has long previously undergone extensive atrophy, so that only here and there small remnants are to be detected; the layer beneath, Langhans' layer, also undergoes degeneration, and so the attachment between fœtus and mother is loosened in preparation for birth. But this does not always happen completely. More particularly, in cases of abortion (in which the fœtus is discharged before these placental changes are complete), and in some cases of blighted ovum in which there is no fœtus which by its metabolism must regulate the placental changes, the villi, or some of them, may persist in intimate contact with the maternal tissues and maternal blood, *and may continue to grow after the normal period of gestation has been attained*. According to the nature and the rate of this growth, so do we obtain two orders of tumor—*the placental mole and the chorio-epithelioma malignum*.

The Placental Mole.—We occasionally encounter cases in which the placenta and membranes are the sole product of conception, the fœtus either being absent or dying and undergoing absorption at a very early age. In these cases the placenta, growing within the uterine cavity, tends to become converted into an irregular flashy mass, *the fleshy mole*, often infiltrated and surrounded by much recent and coagulated blood (*hemorrhagic mole*), while secondary to the hemorrhage and arrest of blood supply, putrefaction may ensue (*putrefactive mole*), with or without eventual infection of the maternal organism.

More particularly in cases of premature birth the portion or portions

[1] Die Einbettung des menschlichen Eies. Leipzig and Vienna (Deuticke), 1899.

of the placenta remaining attached may exhibit a series of remarkable modifications of the chorionic villi. Continuing to be nourished by the maternal blood and to absorb fluid, they may hypertrophy and become distended by an œdematous mucoid infiltration so as to form a relatively huge mass of series of small, clear, grape-like vesicles of varying size, distending the uterus to even a greater extent than does a full-term fœtus. Such is the *hydatid mole*. In the majority of cases there is no sign of an associated fœtus; in some there is the history of abortion; in others a dead fœtus at some period of arrested growth has been found. In a very few cases the hydatid formation has affected one portion only of the placenta, and the fœtus nourished by the remaining portion has been born alive. As the hydatid mole develops, there may be frequent hemorrhages until finally it is extruded.

Fig. 191

A small portion of an hydatid mole; natural size.

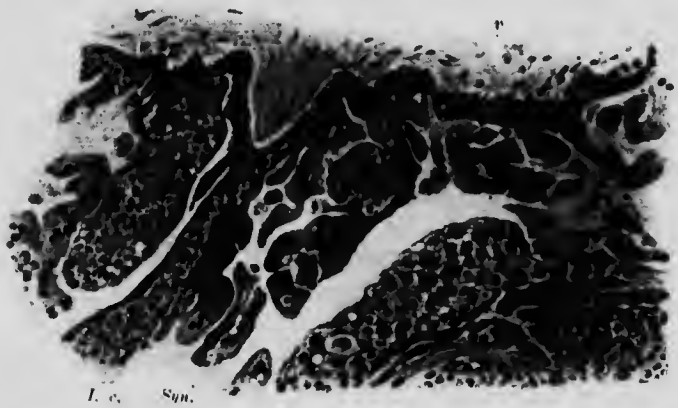
Careful examination of an otherwise healthy placenta occasionally shows here and there a rare cyst in its substance. Such cysts of the fœtal placenta are caused by a similar œdema of portions of an individual villus in which circulation has been arrested.

In all these cases the placental growth remains within its normal limits, but this is not always so. Cases are on record in which such an hydatid mole, continuing to grow, may also fill the maternal uterine sinuses with polypoid masses (destructive placental polypi), and thus we have transition to a yet more remarkable condition, recognized only within the last few years, the fatal form of new-growth which after several changes of name—deciduoma, syncytioma—is now usually termed "chorioepithelioma malignum."[1] This occurs within the uterine wall, but may, indeed, first show itself quite outside the uterus, in the vaginal wall, etc. The outer surface of the villi, as we have said, consists of the layers of fœtal epiderm, the most external, or *syncytium*, formed of cells which stain deeply, showing, as the name implies, a fusion of the cell bodies, so that they appear as large, multinucleated, protoplasmic masses covering the surface of the villi, the more internal Langhans' cells being of fair size, but individual, not fused, and not staining so deeply. It is the former that possess the intense erosive and phagocytic properties whereby the villi penetrate and come to lie within the maternal blood sinuses of the uterus. As

[1] For fuller description, see Marchand, Monatschr. f. Geb. u. Gyn., 1: 1895: 419 and 513, and Ztschr. f. Geb. u. Gyn., 39: 1898: 173.

Schmorl pointed out in his study of eclampsia,[1] certain of those cells are apt to be swept away by the blood current and deposited in the capillaries of the lungs and other organs. It may well be that this is a not infrequent occurrence in the course of pregnancy, although usually these cells become destroyed by the counteraction of the endothelium of the capillaries in which they become lodged. In cases of abortion, more particularly where the normal course of placental development and involution is interrupted, either (*a*) within the uterine sinuses, these cells, both the syncytial and those of Langhans, take on an abnormal proliferation, or (*b*) this proliferation shows itself, not locally, but in some of the cells transplanted to another region, and that not necessarily immediately, but it may be after a considerable period.

FIG. 192



Chorio epithelioma growing within uterus: *V*, wall of uterine sinus; *Syn.*, multinucleate cells of syncytial type; *L.c.*, cells of Langhans' type. (Teacher.)

There thus develops a tumor that is:

1. Cellular, formed entirely of large cells of embryonic type.
2. Entirely within the vessels.
3. Provided with no vessels of its own, and exhibiting no sign of structure save at times an obscure development into finger-like processes (although this would seem to be largely due to its mode of growth along the maternal vessels).
4. Unprovided with a capsule or any definite limitation; and so,
5. Extensively infiltrating the uterus or other organ involved.
6. Peculiarly liable to form secondary growths by detachment of some of its cells, and proliferation of the same in vessels at a distance.
7. Liable to induce hemorrhages by erosion of the walls of the vessel it distends.
8. Rapidly fatal.

[1] Verhandl. Deutsch. Pathol. Gesellsch. 8: 1902: 39.

Most often in sections of such tumors the characteristic deeply staining, multinucleated masses of syncytium are to be recognized in the growth. Occasionally cases are met with in which these are absent. It may be that the cells forming tumors in these cases date their origin to a relatively late period of pregnancy.

The angry debate waged for some years as to the nature of these tumors was based upon the denial by many leading pathologists of the fœtal origin of these cells, and this notwithstanding that it had already been well established by Hubrecht and other embryologists that the syncytium was of fœtal epiblastic development. It was held to be decidual, *i. e.*, of maternal origin. If we are not mistaken, Young,[1] of Manchester, was the first member of the medical profession to grasp the true nature of these tumors.

Fig. 193

Cells of a chorio-epithelioma malignum higher magnification: *a*, syncytial cell mass; *b*, cells of Langhan's type; *c*, broken down erythrocytes. (von Franque.)

As bearing upon the latency of cells destined to give rise to malignant growths, it is instructive to note that several cases of chorio-epithelioma malignum are now on record in which the growth has developed several years after abortion, no subsequent pregnancy having occurred.

More recent studies have demonstrated that cell masses of this type may develop not as the outcome of the fertilized ovum and of uterine pregnancy, but also as the result of teratomatous or embryomatous growth. They have, for example, been found in the male, in connection with testicular embryomas; have been described in connection with mediastinal and cranial teratomas. The origin in all cases must be regarded as the same. The included potential individual in its growth must develop or tend to develop a chorion, and primarily its nourishment must be gained through this chorion, with its cell processes invading the veins of the host. As in the case of fertilized ovum, so here these chorionic cells may take an aberrant excessive growth.

It may be questioned how are we to classify this form of tumor. If we define the teratoma as the product of the aberrant growth of cells from one individual within the tissues of another, then the destructive placental mole and the chorio-epithelioma are teratomas. Histologically, however, they do not represent the embryo, but only the sac in which that is developed; they represent only one tissue; they are formed of cells which under no conditions are capable of giving rise to the individual,

[1] Manchester Medical Chronicle, 1892.

cells which are unipotential, not totipotential. It makes for clearness to regard the teratomas as essentially developed from totipotential cells, and as these tumors are derived from unipotential cells it is best to regard them as blastomas, as teratogenous or heterochthone blastomas. Here also must be grouped those cases in which there eventually develops a malignant sarcoma, epithelioma or gland cancer from one element of a typical teratoma, ovarian, testicular, or sporadic. Regarding them thus, we gain material help in our comprehension of the common autochthone blastomas, the ordinary tumors composed of one type of cell, tumors which, as we shall point out, originate from the aberrant growth of unipotential cells of the individual.

Thus, to sum up, we may make the following broad divisions of the neoplasms proper:

I. **Teratoma.**—Tumors derived from cells capable of giving rise to all the tissues of the individual (totipotential cells).

1. **Twin teratoma** (geminal or heterochthonous).
   Example. Fœtal inclusion.
2. **Filial teratoma** (or autochthonous), due to the segregation and subsequent growth of totipotential cells of the individual.
   (1) From non-germinal blastomeres.
      Example. Epignathus, congenital sacral teratoma.
   (2) From germinal cells.
      (*a*) From aberrant germinal blastomeres.
         Example. Sporadic teratoma of cranium, etc.
      (*b*) From unreduced ovarian and testicular germ cells.
         Example. Ovarian and testicular teratomas.

   Members of this second class may be:
   i. Complete, exhibiting derivatives of all three germ layers, or
   ii. Reduced derivatives of one germ layer failing to develop.
   They may also be (*i*) typical or (*ii*) atypical.

II. **Teratoblastoma.**—Tumors (autochthonous) derived from pluripotential cells of the individual: mixed tumors.

1. **Diphyllic,** containing derivatives of two germinal layers.
   Example. Certain parotid and renal mixed tumors.
2. **Monophyllic,** containing derivatives from one germinal layer.
   Example. Most renal mixed tumors.

III. **Blastoma.**—Tumors derived from unipotential cells.

1. **Heterochthonous** or teratogenic, the cells being derived from another individual.
   Examples. Destructive placental mole and chorio-epithelioma malignum; epithelioma derived from an ovarian dermoid.
2. **Autochthonous,** from the independent growth of unipotential cells of the host individual.
   Examples. All other tumors composed of cells of one order.

CHAPTER XVI.

THE AUTOCHTHONOUS BLASTOMAS (ORDINARY TUMORS).

From these tumors, which are obviously the products of the growth of the cells of one individual within the other, even if those cells be only unipotential, we pass on to the main mass of neoplasms formed by the overgrowth of a single type of tissue, and derived evidently from the aberrant, autonomous growth of tissue cells of the individual or host. That this is their origin must for the moment be taken upon trust; the data to be afforded in the study of the individual forms will amply confirm this view as to their nature. We have now to deal, that is, with the *autochthonous blastomas*.

Before attempting to classify them it will be well to gain a general grasp of their characters. We here include, as has been stated, all tumors, not teratogenous, exhibiting an independent localized growth of tissue cells of one order. To this statement a qualification may be added; all normal tissues possess a stroma or framework of connective tissues in which run the capillaries and lymphatic channels, and so we find in these blastomas that save where we are dealing with tumors formed or developed from the simplest form of connective tissue, similar to that constituting the stroma of organs, a stroma is also present, and we shall see this may vary in amount and importance. With this qualification these neoplasms exhibit the localized growth of one order of tissue. We thus recognize a large number of different forms of tumors —fibromas, composed of fibrous tissue; chondromas, of cartilaginous; osteomas, of bony; odontomas, of tooth; myelomas, of bone-marrow cells; myomas, of muscle fibers; neuromas, of nerve cells; gliomas, of neuroglia cells; epitheliomas,[1] of squamous epithelium; adenomas, of glandular tissue; and the list might be very considerably extended. *For there are many more forms of blastomas than there are forms of individual tissue*— at least twice as many; and this because the cells composing a tumor, while originating from a mother cell of a particular type, may not present the characters of the fully differentiated tissue. It may, indeed, be laid down that they never present complete differentiation; taking the very simplest form, the densest fibroma always contains more cells and larger than does fully formed connective tissue. Nevertheless, in one series of tumors the cell characters are strikingly like those of the normal adult tissue, and with this reservation we speak of them as *typical*. On the other hand, a great number of blastomas depart very far from type.

[1] This term should be employed with caution, so many meanings having been given to it. Thus French writers include all glandular tumors of a malignant type under it.

Whether from certain properties or certain relationships of the component cells, or it may be only from the region of primary growth and comparison with other tumors of like properties which in some of their parts afford the necessary clue, we are able to recognize the tissue from which they originated. The component cells are only partially differentiated or it may be purely of the mother cell or vegetative type. These we speak of as *atypical* neoplasms.

And as a general rule, the more we study, what appear at first sight to be exceptions are more and more found not to be such, and it may be laid down that the properties of these two groups, the typical and the atypical, manifest well-marked differences.

The *typical blastoma* is composed of cells which in their characters approximate to those of some adult tissue. It is *circumscribed* and *slow growing*. The slowness of its growth permits a reaction in the part of the surrounding tissue, so that it is, in general, encapsulated and sharply defined, capable of being shelled out in its entirety from the tissue in which it grows (in some tissues, as in the brain, and to some extent in the bone, in which the capacity for fibrous overgrowth is slight, the capsule formation may be deficient). Growth, indeed, may for a time be arrested and then slowly proceed again. Save when situated in some position in which it comes to press upon some vital part, or when it gradually attains a size so great that it compresses the other organs in its neighborhood and disturbs their proper functions, the growth is harmless so long as it retains the characters here indicated. The shape of the mass varies according to position; embodied within a tissue and subjected to equal pressure on all sides, it tends to be globular; situated on or near a surface, so that the pressure on one aspect is less than on another, it may spread laterally or become lobate, or nodular, or, as in the case of some epithelial outgrowths, cauliflower-like or papillose.

Such a tumor we speak of as *benign*, *i. e.*, harmless in itself. It may grow slowly during the course of long years; may never attain any great size, or if it does, as in the case of some abdominal lipomas (or fatty tumors), which have been recorded as attaining a weight of 60 pounds and more, even then it is not an immediate, but at most an indirect cause of death through mechanical disturbance of other functions.

Yet another feature of the typical blastoma is the character of its growth. This occurs not merely at the periphery, but throughout the mass, in the central parts as well as toward and at the periphery. Such a mode of growth in a mass that is already spherical tends merely to result in the production of a larger sphere. It is spoken of as the central or expansive type of growth. As distinct from the peripheral, we may refer to it as universal, although neither of these expressions is quite happy.

Not all typical blastomas present this form; a chondroma, for example, grows only at the surface of its lobules, and so exhibits what is strictly a peripheral growth. That growth, however, from the inner aspect of its perichondrium, is, if we may so express it, centripetal rather than centrifugal.

The atypical blastomas, on the other hand, are formed of *imperfectly differentiated tissue*, and, as we have repeatedly had occasion to note (p. 87 and elsewhere), with lack of functional differentiation there is a corresponding manifestation of increased vegetative and proliferative capacity on the part of the cells. As a matter of fact, in these tumors the cells are characterized by *active proliferation*. There is relatively *rapid growth*, increase in the number of cells, and increase in size. The rapidity of this growth and expansion of the mass prevents an adequate reaction on the part of surrounding tissue; there is *little or no sign of encapsulement;* the tumor is thus not precisely circumscribed. It may appear so to the naked eye, but examination of sections, of the removed material, under the microscope shows proliferating cells extending between the fibers of the surrounding tissue and by their active growth, if by no other means, causing the compression and atrophy of the specific cells of that tissue, leaving eventually a framework of connective tissue and vessels which becomes the stroma of the advancing growth; or otherwise the atypical blastoma possess the power of *infiltration*. What is more, in this expansive growth, either by extension along the lymph channels, or by erosion and rupture of a surface membrane or of the walls of a vessel, certain of these actively growing cells may become detached from their fellows and, becoming conveyed to a distance either by the lymph stream or by the lymph or other fluid bathing a surface, or by the blood stream, may become arrested in some locality where conditions favor, or do not prevent, their continued growth, and there multiplying, they develop new tumors of the type of the parent growth. Such new-growths are termed *metastases*.

Tumors manifesting these properties are known as *malignant*. Histologically, we recognize two main types, the *sarcomas*, or atypical cellular tumors of the connective-tissue type, and the *carcinomas*, or cancers of a more glandular type. We shall later inquire more fully into other conditions associated with malignancy. To note them here would perhaps raise the false impression that all atypical blastomas exhibited them. That is not the case. We must, indeed, emphasize that the properties above recorded are those of the "type" atypical blastoma. There are, indeed all transitions, from the typical to the atypical form. A tumor may for years have been slowly growing and then in one portion take an active growth; in such cases it may as a whole be surrounded by a capsule, but in one or more areas the examination of sections shows that that capsule is becoming infiltrated; tumors of perfectly benign type—well-formed and typical chondromas and even myomas—are on record as giving rise to metastases; on the other hand, definitely malignant growths rapidly growing and rapidly fatal may exhibit no metastases. Ehrlich,[1] for example, has recently noted that this is the case with his experimental and intensely malignant mouse cancer. After subcutaneous inoculation, there may be metastases in the lungs, but although the primary transplanted growth attains a huge size, these metastases

[1] Zeit. f. Aerztl. Fortbild., Nr. 7: 1906.

are so small as to be recognizable with difficulty and only by careful microscopic search. More than the mere escape of cells from the region of primary growth is necessary to cause metastatic growth.

We shall discuss these variations in properties later. In the meantime it is well to gain, at the outset, a general grasp of these relationships between tumor-cell differentiation and benignancy, on the one hand, and proliferation and vegetative type of cell and malignancy on the other. And that for practical purposes; because it is on these characters and their relationship that we base our diagnosis and prognosis; from them we determine whether a given tumor may be left in the organism, or must be removed, if not already too far developed to render removal in vain. We would only add the warning that for prognosis everything depends upon *what is the adult type of the cell in the case of any particular tumor*, the tumor cells may appear to be of a distinctly vegetative type, as in the so-called giant-celled sarcomas (myeloma), and yet the tumor not be malignant to any marked degree, this vegetative appearance being characteristic of the adult marrow cells from which the tumor has originated; on the contrary, the melanoma which appears to be composed of more highly differentiated spindle-like cells than is the giant-celled myeloma is intensely malignant; no tumor shows more abundant and widespread metastases. Recent studies indicate that it is not the developed pigment cells as such that are the metastatic agents, but unpigmented vegetative precursors of the same, and that it is where these are in abundance that malignancy is most marked. From these examples it is obvious that while the general rules that we have laid down are capable of application and are of distinct use for the grouping of phenomena, nevertheless, for the purposes of safe prognosis, it is essential to have an intimate acquaintance with the life history of each individual form of neoplasm.

MALIGNANCY.

Here it is appropriate to consider what constitutes this state of malignancy which is so striking and important a feature of the atypical tumors. We have already indicated some of the conditions which are factors in its development. These are, briefly:

1. *Vegetative* (embryonic) *character* of the tumor cells.
2. *Rapidity of growth.*
3. *Peripheral extension*, lack of capsule and infiltration of the surrounding tissues.
4. *Tendency to develop metastases.*

These, it will be seen, are all related; they are the expression of an inherent augmented vegetative and proliferative activity of the cells constituting the tumor, over and beyond that possessed by the surrounding tissues. There are, however, other associated features which must be noted.

5. *Tendency to central degenerative changes.* The activity of the cell multiplication in a mass which cannot freely expand owing to the

pressure of surrounding parts must, it will be seen upon consideration, lead to some compression of the vessels supplying the mass as the volume of the cells increases; there must, that is, with growth be increased internal pressure, and, as a matter of fact, we find in all malignant tumors that the peripheral cells exhibit evidences of active growth and mitosis; they are in the best position to gain nourishment from without; the central mass of the tumor shows tendencies toward degeneration and atrophic changes, and this to such an extent that in some large cancer masses we may find the cells in the centre completely absorbed (through autolysis), and a central cavity containing serous fluid. Similarly, where the tumor is superficial, the parts farthest from the blood supply, *i. e.*, the most superficial parts, are liable to undergo necrosis, ulceration being the result.

Certain authorities regard this liability of malignant tumor cells to degenerate as an indication of low vitality on their part. The very reverse would seem to be the case, as we shall point out later. It is the anarchical growth of the tumor cells that brings about the central degeneration.

6. *Liability to Recurrence after Removal.*—This is a property associated with the infiltrating character of these growths. Although not noticeable to the naked eye, the tumor may spread along the lymphatics for a long distance away from the main mass, and this not by detachment of individual cells and groups of cells, but, as indicated more particularly by studies of mammary cancer, by continuous growth of the cells in series along these channels. Such cells, extending far beyond the obvious border of the tumor, may not be excised, and may subsequently, by proliferation, develop into nodules of new-growth. It is this wide extension and danger of recurrence that is the basis of the modern radical and most extensive operations for the removal of cancers.

7. *Cachexia.*—By cachexia we imply a lowered impoverished state of the system, indicated especially by a wasting of the tissues coupled with an abnormal complexion. Several chronic wasting diseases induce a cachexia. The malignant cachexia is more particularly characterized by the extreme degree of wasting which may ensue (it is not always present), by the fact that while the tissues atrophy the tumor continues to grow, and by a peculiar sallowness of the skin. It is difficult, if not impossible, to describe this sallowness; the healthy color disappears and is replaced by an anemic yellowish-gray appearance, which once seen is easily recognized.

8. *Anemia.*—Anemia is a constant accompaniment of malignancy, and, indeed, this altered condition of the blood must be held to underlie the cachexia. In extreme cases this is indistinguishable upon blood examination from idiopathic pernicious anemia (which, indeed, is accompanied by an allied although distinct cachexia). These latter conditions suggest immediately that the actively growing tumor absorbs the nutritive elements of the circulating blood and thereby starves the rest of the system. This may—doubtfully—be a factor. We find, however, that the cachexia is not proportional either to the size or rate of growth of the

tumor. It differs also according to the nature of the growth; there may be a marked cachexia associated with a small carcinoma or atypical glandular neoplasm, and little or none with a relatively large sarcoma or atypical connective-tissue growth. There are, it is true, in some cases of extreme cachexia and wasting, complications which are evidently in part responsible; thus certain tumors of the alimentary tract, notably of the œsophagus and stomach, may so narrow the lumen of the affected part as to arrest the passage of food and lead to starvation. Other superficial malignant growths undergo extensive ulceration, and by the absorption of the foul products from their surfaces and by low forms of infection the general bodily condition may be greatly lowered. But even when these cases are excluded we still encounter cachectic and anemic states associated with malignant growths.

If the tumor cells are not functional, they, nevertheless, in their growth —and it may be more particularly in their degeneration—discharge certain soluble substances into the lymph and blood. The more marked cachexia which accompanies malignant tumors of a glandular type—tumors that are derived from cells which normally secrete bodies of the nature of enzymes—is at least, as Borst points out, suggestive. It has been noted by more than one observer that even the metastatic tumors, outside the liver, of primary liver-cell tumors, secrete bile, and, as we pointed out some little time ago, the remarkable alternation in the mental and other conditions which may follow the removal of adenomatous or glandular tumors of the thyroid is difficult to explain, save in the assumption that the tumor supplies an internal secretion which has a direct influence upon the nervous and other systems.[1] More recently, Waring[2] and M. B. Schmidt[3] have called attention to this active secretion of products by cancer, and Buxton[4] and his associates have investigated the enzymes obtainable from malignant growths. It is probable, then, that the malignant cachexia is primarily the outcome of deleterious products discharged or diffused from the malignant growth, both active modified secretions and the products of autolysis.

While the above conditions *in general* accompany malignancy, this is not, it must be remembered, equivalent to stating that all are *essential accompaniments*. Thus a highly differentiated tumor may afford metastases and, on the contrary, an infiltrating and destructive tumor, such as is characteristically the rodent ulcer, may form none; if imperfectly removed, a benign, well-encapsulated tumor may recur; if removed at an early period and sufficiently thoroughly, of growth a malignant type will not.

Active vegetative and peripheral, as distinct from universal, growth with accompanying infiltration would seem to be the essential features

[1] Triennial Congress of Amer. Surg. and Phys., 4: 1897: 103. It is, however, debatable whether the ordinary localized colloid goitres should be classed as blastomas proper.

[2] Jour. of Anat. and Physiol., 28: 142.

[3] Virchow's Arch., 148: 1897 (on secretory processes in secondary growths of a thyroid cancer in the liver).

[4] Jour. of Med. Research.

of malignancy; the other features may or may not be added, although most often they are present. Or, with Hansemann, we can concisely express it, that the essential distinguishing marks of a benign growth are that it does not infiltrate and destroy and does not form metastases. To this we would add that the benign neoplasm shows not merely peripheral, but universally diffused growth, if slow, throughout its substance. One position, in short, with regard to malignancy is very much that of the astronomers with regard to the solar path. Recognizing certain general laws, they can calculate the sun's position on a given date in relation to the stars in general with very fair accuracy. But always there is a certain error or correction to be made to the figures gained by working out the law. The value of that error or correction, it is true, has been determined by the astronomers; we have not arrived at this point. It represents some unknown influence or force acting upon the sun and deflecting it from its path in space. So here there would seem to be some other factor not as yet clearly determined acting in addition to those we have noted, and causing a tumor to behave otherwise than we would infer it should behave from its structure and relationship.

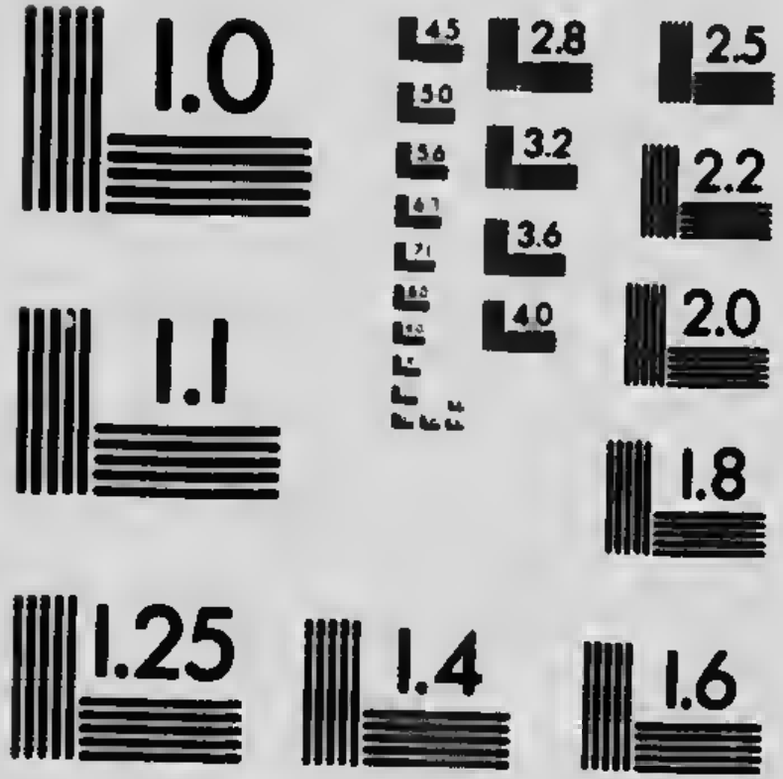
In his "Geschwülstlehre," Ribbert lays stress upon the non-existence of malignant tumor cells *per se*. There are, he says, no malignant cells. Without discussing the reasons which led him to this conclusion, we will frankly say that this view is untenable, and this with all due deference to Ribbert's great authority, and recognition of the much we owe to him in advancing in many directions our knowledge of neoplasia. As well, it appears to us, might one deny the existence of virulent bacteria. Apart from mere general considerations, one fact alone, acquired, it is true, since his work was published, demonstrates the incorrectness of this dictum. We refer to Ehrlich's demonstration[1] that, by passage through mice, mouse cancer can be rendered more and more malignant, until it will surely "take" in close upon 100 per cent. of the animals, instead of, as in the first transplantation, from 5 to 35 per cent.; and grows so rapidly that in seven or eight days the minute portion of tissue transplanted has reached the size of an almond, which, compared with the size of a mouse, is something enormous.

It is difficult to give the exact figures of "takes" at first transplantation. The figures here given are excessive. They are gained from Ehrlich's statements regarding the forms which from the first were of the more virulent type, and were used for the purposes of passage. With 21 tumors of the same adenocarcinomatous type, taken in succession, some more typical and adenomatous than others, inoculating 282 mice, he only gained 2 positive results. In such cases, in which the resisting powers of the tissue of the animals inoculated remain constant, and the vegetative powers of the inoculated cells undergo increase, to deny that we have evidence of increased malignancy on the part of the latter is to juggle with words. *It is the grade of vegetative power of the cells which determines their malignancy, though, as we shall point out* (pp. 628 and 632), *the malignancy of a given*

[1] Zeitschr. f. Aerztl. Fortbild., loc. cit.

MICROCOPY RESOLUTION TEST CHART

(ANSI and ISO TEST CHART No. 2)



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tumor in a given tissue of a given animal is the expression of the interaction between the cell malignancy and the resisting powers of that tissue toward the growth of that particular type of cell.

The above are the characteristics of malignancy *proper*. There are, however, two other conditions, to which, unfortunately, too often the same term is employed without the use of distinguishing adjectives—conditions which are, it is true, malignant in the sense that they tend to a fatal termination, but in which the chain of events is of a different order. These are:

Malignancy in Virtue of Site, or Malignancy of the Second Order.—A slowly growing tumor of any order which, developing elsewhere, would be perfectly harmless, may, by pressure upon vital organs, arrest their function, and so induce death. A relatively minute gliomatous or fibroid tumor of the brain, or its membranes, by pressing upon the medulla, for example, may cause death, and so may be termed malignant. A lipoma of the skin may grow to enormous dimensions, and cause little disturbance; a small lipoma of the intestinal mucosa, by blocking the lumen or causing torsion of the gut, may soon be fatal. Allied to these conditions, when tumors attain great size, they may eventually so press upon surrounding organs as to lead to their atrophy and to the obstruction of their ducts, and so attain to malignancy of this order; and it is noticeable that, attaining great size, they may also induce a cachectic condition. But in all these cases it will be seen that we are dealing with another order of affairs.

Malignancy of Recurrence.—Local Malignancy.—Certain tumors, again, slowly growing and of a typical rather than of atypical, cellular type, are malignant in so far that, after apparent extirpation, they tend to recur. They may be allowed to grow slowly for years without exhibiting any tendency to invade the surrounding tissues or to form metastases elsewhere, but, if extirpated, a second tumor of the same nature is peculiarly liable to develop in the same neighborhood; and what is more, the recurrent tumor tends to be more cellular, to grow more rapidly, to invade the surrounding tissues, and to be definitely malignant of the first order. The cause of this malignancy of recurrence is either: (1) that the extirpation has not been complete, and certain of the tumor cells left behind are incited to active proliferation by the hyperemia and the lessened pressure in their neighborhood after removal of the main mass; or (2) that the tissues of the part have a predisposition toward tumor formation, and that after *complete* removal of the primary growth the two factors above mentioned favor the active proliferation of the neighboring cells, or foci of cells of the same order. For the present it must be left an open question whether we have to deal with one or both of these processes. Fibroid and mucoid tumors (*e. g.*, nasal polyps, more especially present this liability to local recurrence and the eventual taking on of the true malignant properties. It is usual, nowadays, to state that these tumors are from the first sarcomatous; my experience leads me to hold that this is not always so, that certain so-called recurrent fibroids may at first show absolutely

no signs of sarcomatous nature, but belong to the blastomatoid group. to be presently noted (p. 656).

Before leaving this subject of malignancy, it is necessary to point out that a tumor which has for long been benign in its properties may eventually assume malignant characters (of the first order). The preceding pages indicate that true malignancy is a function of the rate and extent of cellular proliferation. From causes not as yet classified and fully studied, cells which at first undergo slow proliferation and complete differentiation may assume rapid growth, and, with this, all the characteristics of true malignancy may be developed.[1] From a prognostic point of view, this is a matter to be continually kept in mind.

METASTASES AND THEIR PROPERTIES.

We saw that in infective inflammation, in pyemia, or in tuberculosis, for example, the specific organisms might be carried from the primary lesion, and, becoming arrested in some more or less distant organ, might there set up new foci of inflammation, leading to, it might be, abscess formation, or new formation of infective granulomata.

These metastatic inflammations have, by many, been compared with the neoplastic metastases, and the similarity of the two processes has been made an argument by those who uphold the parasitic origin of tumors. It must, however, be kept in mind that these two processes of metastasis are absolutely distinct. In infection, the bacteria which are carried to distant parts set up a local reaction, and it is the cells of the part, together with migrating leukocytes, which are the factors in the local tissue disturbance, so that the so-called infective granuloma is composed of new tissue derived from the region affected; no matter what part or organ is the seat of the process, the results are the same, namely, the production of more or less well-developed fibrous tissue, infiltrated with migrating leukocytes.

In the neoplastic metastases the local reaction is purely secondary; *the new-growth is a development of cells which have been carried to the part from the primary tumor*, and these cells give rise to a tumor tissue, which varies in its character in strict accordance with the characters of the primary tumor. It is not the local cells which form the tumor metastasis, but derivatives from the original tumor. Here, indeed, *the migrating cells are the parasites.*

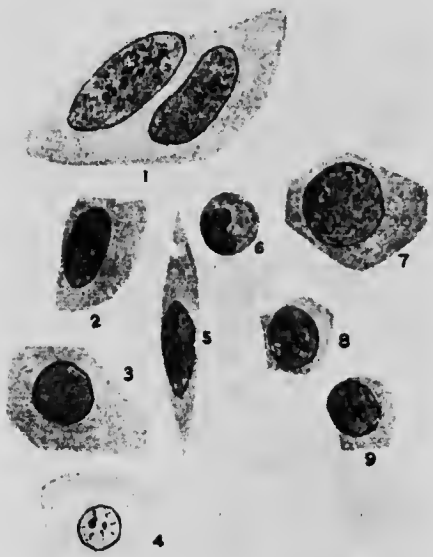
It is a general impression that the metastasis faithfully reproduces the parent growth. This, while most common, is not universally the case. It may but reproduce the *general* type of the parent growth. There is, indeed, a tendency often noted for the metastasis to be more actively growing, to be of a more vegetative type, the cells reverting to a yet simpler condition. An extreme example of this variation was

[1] Despite overwhelming clinical evidence there are still those who, holding fast to the belief that the vegetative powers of the cell cannot undergo augmentation, strenuously deny this conversion.

studied in our laboratory by Woolley,[1] in a case of a tumor of the adrenal cortex, in which every transition was found, from the primary cancer-like mesotheliomatous growth to pure round-celled, sarcoma-like metastases. Jores[2] has published a similar case. This variation has been treated fully by Beneke and von Hansemann.[3]

In such cases a microscopic study of all the metastases demonstrates clearly from the various transitions found that what is here stated is true, and that they are derivatives from the original growth. Occasionally, indeed, the original growth is comparatively insignificant, while the secondary growths obtain an enormous size and expansion. There

FIG. 194



Typical cells, drawn to scale from a tumor of the adrenal cortex and its metastases: 4, from the normal adrenal cortex; 2, 3, from the tumor in the adrenal cortex; 1, 5, 7, from a metastasis in the lung; 8, 9, from metastasis in the brain; 6, a polynuclear leukocyte for comparison. (Woolley.)

may, for example, be a small, insignificant ulcer of the stomach, in the walls of which we may detect evidences of the existence of fibrous or scirrhous cancer or gland tumor, while in the liver the growth may be several inches in diameter, the organ being enormously enlarged. A study of the characters of the two growths points to the conclusion that the insignificant stomach ulcer is older and earlier, and is the point of origin of the metastasis; or, again, in metastatic sarcoma

[1] Virch. Arch., 172: 1903: 30, and Trans. Assoc. Amer. Phys., 17: 1902: 627.

[2] Deutsch. med. Wochenschr., 1894: 208.

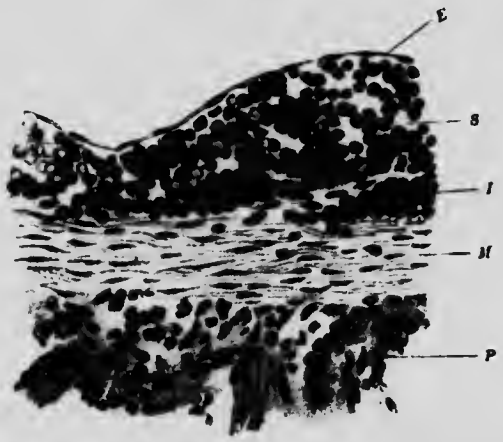
[3] Die Spezifizität , der Zellen, Berlin, 1893. See also Low and Lund, Jour Med. Research, 7: .

(chromatophoroma) of cutaneous origin, the primary growth in a congenital pigmented mole may be no larger than a pea, and yet in numerous tissues we may find metastatic nodules the size of a cherry, and larger. These cases are the exception rather than the rule; in general, the primary growth is larger than any individual metastasis.

Mode of Origin.—Such metastasis, as distinct from local infiltration, may originate in four ways:

1. The cells of the neoplasm, infiltrating between the tissue cells of the part, penetrate into the lymph spaces, and from these certain cells become carried into lymph vessels, and so the new-growths recur, in the first place, along the course of the *lymphatic system*. Often, in the more immediate neighborhood of the tumor, what appear to be separate metastases are found to be in direct continuity with the original tumor, solid strands of tumor cells, injecting the lymph vessels, passing

FIG. 195



Extension of a small round-celled sarcoma (*S*) beneath the endothelium (*E*) of a vein; at *I* the sarcoma cells are infiltrating the middle coat (*M*) of the vessel. (Martin.)

from the primary tumor, and then at one or other point, where the conditions are favorable, more active growth of the cells has taken place, forming definite little tumor masses.

2. The tumor in its growth may erode a vein, and certain of the cells may thus pass directly into the blood stream, and by that be carried to different portions of the body. Or, again, the tumor may originate in immediate connection with the vessel walls, and tumor cells, as in the case of some malignant atypical connective-tissue growths (sarcomata), may replace to a very large extent, or entirely, the normal endothelium lining the vessels both preëxisting and newly formed in the tumor. More often they are found lying immediately beneath the endothelium. In such cases these tumor cells, by the result of slight injury to the tumor, or merely from the very character of the growth, may become free in the vessels. When either of these events

happens, and the cells are carried along the veins, they may occasionally be arrested in the heart and multiply there. In general, however, it may be laid down that they are liable to be arrested in the first system of capillaries to which they are carried by the blood stream. Thus, sarcomas occurring along the branches of the portal system are peculiarly apt to form secondary growths in the liver; those occurring along the main venous system are peculiarly apt to form secondary growths in the lungs. Rarely, as pointed out by Zahn,[1] in cases of small-celled tumors in which growth is in the venous side of the heart, with no secondary growth in the lungs, multiple metastases may be present in distant organs, and can only be explained by passage of individual cells or minute cell masses through the lung capillaries without arrest, the foramen ovale being found closed.

FIG. 196

Sarcomatous transplantation. Abdominal lymphosarcoma; section through two of the close-set small growths: *T T*, covering the surface of the liver *G*. (Martin.)

Such passage must not be regarded as impossible. Along with other observers, inoculating the relatively large cells scraped from a rabbit's liver into a vein in another rabbit, we have found these cells in the renal vessels and those of the renal capsule.

It has further to be remembered that where extension is mainly along the lymphatics, eventually the cancer cells from the lymphatic secondary growths may find their way into the thoracic duct, and so from this into the main circulation, and thus eventually, in these cases also, there may be extension and metastatic growth by means of the main circulatory system.

3. A third means is but a modification of the first. The various serous cavities of the body are essentially large lymph spaces. If a tumor penetrates and affects the lining membrane of one of the serous cavities, certain of its cells may become free, and thus pass to one or

[1] Virch. Arch., 117; 1889; 1

other region of the serous cavity. This is especially well seen in connection with the peritoneal cavity; the cells may become arrested here or there upon the surface, grow, and so there may be formed numerous metastases, scattered all over the serous surface of such a cavity. This method of extension is spoken of as *transplantation*.

Nor may this be wholly confined to the lymphatic system. There are cases in which cancer of the oral cavity has been found accompanied by secondary growths in the stomach, or of the stomach in the intestines. The first and most natural explanation in such cases is that of surface transplantation, and possibly in some cases this is the correct explanation. But careful study in others (more particularly as between stomach and intestines) has demonstrated marked lymphatic involvement, implicating the (retroperitoneal) glands, and thence extending to a distance. This possibility must always be carefully excluded before the decision is reached that a case is one of true transplantation.

4. Somewhat allied to this last form is *transplantation by apposition*. Cases are recorded in which (*a*) where one lip has been the seat of cancerous growth, the other has become, later, involved at a corresponding point, (*b*) where the skin of an arm, coming into contact with an ulcerated, cancerous breast, has become involved, or (*c*) where the parietes opposite to a viscus presenting superficial malignant growth, without showing adhesions, becomes the seat of growth. Here, clearly, cells become transplanted upon another surface, which, presumably by attrition or other cause, has lost its protective covering. Such transplantation does not, by any means, necessarily ensue.

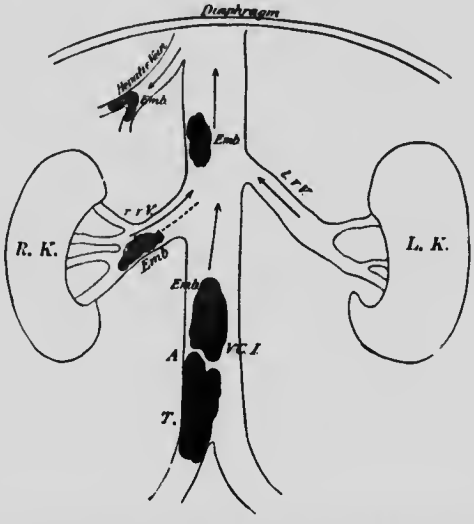
Retrograde Metastasis.—It deserves note that, while the general rule is that tumor cells are carried in the direction of the normal blood or lymph current, and secondary growths occur in conformity therewith, we may encounter paradoxical cases in which the opposite is the case, or in which, at first sight, there appears to be no relationship between the site of the secondary growth and the blood and lymph flow from the primarily affected organ. Thus, in cancer of the breast, it is by no means infrequent to find the head of the humerus of the same size infiltrated with the growth. Such cancer extends in the main by the lymphatic system. Now, the lymphatics from the head of the humerus and shoulder region pass toward, and not away from, the axillary glands. Or a primary malignant growth of the kidney or of the heart region may show extensive secondary growths in the liver, and that with little evidence of growth in the lungs. The kidneys have no relationship with the portal veins. In such cases we have to fall back upon the retrograde passage of cells along vessels. In the first case we have to suppose that the extension of cancer into the axillary glands blocks the normal channels, so that its lymph has to find a collateral or roundabout circulation whereby it and its contained cells may pass along certain channels in the reverse direction.

Another possibility in these cases which has to be borne in mind, and excluded, is that of direct, continuous growth along the lymphatics from this axillary gland. This, however, will not explain all the cases.

Thus, Belin[1] has called attention to the relative frequency of left supraclavicular nodules in cases of visceral cancer, best explained by variation in pressure in the thoracic duct at its junction with the jugular vein, leading to reflux of cancer cells into the neighboring glands.

In the second case, we conclude that when there occurs a negative pressure in the inferior vena cava, cells may be actually drawn back from the right auricle, or fall back from the inferior vena cava into the hepatic veins, until they become arrested in some of the smaller vessels of the liver, and there, growing, cause the development of metastatic tumors.

FIG. 197



Schema of retrograde embolism to illustrate mode of retrograde metastasis: *T.*, may be taken to represent a tumor mass in one of the branches of the inferior vena cava, part of which becomes liberated at *A* and carried upward toward the heart. By temporary stasis and back pressure the mass may pass into the renal or hepatic vein and become lodged there. (After Lubarsch).

Tissue of Predilection.—There is a feature characterizing metastatic tumors which has been little dwelt upon, which, nevertheless, is of high importance, as throwing light upon one important factor determining tumor growth in general. It is a feature parallel with what is seen in infective conditions. It is notable, for example, that in pyemia, where there may be a development of multiple abscesses, this development does not take place indifferently in all the tissues and organs of the body. They may be numerous in the lungs and kidneys, and yet in the same case scarce an abscess may show itself in the liver and spleen, and none at all in the muscles of the body; in

[1] Thèse de Paris, 1888.

children there is a peculiar liability for these secondary abscesses to form in connection with the ends of the bones and joints. This cannot be explained purely by the difference in the size of the capillaries and the arrangement of the capillary network in these different organs. The circulation in the spleen, with its remarkable system of sinuses, is of such a nature that we should expect bacteria to be arrested and metastatic abscesses to form here more easily than in any other organ of the body; but this is not the case. And, to explain the distribution of these abscesses, we are forced to recognize that the resistance or reaction of the tissues plays a part in determining the fate of the bacteria. Circulating in the blood, if they come to rest, the bacteria are taken up by the endothelium of the vessels of certain organs, and are in this way destroyed. They are not so taken up by the vascular endothelium in the vessels of other organs, or, if taken up, they lead to the destruction of that endothelium, and are not destroyed. From either of these causes they proliferate freely, and so form a new focus for infection and inflammation.

Now, the same is true with regard to neoplastic metastasis. We find, for example, that melanotic tumors are especially liable to form new-growths in the liver; malignant glandular tumors of the thyroid are peculiarly liable to form secondary growths in bone; only rarely do we come across metastatic growths of any order developing in the muscles. Numerous other examples might be given, but this curious distribution renders it evident that the escaping cells of malignant tumors gaining entrance into the blood stream, and becoming carried to various organs, *do not by any means necessarily proliferate;* only under certain special local conditions is proliferation in general possible; or, otherwise, in many regions of the body the prëexisting cells react against the invading cells, and lead to their destruction or the arrest of their growth. Only in this way is it possible to explain the remarkable d[illegible] we occasionally meet with in connection with these u[illegible]wths.

[illegible]ansen first called attention to the predilection of prostatic c[illegible]m metastases in bone, a predilection so marked that we ha[illegible]ore this diagnosticated prostatic cancer from the existence of extensive involvement of the pubic bones. Leuzinger[1] noted that while osseous metastases occur to the extent of 2.3 to 3.5 per cent. in cases of uterine cancer, they are 14 per cent. in cancer of the breast, and 20 to 25 per cent. in thyroid cancer. Menetrier[2] and Handford note a liability to muscular metastases in cases of primary lung cancer. Rolleston and others, to bone metastases in the part of adrenal cortical tumors.

Indeed, considering all the facts at our disposal with regard to metastasis, we are forced to recognize that it is not the mere escape of

[1] Inaug. Diss., Zurich, 1886.

[2] Art. Neoplasie, Bouchard's Pathologie Génér., vol. ii. Handford, Trans. Path Soc., London, 39: 1888: 48.

cells from a primary tumor which determines the development of these secondary growths, but that the fact of prime importance is the proliferative capacity of these cells as compared with the reactive powers of the tissue in which they find themselves arrested. Taking into consideration what we know regarding the attempts at transplantation of normal tissues, we are, I think, forced to conclude that the same conditions are in existence here in connection with the tumors. For it is only when tumor cells have peculiarly active vegetative powers that, being carried into regions and surroundings widely different from their original habitat, they are capable of continued proliferation. Or, conversely, it is eminently probable that tumor cells are liable to escape, not merely from malignant, but also from benign growths; but, when they escape from benign growths, their vegetative activity is not in general sufficient for them to grow in altered surroundings, and so it comes to pass that no metastases are formed, and, even escaping from malignant growths, it is only in particular localities that they can grow. Nay, more, as with pyemia we have to recognize that the resisting power of the body and of the individual tissues may vary during the progress of the condition: that depression of the resisting powers on the part of the tissues may ensue whereby metastatic growths eventually can occur within them.

We met with a striking demonstration of this fact some few years ago in the case of an elderly woman, in which the following history was obtained: There had been noticed in the left breast, for some years, a small, dense, scirrhous cancer, which, as sometimes happens, had remained practically stationary. Some months before her death this patient had fallen on some steps and had hurt her back so severely that she was confined to her bed for several days, and, following upon this, it was her lumbar symptoms that most troubled her. At the autopsy a dense, and mainly fibrous scirrhous cancer was found in the breast (which had shown no increase during the eight months she was under observation), with involvement of the axillary and supra- and infraclavicular glands; but most marked was the extensive infiltration of the lumbar vertebræ, more cellular, it is true, than that of the breast, but clearly of the same type. It was impossible to resist the conclusion that here trauma had lowered the tissue resistance, so that now cancer cells, brought to the bone, had found conditions favorable for growth.

This matter of tissue resistance, or relative insusceptibility, has, as we shall later show, a most important bearing upon the etiology of blastomas and upon the arrest and cure of the same.

The Production of Metastases by Tumors of a Benign Type.—Lastly, before scanning up, attention has to be called to the fact that certain tumors of a benign type are liable to produce metastases. The chondromas, or tumors formed of cartilage, afford frequent examples of this, both in man and the lower animals. I have come across more than one example of localized and well-defined chondroma of the mammary glands in the bitch (a not infrequent condition) showing multiple small secondary cartilaginous nodules in the lungs. It cannot

be imagined that fully formed cartilage cells invade the bloodvessels or lymphatics, become detached, and are then brought to rest in the pulmonary capillaries, and continue to grow there. A more rational explanation is afforded by the mode of growth of this particular form of tumor. Unlike the majority of benign neoplasms, the chondroma grows essentially by peripheral cell multiplication. Just as normal cartilage grows from the perichondrium, so at the periphery of a nodular chondroma there is a vascular zone containing actively proliferating cells—chondroblasts—small, actively vegetative cells, of "embryonic" types, and these it is which gain entrance into the circulation and, carried elsewhere, set up metastases. The same procedure, I would add, explains the development of osteomatous or osteosarcomatous metastases. An arm, recently removed by my colleague, Dr. James Bell, for osteosarcoma of the upper end of the humerus, and studied by Dr. Keenan, showed the axillary glands converted into nodules of solid bone. Here it was not the adult bone cells that had found their way into the lymph stream, but proliferating osteoblasts, which, arrested in the glands, and undergoing further growth, had fulfilled their normal function and had given rise to true bony tissue. At least one case about which there would seem to be no doubt has been recorded of multiple metastases of a fibromyoma of the uterus, that by Krische, from Orth's[1] laboratory, of a form of tumor, that is, which, while most common is characterized, by its slow growth and benign properties; cases of this nature are exceptional. Nevertheless, since that date some half-dozen others have been placed on record.

A condition more difficult to name and classify is that seen in cases of so-called *malignant adenomas*. The adenoma is a tumor differing from the glandular cancer in that it is formed of an excessive growth of glandular elements, tubules, and acini, which still retain a typical glandular structure. It is in connection with the liver and with its ducts that are apt to meet with tumors of this type. In connection with cirrhosis numerous cases are on record—on this continent by Finley and myself, Fussell and others—in which multiple tumors have developed formed of masses of proliferated liver cells. It is most difficult to draw the line between compensatory hypertrophy, occurring in the lobules of the liver secondary to cirrhosis, simple adenoma complicating cirrhosis, and adenocarcinoma; but, certainly, in the advanced cases metastases may form in other organs; and what is interesting is that both in the primary nodules and in these metastases there may be a formation of bile. The cells, that is, still retain certain of their functions. In connection with the bile ducts there may be a development of tumors formed of tubes repeating in their structure the normal bile ducts, and these, again, may give rise to metastases.

Equally, if not more remarkable tumors are met with in connection with the thyroid gland; indeed, the tumors of this organ—and they are common and very varied in character—present many aberrant

[1] Inaug. Diss., Göttingen, 1889.

features. In this connection I would point out that not only do well-marked infiltrating cancers of this gland very frequently exhibit still the tendency toward the formation of colloid within the nearly formed but irregular acini, but that we encounter, rarely, it is true, remarkable glandular tissues growing within the bones of the skeleton which reproduce in structure, and in the presence of true colloid material within the alveoli, the young or growing thyroid tissues. These tumors are structurally, therefore, thyroid adenomas, and, what is most remarkable, is that in more than one case careful study of the thyroid gland proper has failed to reveal evidence of any primary tumor there. Structurally, these tumors are of benign type; clinically, they are found to grow extensively, replacing the bone, and manifesting definitely malignant properties.

In short, all these malignant adenomas exhibit the same want of correspondence between structure and properties. In some, at least, namely, those of the liver, a cause of this development of metastases has been determined; the normal liver cells are in very close relationship to the bloodvessels, lying immediately beneath the capillary endothelium, and it has been observed that in their growth the tumor masses project into, distend, and grow along the hepatic vessels; thus, portions of these finger-like masses are liable to be detached and carried to the pulmonary capillaries, etc., where, coming to rest, they produce metastases. The same course of events may take place in other instances. In the thyroid, in the production of these adenomata within the bones, another process would seem to be at work. In the first place, the bones affected may be at such a distance from the organ that the theory of fetal inclusion cannot, in reason, be advanced, by which I mean it is unreasonable to suppose that we are dealing with cases in which, during development, portions of thyroid tissue have become detached and included in the growing bones, to lie dormant for years, and eventually take an active growth. Rather, it would seem, that here we have a state of affairs similar to that noted in connection with enchondromata. The thyroid, structurally, is peculiar in this, that even during adult life there can be detected in it small accumulations of indifferent cells, which, as Wolfler has pointed out, are truly "mother cells," and, under certain conditions, are capable of active proliferation and the production of new acini. As we shall have to point out later, in connection with the subject of cell emboli, it is probable that even cells of considerable size, like liver cells, not infrequently become liberated into the circulation and so become carried to different parts of the organism. Under ordinary conditions these cells become destroyed. There appears, in fact, to be normally in the system a very definite intercellular antagonism, so that cells out of place are acted upon and destroyed by those with which they come into contact. As I have already noted in connection with transplantation, embryonic and actively proliferating cells are not so surely destroyed as are adult and functioning cells. The simplest explanation of these intra-osseous adenomas is that, during the course of the development of new acini

in the thyroid (at a time, that is, when these areas of small vegetative mother cells become richly vascular), certain of these cells become detached into the lymph or blood stream, and, gaining entrance thus into the circulation, if they happen to be carried into a bone, there find conditions favorable to continued growth. No other explanation appears adequate to meet all the circumstances.[1]

The facts and observations here recited are ample to prove that a classification based upon the existence or non-existence of malignant properties cannot be satisfactory. If malignancy itself has different meanings according to circumstances, if a tumor, benign in one region, is malignant in another, in virtue of its position; if tumors, structurally similar, like the adenomas or the chondromas, can indifferently assume either benign or malignant properties, it is hopeless to seek to arrange neoplasms according to this one feature, however important it be from a clinical standpoint. Some other basis for classification has, therefore, to be sought.

Latency in Relationship to Metastases.—It is a significant fact that tumor cells conveyed to other regions may not immediately begin to grow and develop into a metastatic neoplasm, but may remain latent and inactive for months, and, indeed, for years, and then only take an active growth. The proof of this statement is afforded by the fact that a tumor of malignant type may be removed surgically with apparently perfect success, and then months or years later a progressive enlargement is noted in some lymph gland or other organ which, on removal, is seen to present growth of the type of the original tumor. In this way our colleague, Dr. Shepherd, removed a cancerous cervical gland from a woman on whom, eight years previously, he had performed total excision of the breast for cancer. Beeckel and Vernenil have reported recurrences after twenty-nine and thirty years, respectively.[2] In connection with melanotic sarcoma of the choroid of the eye some few cases are on record in which, after total extirpation of the affected eye, growth of similar characteristically pigmented tumors has shown themselves after long intervals in the liver and elsewhere. The longest period of such latency after operation removal that we have found recorded is twenty-one years.[3] Allied to these observations is that of Ehrlich,[4] that, whereas in general a mouse chondroma transplanted into other mice grows almost immediately, and with great vigor, in two cases four months elapsed before any sign could be made out of (subcutaneous) development.

On the other hand, transplanting cancerous and adenomatous tumors, of 94 such tumors, of each of which portions were transplanted into

[1] Several cases are on record of "struma thyroidea ovarii," in part associated with teratomatous masses, in part solitary. Doubt still exists as to whether these last are truly thyroid tissue or follicular adenomas of the ovary. (See Borst, Verhandl. Deutsch. Pathol. Gesellsch. 11: 1908: 98; with literature.)

[2] For literature see Bircher, Centralbl. f. Chirurg., 1907: Nr. 26.

[3] Olshausen, Ztschr. f. Geb. u. Gyn., 48: 1903.

[4] Ztschr. f. Aerztl. Fortbildung, 1906: Nr. 7.

20 to 30 mice, only 11 showed signs of growth, and this usually in but 1 to 3 of the animals inoculated; rarely in 6 or 7. In the great majority of the cases the transplanted material underwent atrophy and absorption. As we have pointed out already, when normal tissues are transplanted, the same is most often the case. When, as in cases of mammary cancer, we find secondary growth only in a single distant organ, such as the liver, we can only conclude that this same destruction has overtaken cancer cells transplanted into other organs. And so it is evident that one of three things may happen to the transplanted cells of neoplasms: (1) immediate growth in the area in which they become arrested; (2) latency for long periods, with or without eventual multiplication; and (3) degeneration and absorption.

The demonstration of this capacity for tumor cells to lie latent has an important bearing upon what is known as the "cell rest" theory of tumor formation, to which we shall refer later. And from these same data another most important deduction may be drawn: If cells of like order, transported to various areas in the one organism gain growth in some, lie latent in some, and undergo absorption in others, and if, again, portions of the same tumor transplanted into the same tissues in different animals of the same species shows a like succession of results, it is obvious that, whether new-growth occurs or not, is not merely dependent upon the inherent vegetative powers of the transplanted cells, but is also governed by conditions obtaining in the tissue which receives these cells; that, in short, *tissue resistance and the extent of the same is a factor in determining blastomatosis*. To this we have already referred.

The Nature of the Stroma.—There are certain other data and considerations regarding the characters of the blastomas which must be noted: first and foremost, the nature of the organic relationship between these growths and the organism in which they develop. The blastomas gain their nutrition from the organism of the host, and possess both a blood and lymph supply. The capsule of the typical blastomas, as we have pointed out, is formed by the tissues of the host, and not only that, but the stroma of all such tumors must also be regarded as afforded by the host. We must conceive, in short, the tumor as originating by overgrowth of a cell, or cluster of cells, which, as they proliferate, make their way between the connective tissue of the region. Even in what become benign, well-encapsulated tumors, showing expansive or diffuse growth, as suggested by Ribbert's observations upon what appear to be early stages of benign kidney tumors, there appears to be this primary infiltration. Such primary stroma may now, as the tumor expands, exhibit a growth *pari passu* with that of the specific tissue elements of the tumor; this in cases of benign neoplasms. In atypical infiltrative tumors the stroma is continually being added to as the tumor advances into the surrounding tissue, causing degeneration and absorption of the specific cells of the tissue, but leaving the connective-tissue stroma to be the framework of the

growing tumor, as has been well demonstrated by Bashford in experimental mouse cancer.

It is somewhat more difficult to understand the relationship in an atypical connective-tissue tumor (sarcoma). Here evidently a double process occurs; the stroma itself multiplies, and again, as the surrounding tissue is infiltrated, its stroma also becomes part of the stroma of the growth.

Blood and Lymph Vessels.—Such stroma of the host is equivalent to the tissue in which run the vessels and lymph channels. The bloodvessels and lymph channels of the host are retained by the growing tumor; and thus it is that the tumor gains nourishment and discharge of its products.

As the tumor grows there may even be a certain amount of vascular growth, this specially in neoplasms of sarcomatous type. *Such vessels never pass beyond the capillary type;* they may become distended to great size (and this is true of persisting capillaries), but there is never formation of muscular walls, of arteries and veins proper; nay, more, it is remarkable that what we must regard as arteries and veins inclosed in the growing tumor become simplified and lose their characters. Even at the outer part of an infiltrating growth it is noticeable how few arteries and veins proper are to be detected. So far as we can see, *a blastoma has no power of regulating its blood supply.*

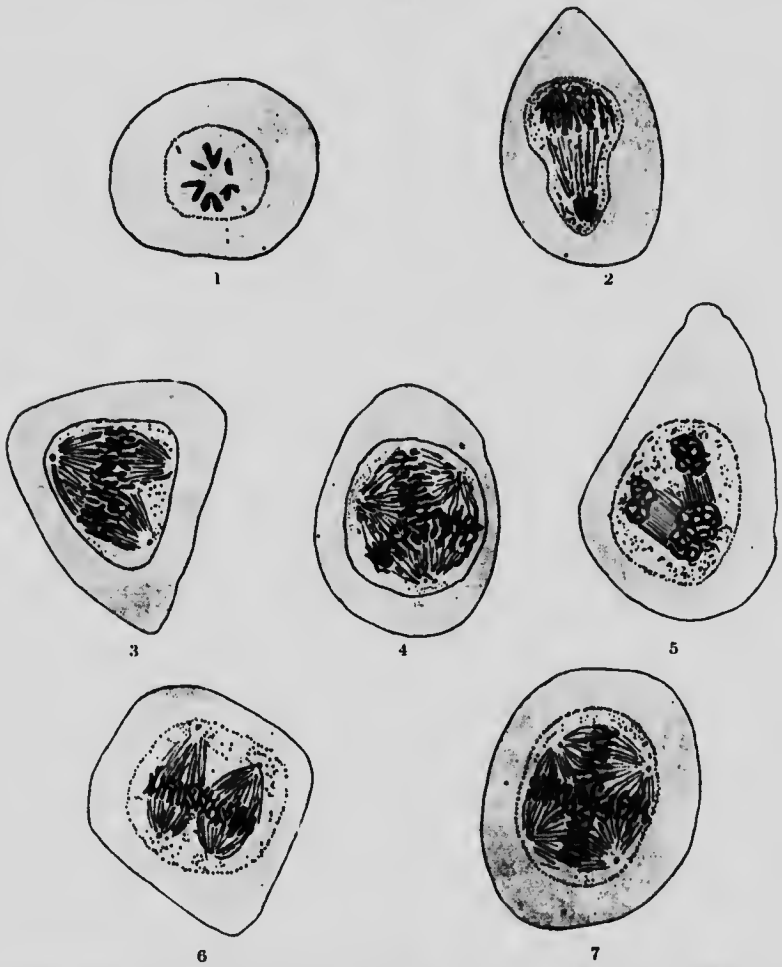
Nerves.—*The host supplies no nerves to the blastoma.* Careful study may show a few filaments passing into the peripheral parts of an infiltrating tumor,[1] but these are evidently the nerves of the persisting tissue of the part, and undergo degeneration, for the deeper parts of a blastoma are wholly nerveless. There is, thus, no nervous control, whether vasomotor or trophic, or of any order on the part of the organism. *The activities, vegetative and otherwise, of the neoplasm cannot be influenced by the organism, save through the composition of the blood and fluids supplied by it, and by alterations in the resisting powers of the surrounding tissues.* The control, such as it is, is indirect.

Degenerative Changes.—This lack on the part of the tumor to control its own nutrition, and on the part of the organism to govern the tumor cells, renders it not surprising that blastomas are peculiarly apt to exhibit degenerative changes, and, as favoring these, another factor comes in, namely, the absence of any secreting or discharging passage proper over and above the imperfect change afforded by the blood and lymph. The products of the more outwardly placed cells may diffuse into the surrounding tissues; the internal cells are apt to "stew in their own juice," and to be subjected to a form of auto-intoxication. Practically, any of the forms of cell degeneration to be noted in a later section may present themselves, notably necrotic changes, cell death, and absorption. And, favoring these, and favored by them, in all those forms of growth in which degeneration is most liable to occur, we are apt to have *hemorrhages*, the thin-walled, dilated vessels giving way.

[1] Young, H. H., Jour. of Exp. Med., 2: 1897: 1.

Nuclear Changes.—Associated with these degenerations we meet with nuclear changes. Whereas, the cells of an actively growing tumor, and particularly those of the peripheral portions of actively infiltrating atypical tumors, are noticeable for their relatively large nuclei, with

FIG. 198



Irregular mitoses in cancer cells: 1, hypochromatic mitosis; 2, asymmetric mitosis, the upper daughter nucleus hyperchromatic; 3-7, various forms of pluripolar mitoses. (Galeotti.)

abundant chromatin, so that in the stained section there is a very pronounced difference between them and the nuclei of the surrounding tissue; the nuclei of the more central parts of such tumors are pale, and poor in chromatin (chromatolysis); often they are vesicular; at other times, shrunken and wrinkled looking; and, when degeneration

is extensive, the nuclei of the dead cells do not take the stain at all, while the degenerating cells bordering on such necrotic areas exhibit nuclear fragmentation (karyorrhexis).

These are not the only changes. The more aberrant the growth, the more do we encounter (in freshly removed sections suitably stained) irregular mitoses, and these of a very remarkable order. We owe to von Hansemann[1] more particularly a study of the same in connection with tumors. We may encounter forms with *hypochromatic* mitoses (reduced number of chromosomes below the number normal for the species), asymmetric mitoses (one daughter cell receiving more chromosomes than the other), *hyperchromatic* mitoses (the number of chromosomes in excess, sometimes greatly, of that normal for the species), *pluripolar* mitoses (there being more than two centrosomes,

FIG. 199

1, mitosis (homotype) in ordinary somatic cell, showing usual form of chromosome; 2, heterotype mitosis in germ cell; 3, irregular heterotype mitosis, with "ring" chromosomes in a cancer cell: at the lower pole aberrant chromosomes passing into the cytoplasm. (Moore.)

each attracting chromosomes, so that there may be developed three, four, six, or, according to Hansemann, as many as twelve to twenty daughter nuclei). Again, we may have scattered *chromosomes*, some becoming free in the cytoplasm, as though by rupture of some of the achromatic spindle elements. It must, however, be remembered that these mitotic irregularities are not peculiar to atypical malignant growths. They may be experimentally produced in various tissues in a variety of ways.[2] They indicate, however, that the cells are subjected to abnormal influences.

Farmer, Moore and Walker[3] have called attention to the existence of "heterotype mitosis" in cancer cells similar to those found, almost specifically, in the stage of maturation of germ cells, and have suggested that in the existence of this type of mitosis and cell is to be found the

[1] Die Mikrose, Diagnose d. bösartige Geschwülste, Berlin, 1897.

[2] Galeotti, Ziegl. Beitr., 20: 1896, and Lubarsch, Allgem. Path., 1905: 44, et seq.

[3] Proc. Roy. Soc., 72: 1903; 499. See also Bashford and Murray, ibid., 73: 1904: 66.

explanation of the vegetative properties of the blastomata. We believe we are correct in saying that further study has demonstrated that there are found to be only one of a series of mitotic aberrations; that they bear no relationship to the malignancy of the tumor; are not, that is, necessarily present in highly malignant growths, and that these observers are not now inclined to lay any stress either upon these appearances,[1] or on the other appearances recorded of nuclear migration and conjugation.

Retrogression and Healing.—These degenerative changes lead to the consideration of the absorption and disappearance of tumors, and from this to the data bearing upon the active healing of the same. Such absorption and disappearance is the rare exception. A blastoma, once it becomes recognizable, even of the most benign type, may remain stationary, but most often grows; rarely does it recede and undergo natural absorption. And yet every surgeon of large experience can recall one or more cases in which he can only explain by such recession. Too often the cases are imperfect and unsatisfactory as evidence; there has been no histological examination of the growth when in its prime, to establish its exact nature. There are, however, cases on record about which there can be no doubt.[2] Thus, Nasse and Starck have each recorded cases of the spontaneous disappearance of multiple exostoses; Kaposi, of a lymphosarcoma of the upper jaw; Reichel, of a spindle-celled sarcoma of the temple; Nitze, of a papilloma of the bladder; Rotter, of a malignant adenoma of the rectum, involving the vaginal wall, which, after repeated removal and recrudescence, eventually disappeared spontaneously. Shepherd has recorded a case of cervical sarcoma with similar history, and even that most malignant form of growth, the chorio-epithelioma malignum, has been seen to recede by two observers (von Franqué and Fleischmann).

If, thus, there can be natural absorption of tumors even of the most malignant type, sooner or later we must penetrate the secret, and find how, by medical or surgical procedures, to bring about cure, *i. e.*, the degeneration, death, and subsequent absorption of the tumor cells. Undoubtedly this has been already secured in a number of instances, and that by very varied procedures—but the results so far have been very uncertain and most often incomplete. Either all the tumor cells have not been destroyed (and this by the recurrence of the original growth appears to be the most frequent event), or the tendency on the part of the organism to produce new-growths has not been arrested. Probably a more correct statement, which will include both these cases, is that the resisting powers of the organism have not sufficiently exalted to arrest the aberrant cell proliferation. To this matter of resisting power and vegetative power we shall again revert when dealing with the theory of blastomatosis.

Of these methods, apart from operative interference, which have been

[1] Cf. Bashford and Murray, Proc. Roy. Soc. B., 77: 1906: 226.

[2] We here in the main produce those selected by Ribbert, who gives the references.

employed with more or less success, may be mentioned the exhibition of arsenic, Coley's method of inoculation of sterilized culture fluid of mixed streptococcus and B. prodigiosus growths (based on the old experience that intercurrent erysipelas may lead to the absorption of malignant growths), method of removal of the ovaries to bring about absorption of mammary cancer, the absorption of uterine myomas following upon electropuncture, and, more recently, the employment of ultraviolet light and the Röntgen rays to cause the disappearance of superficial growths.

Unicentric, Pluricentric, and Multiple Primary Growths.—Lastly, before taking up the subject of the different forms of blastoma, a word must be said regarding the foci of origin.

The majority of primary blastomas are single, and, what is more, appear to originate from a single focus, either a single cell or small collection of cells, separated from the rest of the tissue in which they find themselves. It will be understood that this point cannot be determined. We cannot recognize in the normal tissues a single cell which is destined to give rise to a tumor. By analogy with what occurs in the transplantation of tumors, it would seem that several cells coincidently manifest the aberrant growth. Tumors which appear to grow from a single focus are spoken of as unicentric. Some growths are clearly pluricentric, or multicentric. This would appear to be most often the case in mammary cancer, as has been beautifully demonstrated by Petersen.[1] Whereas, in a single section of such a growth the masses of cancer cells in the alveoli appear to be all separate; this is really not the case. By studying serial sections it can be seen that the cell masses form a branching mass, all directly continuous, springing from common centres, the real foci of growth. By making wax models of successive layers, cutting away the parts representing the stroma, and building the successive layers together, Petersen was able to show that the alveoli, or, more correctly, the cell masses, originate from several separate centres.

In the adrenal tumor studied by Wooley, to which we have already referred, it was possible to see that cells, clearly belonging to different strands or cell collections of the cortex, were undergoing the cancerous change.[2] The cells were larger, the nuclei richer in chromatin, so as to stand out in marked contrast to the unaffected cells next to them. There could be no question in this case regarding fœtal-cell rests; it was the cells of the developed tissue that were undergoing the change. We have recently had a second case of the same nature (Fig. 196.) Van Heukelom, Horst Oertel and others have noted a like series of transitions of liver cells into cancer cells, in cases of carcinomatosis of the liver (p. 769).

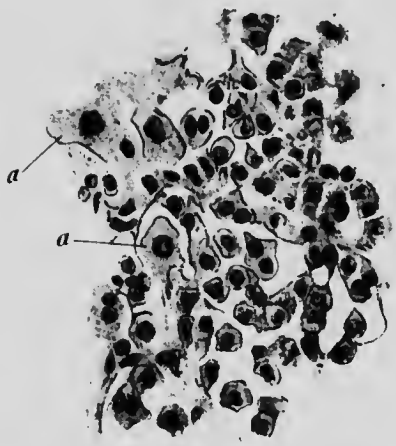
Occasionally we meet with not single or pluricentric single tumors, but what we can only regard as multiple independent primary growths.

[1] Virch. Arch., 164: 1901: 570.

[2] Jores had previously recorded a similar observation, Deutsch. med. Woch., 20: 1894: 208.

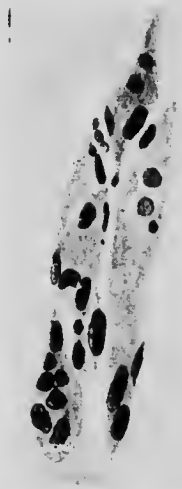
The commonest example of this is seen in uterine myomas. We may find two, five, ten, to twenty or more isolated muscular tumors in the uterus. In the ovaries, also, cases are on record of as many as five separate dermoids (teratomas) in an ovary, and it is relatively common to find coincident dermoids, one in each ovary. With such tumors there can be no question of the one being a secondary, metastatic growth, derived from the other. But the same is true, also, of glandular (adenomatous and cystadenomatous) growths of the ovaries; these show a curious tendency to be bilateral. Here, the growths being of simpler type, it is not always possible to draw a definite conclusion. One might be metastatic from the other, due to tissue predilection.

Fig. 200



From the edge of a small nodule of new-growth in the adrenal cortex, showing every transition from *a*, cells undistinguishable from the surrounding cells of the cortex to small cells with deeply staining nuclei of sarcomatous type.

Fig. 201



Similar conversion or modification of cortical cells of adrenal into tumor cells. (Woolley.)

Were it the latter then occurring in the same tissue, it should be identical. As a matter of fact, we often find differences in the two growths, which suggest strongly that both are primary. Similarly, multiple fibromas, osteomas, and chondromas are not uncommon, and we approach thus close to a condition which we shall treat separately, that, namely, in which a particular tissue in all parts of the body shows a peculiar tendency toward overgrowth.

Passing a stage farther, there have now been a considerable number of cases reported of multiple primary growths in the one individual of different orders; uterine myomas with uterine or breast cancer; different forms of growth along the digestive tract, and this apart from the transitions which may be found from benign papilloma to carcinoma.

The largest collection of these for this literature has been by Walter.[1] Woolley[2] has analyzed the cases in the literature up to 1903, and Nicholls[3] has collected quite a series from our autopsies in Montreal. In one of Walter's cases there was an angiosarcoma of the stomach, a sarcoma of the gall-bladder, an aberrant adrenal tumor, a lipoma of the kidney, and an enchondroma of the right pleura.

Such cases have been taken by the upholders of the cell-rest theory of blastomatosis to indicate a vice in development whereby several cells or masses of cells become segregated, and liable thus to form foci for subsequent overgrowth. But segregation alone does not explain blastomatosis. A more likely explanation is the lowering not merely of tissue, but of general bodily resistance, so that, simultaneously, cells in various parts find conditions possible for active and independent proliferation.[4]

[1] Arch. f. klin. Chir., 53: 1896: 1.

[2] Boston Med. and Surg. Journ., 148: 1903: 1.

[3] Montreal Med. Journ., 32: 1903: 326. See also Wells, Journ. of Pathol., 7: 1901: 357, and Warthin, Journ. of the Amer. Med. Assoc., 32: 1899: 963.

[4] Bibliography of general works upon tumors the fullest and most recent is that by Borst, "Die Lehre von den Geschwülsten," 2 vols., Wiesbaden, 1902. Ribbert's "Die Geschwulstlehre," Bonn, 1904, is not so detailed but gives fully the author's much discussed theory. Lubarsch and others give important studies of the recent literature of different orders of tumors in the successive volumes of Lubarsch and Ostertag's "Ergebnisse." It cannot be said that there is any authoritative book on the subject of tumors in our language. Senn's work, valuable from a surgical point of view, is hurried and ill-digested in its pathology. More important is Bland-Sutton's "Tumours, Innocent and Malignant," which is individual and replete with matter difficult to encounter elsewhere, but its pathology is gross rather than minute.

CHAPTER XVII.

THE AUTOCHTHONOUS BLASTOMAS.

CLASSIFICATION OF THE AUTOCHTHONOUS BLASTOMAS.

In what order are we to treat the individual forms of tumors? How are we, that is, to classify them so as to bring together those which are most nearly related, and by its position in the scale gain a grasp of the properties of any particular form?

We have already discussed at length the one main division which for practical purposes is most important, that into typical and atypical blastomas, and the conclusion gained from the study can only be, that while most useful this is not wholly satisfactory because of the existence of (1) transitional forms between the two groups, and (2) apparent or real exceptions to the laws we have noted as, in the main, governing either group.

Two courses are open to us: Either, studying these exceptional cases and noting the variation in properties of different forms, we may assume the agnostic position—may say that, despite the enormous amount of material collected, we still have not sufficient data to permit us to make a pronouncement, and, doing this, fall back upon a purely histological and admittedly provisional arrangement based almost entirely upon the characters of the cells constituting the tumors, with no regard to the properties of the individual forms save that which follows from a coincident separation of the typical from the atypical forms. Or, on the other hand, we can start from the basis that the properties of any given form of cell are an inheritance; have been impressed upon that cell by the successive forces to which its ancestry have been subjected; that these inherited properties, along with the forces acting upon the cell itself, determine its characters; so that if we can surely determine the derivation of the different forms of tumors, then an embryogenetic classification must be a natural classification.

The first of these courses is that which from Hamilton[1] (1889) onward has been increasingly adopted, and nowadays it is that employed by Hansemann,[2] Lubarsch, Menetrier, Prudden, and the writers of the two most important recent treatises on the subject, Ribbert and Borst. Hansemann goes so far as to state that the only logical course is to take each organ in turn and describe separately the primary tumors which may originate from its component cells, or, in others words, to make as many

[1] Text-book of Pathology.

[2] Die bösartige Geschwülste, Berlin, 1897: 22.

classes as there are different tumors of different organs or tissues. But this is to construct a Chinese alphabet.

Borst's classification is:

1. Connective tissue tumors of maturer tissue (so-called benign connective-tissue tumors).
   (*a*) Connective-tissue tumors proper.
   Fibroma, myxoma, lipoma, chondroma, osteoma, angioma.
   (*b*) Tumors of the muscle and nervous systems.
   Myoma, neuroma, glioma.
2. Endothelial tumors.
   Lymphangio-endothelioma, hemangio-endothelioma, and perithelioma, cylindroma, psammoma, cholesteatoma.
3. Connective-tissue tumors of immature tissue (sarcoma).
   (*a*) Sarcomas of simplest type.
   Round-celled, spindle-celled, giant-celled.
   (*b*) The more highly developed sarcomas.
   Mixed sarcomas (fibroma sarcomatosum, osteoma sarcomatosum, etc.), melanosarcoma, chloroma, lymphoma sarcomatosum, myeloma multiplex, angioma sarcomatosum, myoma, neuroma, glioma sarcomatosum.
4. Epithelial tumors
   (*a*) Of mature type.
   Papilloma, adenoma, cystadenoma.
   (*b*) Of immature cell type (carcinoma).
   Of skin, squamous epithelioma; of mucous membrane, cylindrical-celled cancer; of glands, carcinoma adenomatosum.
   Appendix. Adrenal tumors: Chorionic tumors.
4. Mixed tumors.
   (*a*) Cystic mixed tumors.
   Dermoid cysts of skin, testes, ovaries, branchiogenic cysts, ciliated epithelial cysts of brain, enterocysts.
   (*b*) Mixed tumors in the narrower sense.
   Of kidneys, vagina, bladder, testes, mamma, face.
   (*c*) Teratoids and teratomata.
   Of testes and ovaries; of anterior and posterior ends of body axis; bigerminal sacral teratoma, monogerminal sacral teratoid, teratoids and teratomata of the body cavities, teratoids and teratomata of neck, cranium, and ventricles.

If we analyze this we find that it is constructed on the principle of recognizing three groups of tissues, the connective, the endothelial, and the epithelial, of which the first two afford atypical tumors of like order (sarcoma); the last affords the carcinoma. It is interesting to see how close a carefully thought-out classification constructed purely on these histological principles brings us to the embryogenetic classification to be presently noted. There are it will be seen certain "jumble" departments; the myoma and the glioma have little in common; the adrenal tumors and the chorionic tumors have to be treated as an appendix, an admission of doubt as to their exact place in the scheme; simple epithelial cysts and

the complicated ovarian and testicular teratomas come into the same section. But on the whole the teratomata and the teratoblastomata (mixed tumors) range themselves very much according to the classification we have already afforded from embryogenetic considerations.

In this connection may be mentioned a suggestive grouping of tumors proposed by Lubarsch, who would primarily divide them into three main groups:

1. Those departing but slightly from the type of mother tissue and showing little or but temporary growth (teratoma, congenital nevus, congenital adenoma, myoma, lipoma, osteoma, chondroma). In all of these cases we have probably to deal with a local transposition of tissue.

2. Those which while showing autonomy still comply with the ordinary rules of life and respect physiological limits (the larger myomas, adenomas, angiomas, etc.; these may for long remain in a resting state, with periodical accessions of growth and absorption).

3. Tumors fully emancipated from physiological laws (malignant tumors proper, sarcoma, and carcinoma).

While this division is suggestive, and valuable as calling our attention to the properties of different orders of tumors, it is not a classification of the different forms of tumors in the proper sense. Growths of the same type occur in more than one class; an adenoma may belong to all three groups; a congenital mole may assume malignant properties and pass from the first to the third group; a tumor due to local transposition of tissue, for instance, the aberrant suprarenal growths in the kidney, may, while congenital, be fully emancipated from physiological laws and show malignancy even before birth.

Embryogenetic Classification (Waldeyer).—With the development of the science of embryology it was noted that from the primitive germ layers different tissues were derived; that the connective tissues of the body, including bone, cartilage, and muscle, were of mesoblastic origin, while broadly (and, as I shall point out later, incorrectly) the specific cells of the epithelia and the acini of glands were derived from either epiblast or hypoblast; and as neoplasms originate from preëxisting tissues or their precursors. Waldeyer introduced the division of tumors into those of epiblastic or hypoblastic and those of mesoblastic origin, subdividing according to the nature of the tissue, and again according as to whether the arrangement of the component cells was typical or atypical. A further class had to be made for the mixed tumors, those namely containing overgrowths of both epi- (or hypo-)blastic and mesoblastic elements.

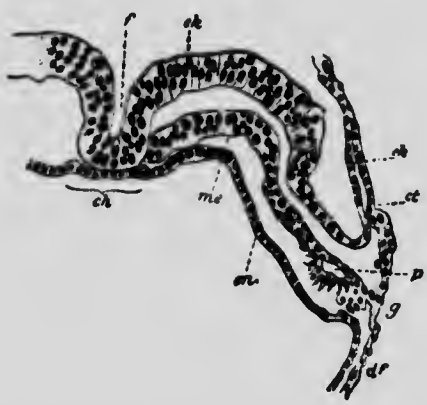
It is unnecessary that we here give the full classification according to this scheme. Such classification was popular during the last quarter of last century, but even those who used it recognized its defects. Of these, the greatest was that it ignored the fact that the mesoblast also gives rise to definite glandular organs; another, that it separated the gliomas (tumors derived from the neuroglia and so of epiblastic origin) from the sarcomas or atypical connective-tissue tumors, of mesoblastic origin, although histologically the growths are closely related, the glioma showing no close relationship to the carcinomas or atypical glandular and epithelial

tumors. These were grave defects, and their recognition it was that led to the reaction indicated by the present attitude of most modern writers.

Histogenetic Classification.—Now, the principle underlying the above attempt at classification was a right one. Just as the form and structure of the individual of any species is the outcome of the phylogeny of that species, is the resultant of the special conditions to which that individual and its progenitors have been exposed in the course of countless generations, so the component tissues of the individual with their special characters are the resultant of both past and present forces.

A given cell of the embryo in a given relationship to the rest of the embryo has inherent tendencies to give origin to cells of a particular order. The weakness of Waldeyer's classification lay in this, that it was

FIG. 202



Cross-section of a human embryo of 1.54 mm.: *f*, dorsal furrow; *ek*, ectoderm or epiblast; *st*, somatic mesoblast; *p*, beginning of the embryonic coelom; *g*, junction of the extra-embryonic somatic and splanchnic mesoblast; *df*, splanchnic mesoblast; *en*, entoderm or hypoblast; *me*, mesoblast; *ch*, notochord. (Graf von Spee.)

based upon an inadequate embryology. It does not follow that a fuller and more accurate knowledge of histogenesis will not afford us valuable aid. Each tissue has a definite origin and mode of development, and if neoplasms are derived from definite tissues, and their component cells represent stages in the development or degeneration of these tissues, then it is possible to establish a rational classification of tumors upon histogenetic lines.[1] We have to start from the very earliest stage of the developing ovum to gain a proper grasp. The earliest stage to be recognized in the development of the fertilized ovum, once it has proceeded to segment, is the *morula*, in which the blastomeres or cells form a cluster or group of cells of the same order with almost complete lack of differentiation. Rapidly this gives place to a second stage, in which these

[1] I here follow very largely my article "Upon the Classification of Tumors," Jour. of Pathology, 4: 1902: 243.

cells arrange themselves into two layers, into the primordial layers of *epiblast* and *hypoblast*. In this way at a singularly early stage the future epiderm and endoderm become recognizable. The next stage to be noted is that the hypoblast, or more internal of the two primitive layers, gives rise by proliferation of its cells to a group or mass of cells showing no definite arrangement among themselves and not forming a true layer. This is the *mesoblast* and *anlage* of the organs derived from that layer. The hypoblast, while it in the main gives origin to these cells, still remains as a distinct layer or membrane. The epiblast participates to a less extent. Waldeyer went so far as to recognize these three layers, but there he stopped.

The reader must dispel as erroneous the old deeply rooted idea that connective tissues, and connective tissues only, arise from mesoblast; epithelia and glandular tissues and nerves, and these alone, from epiblast and hypoblast.

From the epiblast, whose cells in general are from the earliest period arranged in regular order, there is developed, along the dorsal groove, a marked proliferation of the cells, those away from the surface being no longer arranged in strata. Indeed, it is legitimate to compare this development of the *neuroblast* or *anlage* of the nervous system with the earlier development of the mesoblast. With the further infolding of the dorsal groove this portion of the original epiblast becomes cut off from the rest, the only portion recalling the original epiblast being the ependymal cell layer immediately around the central canal, the cells or descendants of cells which have originally been the outer layers of the dorsal epiblast. A very similar ingrowth of cells, irregularly arranged, occurs from the hypoblast to form the basis of the *notochord*.

The mesoblast in its turn undergoes changes: with the development of the primitive body cavity those cells abutting in that cavity become arranged as one orderly layer, the *mesothelium*, the remaining portion of this "layer" not thus arranged constituting the *mesenchyme*. From the mesothelium again, by a process of active growth and heaping up of cells, are developed localized masses of cells on either side, which we may compare with the neuroblast and notochord; these are the *myotomes*, the *anlagen* of the future striated muscles of the body, and later from the *mesenchyme* a final true layer is developed, the *endothelium*, lining the vascular cavities, both blood and lymph vascular.

We thus find that the embryo comes to exhibit cell collections of two orders, which may be termed "lining membranes" and (for lack of a more expressive word) "pulps," the lining membranes being the persistent epiblastic, hypoblastic, mesothelial, and endothelial layers, the "pulps" being the main mass of the neuroblast (of epiblastic origin), the notochord (of hypoblastic), and the mesenchyme (of mesoblastic). And now, following up the further development of these different cell collections, we observe that the adult tissues derived from these two series exhibit well-marked differences, so that we can divide adult tissues into two great groups, the *lepidic* (from λεπις, λεπιδος, a rind, skin or membrane) and the *hylic* (ὑλη, crude undifferentiated material).

The characteristic of the lepidic tissues is that the specific cells which give them their main features are arranged either in layers or clusters *in direct apposition; they are not separated by lymph spaces or by blood-vessels;* they possess, nevertheless, a supporting framework or stroma of hylic tissue in which run the nutrient vessels. Of hylic tissues the features

Fig. 203

Diagrammatic representation of section through vertebrate body to show ontogenetic relationship of the various order of tissues. *A*. Of lepidic type: 1, epiderm and its glands (epiblastic); 2, mucous membrane of digestive canal and its glands, liver, etc. (hypoblastic); 3, endothelium lining serous cavities (mesoblastic) and glands like renal cortex of mesothelial origin; 4, vascular endothelium of late mesoblastic origin. *B*. Of hylic type: 5, spinal cord, brain, and nerves (epiblastic); 6, notochord (hypoblastic); 7, connective tissues of the body (mesenchymatous); 8, myotomes, striated muscle of body (mesothelial); 9, lumen of digestive tube; 10, body cavity.

are the opposite: *separating the cells there is a matrix of intercellular substance* either homogeneous or fibrillated, while *lymph spaces and blood capillaries tend to separate and run between the individual cells.* If in the lepidic tissues there is a stroma of hylic tissues, so here in the hylic there always enters lepidic tissue in the shape of the living endothelium of the blood and lymph vessels. In either case the elements of the other order

occupy a subordinate position. While some pathologists, like O. Israel[1] and Buxton,[2] have already noticed this distinction, the histologists and embryologists have laid little stress upon it. The more we study tumors the more we realize this importance of the distinction.

On this basis we obtain the following classification of normal tissues:

I. LEPIDIC OR LINING MEMBRANE TISSUES,

in which the bloodvessels do not penetrate the groups of specific cells and in which there is an absence of definite stroma between the individual cells, although such stroma, of mesenchymatous origin, may be present between the groups of cells.

1. Epiblastic:
   Epidermis. Epidermal appendages of hair, nails, enamel of teeth, etc. Epidermal glands. Epithelium of the mouth and salivary glands. Epithelium and glands of nasal tract and associated spaces. Epidermal portion of hypophysis cerebri. Lens of eye. Epithelium of membranous labyrinth of ear, anus, male urethra (except prostatic portion).
2. Hypoblastic:
   Epithelium of digestive tract and glands connected with it. Specific cells of liver, pancreas, tonsils, thymus, thyroid. Epithelium of trachea, lungs, bladder, female urethra, male urethra (prostatic portion).
3. Mesothelial:
   Lining cells of pleuræ, pericardium, peritoneum. Specific cells of suprarenals, kidneys, testes, ovaries (Graafian follicles). Epithelium and glands of Fallopian tubes, uterus, vagina, vasa deferentia, vesiculæ seminales, etc.
4. Endothelial:
   Lining endothelium of bloodvessels and lymphatics.

II. HYLIC OR PRIMITIVE PULP TISSUES.

Organs and tissues in which the special characteristic is that the specific cells lie in, and are separated by, a definite stroma, homogeneous, or fibrillar, in which there may or may not be blood and lymph vessels.

1. Epiblastic:
   Nerve cells, neuroglia.
2. Hypoblastic:
   Notochord.
3. Mesenchymatous:
   Fibrous connective tissues, cartilage, bone, reticulum of lymph glands, bone-marrow, fat cells, involuntary muscle tissue, spleen, bloodvessels, blood corpuscles.
4. Mesothelial:
   Striated muscle, including cardiac muscle.

[1] Berl. klin. Woch., 37: 1900: 609, 644, and 667.

[2] Jour. Cutan. and Genito-urin. Dis., New York, February and April, 1901.

Following this scheme of classification of the normal tissues, we may now divide the tumors arising from the specific constituent cells of the various tissues into two main genera—the *lepidic* tumors, or *lepidomas*, originating from the above "lining membrane" tissues and the hylic tumors (*hylomas*), originating from tissues derived from the embryonic "pulp." We can further distinguish two broad groups of lepidic tumors, the *primary*, those whose cells are derived in direct descent from the original epiblast and hypoblast; and *secondary*, or *transitional*, whose cells are derived in indirect descent from the same, *i. e.*, have, in the course of development, passed through a mesoblastic or mesenchymatous stage before coming to form portions of a lining membrane. We shall explain the use of the term *transitional* later.

I. LEPIDIC, OR RIND TUMORS.

(*A*) *Lepidomas of the First Order.*

1. *Of epiblastic origin.*
   Tumors whose characteristic constituents are overgrowths of tissues derived directly from the epiblastic lining membranes, or epiderm.
   (*a*) *Typical.*—Papilloma, epidermal adenomata (of sweat, salivary, sebaceous, and mammary glands, etc.).
   (*b*) *Atypical.*—Squamous epithelioma, carcinoma of glands of epiblastic origin.
2. *Of hypoblastic origin.*
   (*a*) *Typical.*—Adenoma and papilloma of digestive and respiratory tracts, thyroid, pancreas, liver, bladder, etc.
   (*b*) *Atypical.*—Carcinoma developing in the same organs and regions.

(*B*) *Lepidomas of the Second Order, or Transitional Lepidomas.*

3. *Of mesothelial origin.*
   Tumors (mesotheliomas) whose characteristic constituents are cells derived in direct descent from the persistent mesothelium of the embryo.
   (*a*) *Typical.*—Adenoma of kidney, testicle, ovary, urogenital ducts; adenoma of uterus and prostate; adenomas originating from the serous membranes, "mesothelioma" of pleuræ, peritoneum, etc.
   (*b*) *Atypical.*—Cancer of the above-mentioned organs; squamous endothelioma, so called, of serous surfaces, epithelioma of vagina; adrenal mesotheliomas, hypernephroma.
4. *Endothelial Lepidomas.*
   Tumors originating from the endothelium of the blood and lymph vessels; lymphangio-endothelioma, hemangio-endothelioma, perithelioma, cylindroma, psammoma, cholesteatoma.

II. HYLIC, OR "PULP" TUMORS.

1. *Of epiblastic origin.*
   Tumors whose characteristic constituents are overgrowths of tissues derived from the embryonic pulp of epiblastic origin.
   (*a*) *Typical.*—True neuroma, glioma.
   (*b*) *Atypical.*—Gliosarcoma.
2. *Of hypoblastic origin.*
   Tumors derived similarly from embryonic pulp of hypoblastic origin.
   Chordoma.
3. *Of mesenchymal origin.*
   (*A*) *Mesenchymal Hylomas.*—Derived from tissues originating from the persistent mesoblastic pulp, or mesenchyme.
   (*a*) *Typical.*—Fibroma, lipoma, chondroma, osteoma, myxoma, leiomyoma, angioma, myeloma.
   (*b*) *Atypical.*—Sarcoma (derived from mesenchymatous tissues), with its various subdivisions, fibrosarcoma, spindle-celled sarcoma, oat-shaped-celled sarcoma, chondrosarcoma, osteosarcoma, myxosarcoma, lymphosarcoma, chloroma, angiosarcoma; of origin still debated, melanosarcoma.
   (*B*) *Mesothelial Hylomas.*—Tumors which are overgrowths similarly of tissues derived from embryonic pulp of definitely mesothelial origin. Rhabdomyoma.

If this classification be studied, it will be seen that we have done away with that deficiency in the earlier embryological classifications, whereby tumors of unlike orders and histological appearances were grouped together, and those of like characters separated. Gliomata, for example, come to be placed close to the mesenchymatous tissues; the gland-like tumors of mesoblastic origin become grouped along with those of epiblastic and hypoblastic origin.

Have we, in accomplishing this, introduced any new difficulties? One objection will undoubtedly present itself, namely, that among the lepidomas of mesothelial origin we have grouped together tumors some of which are of a strongly epithelial or glandular type; for example, the cancers of the uterus, with others like the hypernephromas, tend to take a definitely sarcomatous character. We fully admit this difference in properties.

Two possibilities exist: either the neoplastic properties of the different portions of a given germ layer become differentiated, according to the ultimate function assumed by those portions—to admit which is, we confess, tantamount to acknowledging that little weight can be attached to embryogenetic considerations; or that the epithelium lining certain organs in which we find tumors not of the characteristic transitional type, is not mesothelial; that, for example, whereas primarily the vagina, uterus, and Fallopian tubes originated from Müller's duct, and so were of mesothelial origin, in the course of development the cloacal hypoblast has overgrown and replaced the

original mesothelial lining of uterus and tubes, the epiderm from without has grown into and replaced the mesothelium of the vagina and cervix uteri. This has already been suggested. Certainly the characters of the vaginal epithelium are unlike those of any other mesothelial structure, and primary vaginal tumors are of an epiblastic, and not a mesothelial, character; while, similarly, the mucous membrane of uterus and tubes strongly recalls that of the alimentary tract, as do the tumors arising from the same.

With this admission, and, it may be, only apparent exception, the striking feature of these secondary lepidic tumors, as a class, *is their liability to present transitional characters*—and this in the lack of recognition of the underlying cause has created an appalling amount of confusion. A tumor of the adrenal, a "hypernephroma" of the

FIG 204

Transition from adenomatous to sarcomatous type of growth in a renal mesothelioma. (Birch-Hirschfeld.)

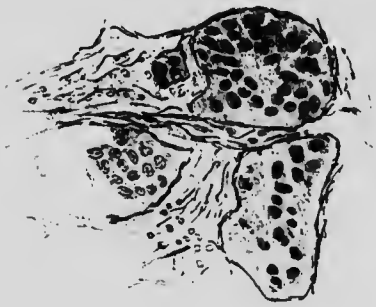
kidney, a testicular neoplasm or ovarian growth, and the same is true of the whole class of endotheliomata, may, if of slow growth, present all the characters of a cancer—a glandular tumor—if actively vegetative be indistinguishable from a sarcoma; and frequently in this group we meet with intermediate types, in which one part of a growth shows the cancerous, lining membrane type of structure, and other parts have taken on the hylic, sarcomatous type. Such tumors form an important proportion of the cases of so-called *carcinoma sarcomatodes*. Nay, more, in such a tumor, as Woolley,[1] from our laboratory, has pointed out: using Mallory's connective-tissue stain, so as to follow accurately the ramifications of the stroma, the transition from

[1] Johns Hopkins Hospital Bulletin, 14: 1903: 21.

the lepidic to the hylic type is found to be not apparent, but actual; certain cell clusters, as in cancer proper, lie wholly free from any intervening stroma; others, on the contrary, are separated and isolated by a matrix, which contains connective-tissue fibrils, a stroma proper, such as we find in sarcoma.

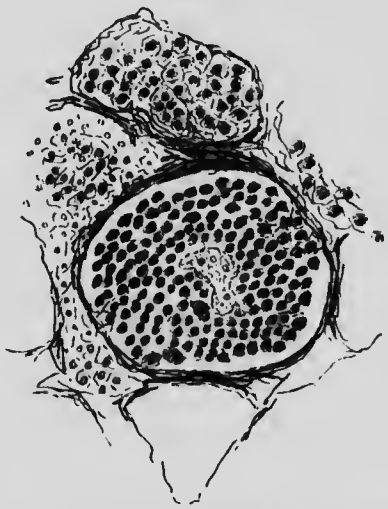
And, what appears to be an adequate reason for this difference in properties, suggests itself. As we have emphasized more than once, *properties which are of oldest acquirement are those which are last to be lost;* those of later acquirement are yielded up with greater ease. The primary lepidic tumors are derived in direct descent from cells which, from the earliest embryonic period, have taken on lepidic, or

Fig. 205



Section of carcinoma simplex of breast, treated with Mallory's connective-tissue stain, to demonstrate complete absence of passage of intercellular fibrils between the individual members of the alveolar cell groups. (Woolley.)

Fig. 206



Section of an endothelioma similarly treated. The alveolus below reacts almost wholly like an epithelial cancer, that above exhibits intercellular connective-tissue fibrils, like a sarcoma. (Woolley).

linin-membrane characters; whereas, these transitional tumors, one and all, are derived from cells which, from being lepidic (in hypoblast or epiblast), have become hylic, and only at a later embryonic period have again taken on lepidic characters. Such cells in newgrowth revert more easily to the hylic, sarcomatous type, than do the cells of the primary lepidic tumors. Here, indeed, histogenetic considerations show themselves of singular value in clearing up one of the enigmas and great difficulties in the study of tumors.[1]

In laying this down I do not coincidently imply that primary

[1] We do not claim credit, save in establishing this as a general principle explaining the feature of secondary lepidic tumors as a body. For O. Israel had already recognized fully this same dependence of the characters of the endotheliomas upon the embryogeny of the mother tissues.

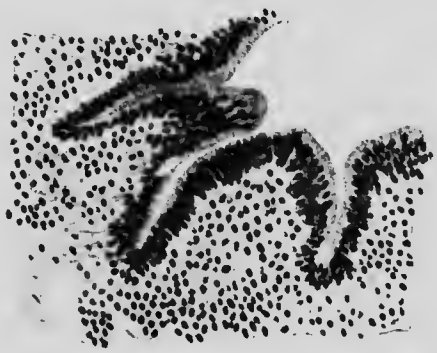
lepidic tumors, under these conditions, manifest the same tendency to reversion or conversion to a hylic type. It is, I know, the general impression and the common teaching that epiblastic and hypoblastic "rind" tumors, squamous epitheliomas, glandular cancers of the mamma and digestive tract, for instance, are always typically cancerous. This is not so; one has but to study the advancing edge of a highly malignant, rapidly growing epithelioma to see that here and there individual cells, of epithelial type, become surrounded by (or probably directly make their way into) the connective tissue; while still farther out from the main mass of the growth it is impossible to say whether the largest cells seen are of epithelial or connective-tissue origin. And more recent studies of melanotic tumors, and of what Krompecher has termed "basal-celled" cancers, has established, it would seem beyond any doubt, that cells of epidermal, epiblastic origin can give origin to tumors undistinguishable from connective-tissue sarcomas in histological structure. What we would say is, that *such reversion is so frequent as to be a distinguishing feature of the secondary lepidic tumors;* it is the exception in the case of the primary.

I am strongly adverse to the coinage of new terms in our subject, but, at times, when a new idea or new relationship has to be expressed, such coinage becomes essential, and this was the case when I suggested lepidic and lepidoma, hylic and hyloma, respectively. They were necessary for the expression of my conception of tumor relationships. Whether others will find them so useful, not to say essential, as I have found them, time must tell. At present I regard them as a framework around which to group ideas, and do not suggest their employment—in fact, do not personally employ them for daily clinical purposes. For such, the names of the different typical tumors and the terms carcinoma, sarcoma, and endothelioma are adequate. As will have been gathered, it is obvious that the terms carcinoma and sarcoma must be given a purely morphologieal significance. It is impossible nowadays to attach to them any histogenetic significance, once we recognize that tumors of identical type, hylic or lepidic, may originate from any of the germ layers. Here we find ourselves wholly in accord with Lubarsch,[1] and strongly urge that his recommendation be put into general practice: "So I come back to this, that a combination of morphological and histogenetic [illegible] of nomenclature is necessary. The chief word must be determined by the morphological structure; if we can with certainty give the genesis, then indicate that by an adjective, as, for example, *endothelial adenoma, epithelial adenoma*, etc." To these examples we would add, as further indications of the method, *osteosarcoma, cutaneous melanoma, choroidal melanotic sarcoma, mesothelial cancer.* For practical purposes, the binomial and trinomial method is essential; there are marked differences in the malignancy of endothelial and epithelial growths; thus, to label both cancer is to afford no information, or to mislead the surgeon or clinician.

[1] Ergebnisse, 6: 1900: 968.

This, it may well be repeated, we note in all tumors, that the more rapid the growth, and the more the cells depart from their normal and mature environment, the more do we observe that those features of the tumor cells which are specific for one or other tissue tend to disappear. In the most rapidly growing and most aberrant tumors the individual cells afford us little or no clue to the tissue of origin. It is the general arrangement of the cells that aids us in making our diagnosis, and even then the general arrangement is not so much that peculiar to the fully formed tissue as that common to connective tissue in general, or to glandular and lepidic tissues in general. We recognize a reversion to an earlier, simpler, or, as it is often expressed, a more embryonic type. The essential feature of the cell of the atypical tumor is the more or less complete replacement of functional by vegetative or proliferative activity, and the consequent loss of those features directly associated with the performance of function.

FIG. 207



"Pseudoepithelium," or secondary epithelium without basement membrane lining a cyst in a glioma, formed by modification of the superficial layer of glioma cells. (Saxer.)

Lastly, as bearing upon the subject of classification, it may be asked, Can cells which, through neoplastic proliferation, have lost specific functional properties, regain them? The answer to this must be that everything indicates that the power of reacquirement is minimal. A hylic tumor cannot take on lepidic characters. At most, modified relationships may bring about modification in properties, but this must be regarded as an adaptation, an assumption of new properties, not, it seems to us, an awakening into activity of properties which we would regard not as merely dormant, but actually lost. Here we may be mistaken, but it is thus we would explain Saxer's[1] case of the eventual clothing of degeneration cysts in gliomas with an imperfect layer of glial cells taking on epithelial characters; those cells do not form a true epithelium, and become cut off from their fellows; no basement membrane is formed, and we find every transition from the typical glioma cell to cells which, lying in apposition to the fluid of the cyst, take on a more epithelioid type; now there is a single layer of such cells, now two or three layers.

[1] Ziegler's Beitr., 38: 1905.

CHAPTER XVIII.

TYPICAL HYLIC TUMORS OF MESENCHYMATOUS ORIGIN.

It would, perhaps, seem natural to discuss now the causation of neoplasia or blastomatosis. But, without a knowledge of the mode of recurrence and properties of the different forms of growth, it is difficult to treat this most difficult subject in a satisfactory manner, or to grasp the relative importance of the different arguments brought forward. To prevent undue digression and repetition, it is better first to pass in review the various forms, thereby forming a basis for our treatment of causation. In so doing it will be better, also, not to follow slavishly the order of the classification just given, but to consider first the simpler hylic or connective-tissue tumors, and later the more complicated lepidic and glandular forms. And here, following the example of descriptive biologists, it will be well to describe type forms first; as, also, to call attention to certain departures from type—certain impure blastomas, if we may so describe them—forms which do not conform in all respects with the definition of blastomata in general, and, indeed, possess different properties. It would be better to consider these as a class apart, and this we may be able to do in the future; at present it is so much the custom to include them under the same heading, that to divorce them absolutely would confuse the student consulting other works on the subject. Thus, where necessary, we shall call attention to these examples of *blastomatoid* growth. Indeed, the frequent notes of the existence of these conditions may be of more service to calling attention to the difference than would a special section devoted to the subject.

FIBROMA.

As its name implies, the fibroma is a tumor composed of fibrous connective tissue, and as such connective tissue is peculiarly widely distributed, so tumors of this nature may be met with in all regions of the body, although, as will be pointed out, there are certain regions and tissues in which these tumors are especially apt to develop. And as ordinary connective tissue varies in its composition, being in some regions loose and areolar, with loose bundles of fibrils and relatively frequent cells, being in others dense and firm, with abundant fibrillar substance and relatively few cells, and those much compressed, so, largely according to the seat of origin, do we meet with fibromas of different density of formation. Thus, we are accustomed to distinguish *soft* and *hard* fibromas respectively, the latter more particularly devel-

oping from connective tissues of a dense type, as, for example, from tendons, fasciæ, and periosteum; the former from looser, more areolar tissue, *e. g.*, subcutaneous connective tissue.

Wherever growing, the fibroma has for its essential and predominant constituent connective-tissue elements. As such, it is composed of connective-tissue cells, bands of white connective-tissue fibrils, blood-vessels, and, to a greater or less extent, elastic fibers. Lymph spaces and channels are also present, few and inconspicuous in the hard variety, frequent and large in the softer forms.

Typically, such growth forms a well-defined nodule, which, as it enlarges, leads to the atrophy, absorption, and replacement of the tissues immediately surrounding it. Growth is slow and expansive. Where rapid, there histological examination shows the existence of abundant cells, not of the typical, fully formed, connective-tissue type, but resembling fibroblasts, and, like them, possessing deeply staining nuclei of fair size and a relatively abundant protoplasm.

We have here the vegetative type of connective-tissue cell. The existence of great numbers of these fibroblasts, or spindle cells, indicates a transition to the sarcomatous condition and the assumption of more malignant characters. When the cellular character is very prominent, we speak of a *fibrosarcoma*.

It must be borne in mind that all fibromas are more cellular than normal adult connective tissue. It is when this fibroblastic overgrowth is a striking feature, and particularly where it is marked in one or more areas of the tumor, that we are justified in speaking of fibrosarcoma. Growth in all cases is from such fibroblasts, and not from fully formed connective-tissue cells.

All typical fibromata are pale on section, and those of the firmer type are glistening, the light glinting from the cut surface somewhat as from watered silk. This is due to the fact that the fibers run in bands, the various bands being cut in different directions. This structure is to be explained by the development of the connective tissue, which occurs in the main around the bloodvessels in the tumor; newly formed fibers are laid down roughly parallel and concentric to these vessels, and as the vessels course in various directions, so do these bands of fibrils. The tumors are readily enucleated, and, in most cases, the border of the tumor is to the naked eye sharply circumscribed. It will, however, be easily understood that both the more concentrated tissue immediately around the tumors and the tumors themselves being composed of fibrous tissue, there is, under the microscope, no sharp outline to be distinguished between the two; the neoplastic and the surrounding non-neoplastic tissue appear, under the microscope, to pass into one another.

Degenerative Changes.—Fibromata of long standing are apt to exhibit degenerative changes; through arrest of the blood supply, by tension, or other cause, they may undergo necrosis, with abundant formation of cholesterin and fatty debris, or they may become so infiltrated with calcareous salts as to be converted into calcareous

nodules. Bony and cartilaginous masses have been noted in some cases of old standing; it is not always easy to decide whether we have to deal with original osteoid or cartilaginous inclusions, or with metaplasia induced by modified nutrition and cell relationships. Through obstructed lymph discharge, tumors may be found œdematous, or lymphangiectatic, cystic or mucoid (*fibroma mucinosum*). Such conditions must be distinguished from the conversion of areas of a fibroma into definite myxomatous tissue (p. 662) when we deal with a *myxofibroma*.

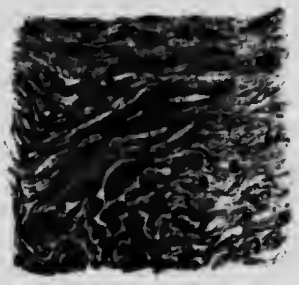
Occasionally, in the kidney and elsewhere, we accidentally encounter what appears to be the earliest stage of fibromatous growth; small collections of proliferative fibroblasts, which are infiltrating the immediately surrounding tissue. At a later stage, it appears that infiltration ceases, and the surrounding tissues are pushed aside by the expansive diffuse growth of the tumor, which thus gains a capsule and becomes sharply defined. In this way it would seem to be that occasionally we encounter in what is otherwise a pure fibroma rare glandular acini, and, it may be, other tissue elements. So, also, it is possible that in adult life what had been at first purely an interstitial inflammatory fibrosis in a gland, such as the mammary gland, takes on, in parts, active tumor growth; and, in like manner, there become developed isolated tumor masses which contain glandular or other elements. So long as these included tissues show no sign *of independent proliferation, all such apparently mixed tumors should still be referred to as fibromas*, as fibromas with inclusions of one or other order; only when there is *coincident aberrant growth of the other element*, along with evidence of like growth of the interstitial fibrous tissues, is it permissible to speak of fibro-adenoma, osteofibroma, etc. This rule, unfortunately, is more honored in the breach than in the observance; indeed, the majority of the fibro-adenomas, of which the commonest example is afforded in the mammary gland, are not fibromas in the true sense. The fibroid overgrowth is not limited and sharply defined. It passes diffusely into the surrounding tissue; it is, at most, *fibromatoid*, and is to be considered along with the blastomatoid conditions, to be presently noted.

Fibromata proper do not form metastases, and, similarly, it may be laid down that they do not recur. If recurrence does happen, either the primary tumor, on examination, is found to exhibit fibrosarcomatous changes, or we are dealing with a fibromatoid condition, *i. e.*, the original tumor was not a sharply defined, limited mass, but possessed a definite root or base, through which it passed imperceptibly into the surrounding connective tissue, recurrence being thus the manifestation of a tendency toward diffuse regional overgrowth on the part of the surrounding tissue, which, it may be, has been stimulated by the removal of the primary growth (see p. 620). This would appear to be the most satisfactory explanation of the recurrence of fibroid, fibromyxomatous, and other nasal polypi.

Hard Fibromas.— Hard fibromas, as isolated nodular growths, occur more especially in connection with tendons. While this is most

often the case, it is not the absolute rule, for occasionally we meet with soft fibromas in fasciæ, and those developing in "soft" tissues, such as the kidney, may be hard. Most often there is no history of previous injury or irritation. Sometimes, as in the mammary gland, we encounter the hard, well-defined variety, and here there may be a history of previous inflammation.

Fig. 208

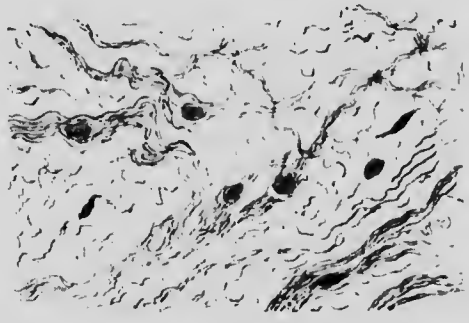


Hard fibroma. (Ribbert.)

Another variety of hard fibroma develops in connection with the jaws, the characteristic *epulis*, a term properly applied only to these fibromatous growths, but often given to osteoid and osteosarcomatous growths. These develop from the periosteum, and, according to Bland-Sutton, originate always in connection with the root of a decayed tooth. In their growth they cause absorption and replacement of the bone. Fibromata of the uterus will be discussed along with the myomas of that organ.

Soft Fibromas.—These may be single, but frequently are multiple. Upon analysis of the cases, it appears that the majority come under the fibromatoid growths, to be presently noted. They occur more especially in connection with the skin and submucosa of the pharynx and digestive tract. Those in connection with the nose and throat are

Fig. 209



Soft fibroma.

peculiarly soft—mucoid polyps—and of the true fibromyxoma type. Here and in the nasal region, there may be inclusions of mucous glands.

Fibromatoid Growths.—In this group of blastomatoid growths must be placed a series of conditions intermediate between simple hypertrophy and true tumor formation. Failure to recognize their peculiar properties have frequently introduced vagueness into the treatment of simple hypertrophy on the one hand, true tumor formation

on the other. These are conditions which Klebs and other German writers have classified as one form of Riesenwuchs (giant growth), which, also, C. P. White has recognized as "progressive hypertrophy." Such growths as a class (1) affect one particular tissue; (2) are multiple; (3) of congenital origin, frequently manifest in early life, and affecting several members of a family; (4) may be diffuse, or if not diffuse, *show no demarcation from the surrounding unaltered tissue, verging into this imperceptibly;* (5) the apparent encapsulation which such growths may exhibit on one or more aspects is due to their strictly respecting the

FIG. 210

Multiple fibromatoid overgrowths along the course of the cutaneous nerves. (Herczel.)

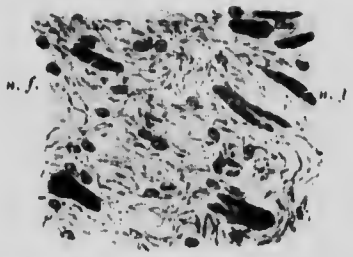
limits of the part in which they find themselves, and represents those limits; (6) they are of very slow growth, extending over years; (7) eventually, they may take on sarcomatous characters, but this is an epiphenomenon; it is but in accordance with the principle that tissue which has developed in excess of function is liable to take on aberrant growth.

As already noted, we regard the submucous connective tissue of the posterior nares and pharynx as a favorite seat for this fibromatoid development. Another not uncommon seat is in the nerve sheaths, leading to the conditions that used to be termed *plexiform neuroma*

FIG. 211

Tumors of sciatic nerves and their branches. At *a*, large tumor connected with small internuscular nerve. (Preble and Hektoen.)

FIG. 212



Section through a fibromatoid cutaneous nodule showing the nerve fibers (*n.f.*) separated by fibroid overgrowth. (After Ribbert.)

(Rankenneuroin), multiple neuromata, and molluscum fibrosum. In the multiple neuroma forms there may be from two to three to hundreds of oblong or spindle-shaped thickenings of the individual nerves —veritable tubers along their course. *The nerve fibers show no proliferation; they run through* the swellings, often, it is true, in a spreading fashion, separated by interstitial fibrous tissue; but the new-growth is essentially of this fibrous tissue. It is a localized overgrowth of the same, an exaggeration of the normal perineurium and endoneurium, bounded laterally by the outer sheath of the nerve, and at either end of the node becoming less and less marked, until apparently perfectly normal perineurium is reached The condition may affect the nerves generally or only those of one region, *e.g.*, arm optic nerve; may more particularly affect the medullated nerve tracts, though cases are on record of special involvement of the abdominal sympathetic system, and there is at least one case in which an apparently true fibroma of the uterus was found to contain non-medullated nerves, and even ganglion cells, and so it would seem to come under this category.

Even more remarkable is the appearance presented by cases of

molluscum fibrosum, which, for long thought to be examples of multiple soft fibromas, have been convincingly shown by Recklinghausen to come into this group. Here we meet with soft, subcutaneous, sometimes pedunculated, nodules, varying in size from little more than that of a pin's head to that of an orange, and affecting either a single cutaneous nerve and its branches, or being universally distributed to the number of several thousands, giving to the unfortunate possessor a most extraordinarily gnarled, nodose or "nobby" appearance. These tumors develop in connection with the sheaths of the peripheral cutaneous nerves, and, the latter being so small, and the overgrowths obtaining so relatively and actually great a size, the individual nodes may appear to be self-enclosed; nevertheless, examination shows the same relationship or outgrowth from the natural nerve sheath; they come into the same class.

A very full study of this condition of fibromatosis affecting one nerve has been made by Dr. Byers,[1] of Montreal, who has shown that all true intradural tumors of the optic nerve are of this nature. Of these, more than one hundred are on record. His studies indicate that there is some relationship between these growths and obstruction of the lymph channels of the affected parts. There was a dilatation of the lymph channels and development of appearances resembling those seen in *elephantiasis*. It is deserving of note that the lymphatics of nerves form a system distinct from that of the tissues they traverse. In nasal polyps, judging from the frequent œdematous and mucinous condition, we have a very similar state of affairs, and here, also, we encounter the *fibroma cavernosum*—forms with greatly dilated vessels, evidently brought about by a similar blood-vascular obstruction. In elephantiasis proper we encounter a like tendency to subcutaneous overgrowth and productive of conditions which, if more diffuse, have nevertheless much in common with fibroma molluscum. Such disturbed nutrition, if, as we suggest, a factor in these cases, must in its turn be due to a vice of development, for all these conditions of fibromatosis characteristically make their appearance in early life, or are familial.

CHELOID, OR KELOID.[2]

Closely related, though distinctive in etiology, and to some extent histologically, is the condition of cheloid. This consists in an excessive development of subcutaneous fibrous connective tissue, sometimes so excessive as to produce large overlapping masses, or lobes, of new-growth, covered by stretched skin. Two factors would seem to be at work leading to the conditions, namely: (1) a congenital predisposition; (2) irritation or injury. Thus, cheloid is especially common in negroes,

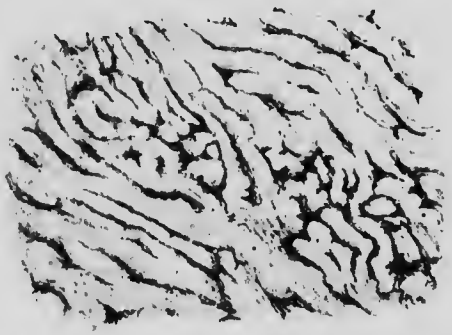
[1] Studies from the Royal Victoria Hospital, 1: 1900: 1.

[2] Some authorities derive the name from *κηλις*, a crab's claw (from the cancer-like way in which the processes spread into the surrounding corium); others from *χηλη*, a scar (from the relationship of the growth to cicatricial tissue). The mode of spelling is thus still in dispute.

male and female, and in those, both of colored and white races, who present the condition, slight cutaneous injuries, which, in ordinary individuals, lead to but temporary disturbance, are liable to be followed by excessive growth of connective tissue and formation of a tumor-like mass. In a case studied by Martin, working in my laboratory, the mere running the point of a pin along the forearm, with a force sufficient to cause reddening without bleeding, was followed by the development of little fibroid nodules along the track of the pin.

It has been the custom to divide the cases into the traumatic and the spontaneous, but the more fully cases are investigated, the more are we convinced that in all cases the growth follows irritation, though this irritation is often such as in ordinary individuals leads to no after-effects; we have thus seen it to follow vaccination. Cases are on record in which the pressure and rubbing of a shirt stud have been followed by one of these growths, and in one frequently quoted instance there was a massive development in the skin over the shoulder, following upon the carriage of a basket on the naked skin of that region.

FIG. 213



Section from a growth in a case of cheloid to show the coarse, hyaline connective-tissue bundles. (After Ribbert.)

Here, as in cases of fibromatosis proper, microscopic examination reveals the absence of a capsule; the process of fibrous connective-tissue overgrowth extends, by more or less radially situated processes, in the subcutaneous tissue, and there is an imperceptible transition from the overgrown, cicatricial-like, to the normal connective tissue. The fibrous tissue of the keloid itself is often, though not always, characterized by the presence of extremely thick homogeneous bundles or strands of almost hyaline character, between which lie well-developed fibroblast-like cells.

Another feature is the liability of these cheloid growths to spontaneous absorption. Recent observations indicate that steady pressure on the growths is followed by their atrophy and disappearance.

Thus the distinguishing features of cheloid growths are:

1. They are composed of fully formed connective tissue.

2. They develop in consequence of relatively slight irritation or trauma.

3. They develop in those showing congenital or racial predisposition.

4. They have no capsule, but merge imperceptibly into the surrounding connective tissue.

5. They are liable to retrogression and absorption.

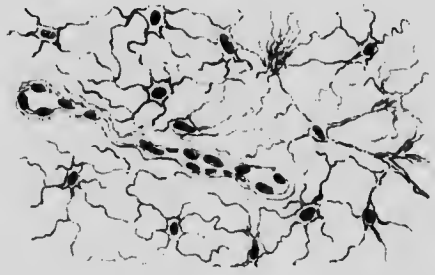
Just as in connection with the previous forms of fibromatosis we observed a transition between the blastoma proper and strain hypertrophy, so here it will be seen we observe a relationship or transition between blastomatosis and irritation overgrowth. It will be useful to express these relationships and differences in tabular form:

Nature of growth.	Character of tissues.	Capsule.	Congenital predisposition.	Other possible factors in etiology.	Recurrence.
Fibroma.	Fully formed connective tissue, but of atypical arrangement, growing independent of surrounding tissue.	Definitely present and complete save where vessels enter. Encapsulation easy.	Sometimes well marked.	Rare history of previous irritation. Most often no cause suggested.	Very doubtful after complete removal.
Fibromatoid growth ("Fibromatosis").	Fully formed tissue; arrangement more typical; at one or more areas in continuity with surrounding tissue.	Incomplete; possesses a definite hilum or hila.	Characteristic.	None.	Very frequent.
Cheloid.	Fully formed tissue merging gradually into surrounding tissue; exaggeration of cicatricial type of fibrous tissue.	Wanting.	Often marked.	In all cases with full history, a history of (minimal) trauma.	Very frequent.
Elephantiasis.	Fully formed tissue; arrangement least atypical; hypertrophy of normal connective tissue of part.	Wanting.	Absent.	Lymphatic obstruction main cause.	Absent; where cause can be removed condition undergoes absorption.
Fibrosis.	Fully formed connective tissue; dense; overgrowth more moderate, diffuse or localized.	Absent or whole overgrowth may be capsular.	Absent.	Irritation, or replacement.	Absent, unless cause continues in action.

MYXOMA.

The myxomata are tumors composed, in the main, of a tissue resembling none found normally in the adult organism, namely, a tissue composed of well-formed isolated cells of a somewhat stellate or polyhedral appearance, giving off delicate processes, the individual cells being separated one from the other by a matrix containing varying amounts of mucin, which takes on a differential stain with thionin. In this matrix there run large but thin-walled vessels. Some leukocytes are also present. We say formed in the main of such tissue, for it is very rarely that we come across what may be termed pure myxoma; in general, areas of the tumor show more condensed fibrous tissue, or cartilaginous masses, or frequently lobules or collections of fat cells, while in other cases portions are of sarcomatous type and show close collections of spindle cells. Thus, many pathologists doubt

FIG. 214



Section from typical portion of a mucoid polyp. (Collection in Royal Victoria Hospital.)

whether we ought to regard the myxoma as a separate form of tumor, and urge that we should speak rather of myxomatous modification or degeneration of some one or other form of connective-tissue neoplasm —of lipoma, or chondroma, or fibroma myxomatodes, rather than of myxolipoma, etc. As such the majority of so-called myxomas must be regarded. But Ribbert has described small pure myxomatous tumors of the endocardium. Further, cases have been recorded as congenital myxoma, the tumors being recognized at the time of birth.

These tumors are slowly growing, are soft and fluctuating, so as to give the impression, at times, of being cystic or fluid masses. They never form metastases, but, if imperfectly removed, are liable to recur, while, again, a certain number take on sarcomatous properties, and so may become malignant; in such cases the metastases are not myxomatous, but wholly sarcomatous.

A frequent seat of these myxomas is the nasopharynx, where they are either pure, or present a condition of fibromyxoma or myxosarcoma; they form multiple soft polyps, appearing in the upper portion of the nasopharynx, or, again, actually in the nasal passages. Others develop, at times in the interstitial tissue between the muscles, and then, as a

rule, are solitary, and, growing slowly, may attain a large size. A favorite seat for such tumors is the buttocks, between the glutei. Some of the largest forms of this order occur beneath the peritoneum, and then are found to be associated with fatty tissue, forming lipoma myxomatodes. Apparently associated also with fatty tissue are occasional small subcutaneous myxomata. Chondromata are peculiarly liable to show myxomatous areas, as, again, occasionally do large fibromas and fibromyomas. The mixed tumors of the testis and parotid very commonly, also, show more or less extensive myxomatous development.

The tissue which in appearance the tumor tissue most nearly approaches is the developing connective tissue, more especially the Wharton's jelly of the umbilical cord and the developing fatty tissue of the fœtus, as, for example, the developing subcutaneous fatty tissue. Of pathological conditions, it is to be noted that in the newly forming fibrous tissue around areas of inflammation we at times meet with fibroblasts lying in a more or less mucinous matrix; indeed, mucin is a constituent of all the connective tissues, even, as recently pointed out, of bone.

Resembling thus developing connective tissue of certain orders, it might seem that this form of tumor ought to be of a malignant type; this, as above stated, is not the case. It may be pointed out that in the myxoma the cells in general are fully formed, and that the appearance of delicate branches is due to the fact that here the individual connective-tissue cells are well dissected out by the surrounding transparent matrix. In short, the presence of processes is no indication of arrest of these cells at an early stage of development; on the contrary, when the myxoma does take on malignant characters and becomes sarcomatous, these processes become unrecognizable, and the mucinous matrix disappears; and it may be pointed out that the amount of mucin is by no means an indication of vigorous vegetative growth, but of the reverse. Rather, indeed, it would seem that there is some relationship between the vascular supply of the tumor and the development of the mucoid matrix.

Whether the œdematous condition of the matrix favors the non-removal of the mucin, or whether, on the other hand, the existence of mucin leads to increased absorption and retention of the fluid which diffuses out from the vessels, is an open question. But, certainly, on observing a large series of connective-tissue tumors, we appear to have every transition from simple œdema of the neoplasm to extensive mucinous infiltration and true myxomatous condition. To distinguish between the two conditions, acetic acid is to be employed. If mucin be present, the interstitial substance of the section becomes granular, and shows a network.

With regard to the causation, as already remarked, some cases are apparently congenital, and must be ascribed to isolated rests of either imperfectly developed fatty or fibrous connective tissue.

Of such congenital myxomas, Borst reports a colossal growth upon

the mesentery of a nine-months-old child. This exhibited extensive lymphangiectases, to which he ascribes the soft nature of the growth; there were correspondingly dilated bloodvessels. He ascribes the tumor to a persistence and continued growth of the embryonal mucoid tissue of the mesentery.

Other cases, notably the mucoid nasal polyps, which are apt to show themselves between the ages of twenty and fifty, appear to follow chronic catarrh and inflammatory conditions of the region of development. As already stated, it is only a relatively small proportion of such nasal polyps that are truly mucin-containing; the majority are simply œdematous.

LIPOMA.

The lipomas are sharply defined tumors composed typically of pure fatty tissue, that is to say, of fat cells lying in a vascular connective-tissue matrix. These cells are so abundant that but little else is to be recognized. The fat tends to differ from normal fatty tissue in being paler and not so deep-colored, while in general the individual cells are larger than those of normal tissue. Thus, even where situated in a fat-containing tissue, the neoplasm is well defined from the surrounding parts. In shape, these growths appear as rounded masses or frequently the tumor, while forming a single mass, is separated into a number of finger-like processes radiating from the central portion. This is especially noticeable in connection with subcutaneous lipomas.

In number, these tumors are most often single, but they may be multiple, in size they vary from minute, almost microscopic growths, such as are not infrequently met with in the kidney, to masses more than 30 kilos in weight (63 pounds), as in the retroperitoneal lipoma recorded by Waldeyer. We have recorded a similar case weighing more than 41 pounds.[1] These larger lipomata are often composed of multiple rounded or lenticular lobules, and show no tendency to form finger-like processes.

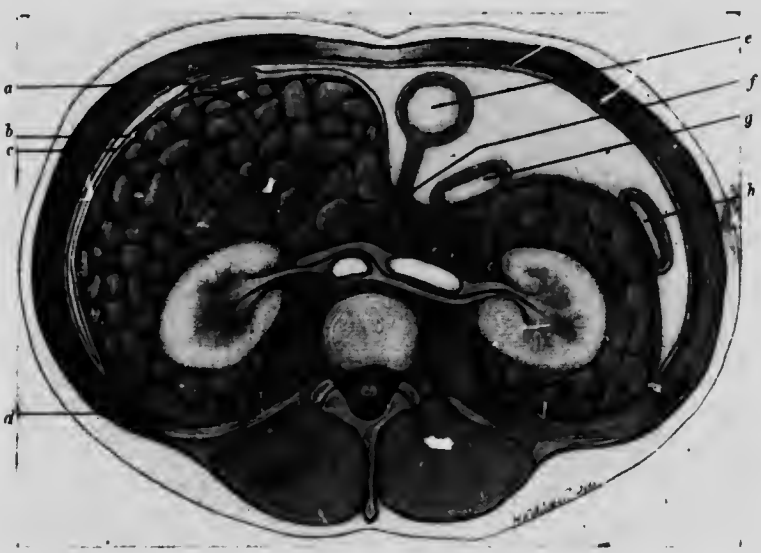
These tumors are essentially benign and of slow growth, nor do they recur after complete extirpation. They are liable to exhibit a restricted series of modifications; thus, the connective-tissue matrix may predominate, and separate off relatively small lobules formed of fat cells, in which case the tumor is of firm consistency; not infrequently the fat cells appear to give place to a more mucoid tissue, and the tumor then assumes a more jelly-like consistency; such cases are spoken of as *lipoma myxomatodes*. The pure lipoma, however, is also very soft and fluctuating, and the larger growths have very frequently been mistaken for cysts and localized collections of fluid. More rarely, portions of the tumor take on a sarcomatous development; at times the central portions of these tumors undergo necrosis, and thus oil-containing cysts may be formed within them. Several cases are on record in which nodules of cartilage, and in at least one case (Dreschfeld)

[1] On Perirenal and Retroperitoneal Lipomata, Montreal Med. Jour., 25: 1897: 529 and 620.

of true bone, have been found within the tumor mass. It is still an open question whether here we are dealing with preëxistence of cartilaginous or bony "rests" within the primary tumor mass, or whether we are dealing with metaplasia, a modification of the tissue being brought about by altered nutrition and cell relationship.

Regions of Occurrence.—Lipomas have been recorded from several regions of the body; most frequently they are found as subcutaneous outgrowths of varying size; these are especially common in the region of the shoulder; occasionally they are multiple; more rarely they may be symmetrical. Another form occasionally met with develops in the submucosa of the intestine, and here it is liable to

FIG. 215



Semidiagrammatic cross-section through a perirenal lipoma at the level of the renal vessels, seen from above. The perirenal and retrorenal fascia unite to form the transversalis fascia. The whole intestinal tract lies in front of the perirenal fascia: *a*, descending colon; *b*, perirenal fascia; *c*, peritoneum; *d*, retrorenal fascia; *e*, small intestine; *j*, superior mesenteric artery; *g*, duodenum; *h*, ascending colon. (Reynolds and Wadsworth.)

develop into solitary pendulous or pedunculate masses, which at times have led to intestinal obstruction. In the kidneys it is not uncommon to meet with minute nodules of fatty growth; rarely these may attain large dimensions (Warthin).[1] An organ in which they have rarely

[1] I cannot accept the guarded conclusions of Archibald and Keenan (Jour. of Med. Research, N. S., 11; 1907; 121) that these renal lipomas originate from aberrant and included adrenal cells. A simpler, and, I think, adequate view is that, like the renal fibromas and hypernephromas, they owe their origin to cells, in this case of connective-tissue origin, which have become nipped in between the renculi in the process of development.

been met with is the brain and its membranes; and here, again, they are of small size. Occasionally, also, there may be a lipomatous development in connection with the synovial membrane of the joints, in which cases rather flattened, much fringed processes project into the cavity. Tumors have also been met with in connection with the peritoneum, occurring here either in the mesentery or the omentum, or as excessive developments of one or more of the appendices epiploicæ, originating beneath the pelvic peritoneum. Larger forms have been recorded developing from the perirenal fat, which, in their growth, project forward, so as to push the peritoneum and the colon in front of them, the kidney tending to be compressed at the back of the tumor. In the huge retroperineal tumors it is noticeable that the mass continues to grow and to enlarge at the expense of the rest of the body; the patient may become markedly emaciated, the fat disappearing from the subcutaneous tissues and elsewhere.

Lipomatoid Conditions.—Just as in connection with the fibromas we noticed that there might be a progressive overgrowth of fibrous tissue, or fibromatosis, so here, to repeat, in connection with fatty tissue we have to recognize the existence of a condition of lipomatosis tending to be regional.

The "Hottentot apron" is clearly a racial or stock inheritance. Other conditions of general lipomatosis, even that developing late in life, are often familial. As indicated by the effects of thyroid treatment, they may be an indication of congenital lack of equilibrium between the tissues. Cases of *adiposis dolorosa* suggest strongly some trophic disturbance, and, as a matter of fact, Dercum, who has especially called attention to this malady, has reported two cases in which he has found disturbances of the pituitary, growths involving the nervous portion of this organ.

XANTHOMA.

The xanthoma is a small, benign, fatty tumor, as to the exact nature of which we are not as yet determined. Single or symmetrical xanthomata occur not infrequently as flat, subcutaneous growths of a yellow color affecting the skin in the immediate neighborhood of the eyelids near the inner canthus. They may be present as multiple small nodules beneath the skin, forming slight prominences on the palms of the hands, in the neighborhood of the flexures of the joints, etc.; these are occasionally found also in the internal organs. These tumors have a more or less abundant connective-tissue stroma, in which are larger cells, containing markedly yellow, fatty globules, which give the xanthomas their peculiar color and name. The pigment is stated to be of the nature of a lipochrome. It is with regard to the origin of these cells that there is grave doubt, some authorities regarding them as being of pure connective-tissue origin; others, again, as endothelial. In some cases, though by no means in all, there appears to be a relationship between the development of these and a condition

of cholelithiasis without definite jaundice, although the skin is often found distinctly sallow; others are obviously of congenital origin. While multiple, they never form metastases or take on malignant characters.

CHONDROMA.

Chondromas are tumors formed of one or other variety of cartilage, hyaline, fibrous, or reticulated (hyalo-enchondroma, fibro-enchondroma, reticulated enchondroma). They may be single or multiple, possessing in general a well marked fibrous capsule, and are globular, or, if of any size, distinctly lobulated. Two varieties are in general distinguished, the *ecchondroma* and the *enchondroma*, or chondroma proper, the former occurring as overgrowths of regions where cartilage is normally present and persistent, *e. g.*, they arise from the cartilages of the ribs, the larynx, trachea, and intervertebral disks. When these, as is most often the case, are in direct continuity with those cartilages, they should certainly not be classified as true tumors, for they have not an independent existence, but, rather, are local hypertrophies; I therefore include those ecchondromas under the heading of chondromatoid. Only where they have no connection with a parent matrix do we have true tumors. It will thus be seen that, clinically and histologically, it is at times difficult to draw a distinction between the ecchondroses, or such localized hypertrophy, and true and proper ecchondromatous development.

Therefore, in the chondroma proper, or enchondroma, we have to deal with well-marked independent nodules of cartilaginous growth. These enchondromata may occur in many regions of the body, notably in connection with the bones; they are also found in connection with the parotid and submaxillary glands, in the testes, mammary glands, the lungs, and, very rarely, in the corpus cavernosum, the ovaries, and other internal viscera. It is interesting to note that they never develop from the articular cartilages of joints, although they may form in the fringes of the synovial membranes, and thus give rise to single or multiple "loose cartilages" in joints.

As in normal cartilage, few or no bloodvessels are to be found in the substance of these tumors. This would seem to be the explanation of the lobulated character of the larger growths. Bands of connective tissue containing vessels divide the mass of the tumor, and afford nourishment. Growth occurs at the periphery, along the zone of the perichondrium, although in soft hyaline or myxo-enchondromata we obtain frequent evidence that the cells of the partly formed cartilage multiply actively; in short, obtain appearances such as are seen in the growing portions of fœtal cartilage. Where the growth is at all large there is a peculiar liability for the deeper cartilage to be replaced by true bony tissue (osteo-enchondroma); or, without the formation of true bone, there may be extensive calcareous infiltration (enchondroma petrificum). Again, in the large enchondromas, from the increasing

lack of nourishment of the central parts, as the tumor develops at the periphery, there may be a central degeneration and necrosis, the cells showing fatty degeneration, the interstitial substance undergoing liquefaction. If the tumor project beneath the skin, and, through ulceration, the necrotic centre comes to communicate with the exterior, a fistulous track is formed, which shows no signs of healing; then, if the whole tumor be not excised, the atonic character of the process is peculiarly apt to favor general sepsis. In the parotid and testes these tumors are in general mixed, there being combined overgrowth of cartilage and of the glandular tissue, and these mixed tumors, more especially of the testes, are liable to take on sarcomatous characters, and to become extensively malignant; these are solid teratomas (p. 603).

In these and in other chondromas there is a tendency to transition into myxomatous conditions; in place of a definite cartilaginous matrix there is a mucinous, intercellular substance, and the cells take on all the characters of mucoid tissue, with long, delicate processes traversing the matrix (*myxo-enchondroma*); or sometimes appearances are not so definitely myxomatous; then we speak of *enchondroma mucinosum*.

Fig. 216

Enchondroma exhibiting calcareous infiltration (*E. petrificum*). (Ribbert.)

As already stated, although these tumors are slowly growing and of firm consistency, and are in general of a benign type, only being dangerous on account of local disturbance of function, it is not infrequent that they form metastases. Here, at least, three different conditions have to be distinguished as favoring metastatic development: (1) in some cases, as, for example, in connection with the mixed cartilaginous tumors of the testis, there is a marked tendency for the growths to become more cellular and more sarcomatous in character; there is a definite assumption of malignant properties; (2) in other cases, as pointed out by Virchow, the tumor in its growth may penetrate into a vessel, and there may be extension along the vessel, portions of a young, rapidly growing process becoming detached and carried to the lungs and other organs; (3) in some cases, as in a slowly growing nodular chondroma of the mammary gland of the bitch, studied by Bontelle in our laboratory, neither of these conditions is discoverable, and the only explanation afforded of the numerous metastases in the lungs, etc., is that certain cells from the rather richly cellular perichondrium—chondroblasts—have gained entrance into the veins, and been brought to rest in the lung, and there have developed into fully formed cartilaginous tissue. This may be regarded as a variant to the first case; what we would again point out is that in such cases no portion of the tumor need show any evidence of multiplication of a sarcomatous type.

Studying the etiology of these tumors, it is noticeable how, in the majority of cases, they develop in childhood and early life. This is noticeably the case in chondromas developing in connection with bones, where, again, the condition is frequently multiple. Virchow has afforded a well-studied explanation of this condition. It is especially in those showing signs of rickets that these multiple chondromas develop. Now, in rickets the prominent disturbance is an undue preparation for the formation of cartilaginous bone, coupled with an incomplete or tardy formation of that bone. Thus, in the region of the epiphyses we find a very extensive cartilaginous development, and processes of this new cartilage project into what is destined to be the shaft of the bone, and here may become isolated and cut off from the main mass, and, as Virchow has shown in examining rickety bones, we may frequently meet with these minute islands of persistent cartilage. It would seem evident that these islands may, under certain conditions, take on an independent and aberrant growth, and give origin to enchondromata, or osteo-enchondromata, or sometimes true osteomata. In a certain number of cases the development appears to be hereditary, appearing in several members in one or two successive generations of a family, and in other cases traumatism appears to be a predisposing factor. According to Otto Weber, a history of traumatism can be obtained in 50 per cent. of cases of this form of tumor.

In yet other regions of the body it is probable that embryonic or developmental rests afford the nidus for the development of these tumors; indeed, most modern authorities are inclined to lay down that in every case we have to deal with these as a prime factor.

Thus, it has been pointed out that parotid enchondromas originate from cartilaginous remains of the hyoid arch; chondromas occurring in the neck, from the remains of other branchial arches; chondromas of the testicle, from portions of the "anlage" of the vertebral column included in the developing testis when it lay against the vertebral column before its migration to the scrotum; and chondromas of the mammary gland, from included portions of the sternal cartilages.

For ourselves, while in certain of these instances we are inclined to believe that this is the explanation, we are far from prepared to accept it as the general rule. Why, for example, should cartilaginous tumors of the testis be relatively so common, while those occurring in the homologous organ, the ovary, are so very rare? Why, again, should enchondromas be liable to occur in mammary glands and not in the skin and other structures situated over the sternum, or in the anterior mediastinum? The mammary gland develops as a downgrowth from the skin, and has no special close relationship to the costal cartilages. I cannot, therefore, but consider that in some cases the "anlage" of the chondroma has to be sought for in the metaplasia of the connective-tissue cells of a glandular organ, brought about by some modification in the nutrition and vascular supply of the part. The not infrequent occurrence of cartilaginous islands in other forms of connective tissue tumors of old standing would seem to favor this view; as, again, does

the obviously metaplastic origin of some overgrowths formed of the closely allied tissue—bone (see p. 673).

The loose cartilages in joints, when truly cartilaginous, and not merely fibrous, are found to occur more especially in those of a rheumatoid tendency, and to develop not in connection with preëxisting cartilage, but in the synovial fringes, which either are originally finger-like, or, through the growth of the cartilage within them, become more pedunculated, the pedicle then becoming twisted or broken off.

Here, then, in connection with the chondromas, we again see the action of certain tendencies leading to the formation of the tumor: (1) heredity in some cases; (2) the production and subsequent growth of developmental "rests" in others; while, again, (3) traumatism or irritation in a certain proportion of cases seems to afford the stimulus for progressive growth.

OSTEOMA.

In the sense in which we speak of fibromas and lipomas, that is to say, as defined tumors having a growth of their own, independent of the tissue in which they find themselves, *true osteomas are distinctly rare*. Osteomatoid conditions, on the other hand, are very common; of these, in fact, there is a bewildering variety. A mere metaplastic formation of bony masses in another tissue ramifying between the cells of that tissue cannot be regarded as a tumor proper; it has not an independent growth; the growth is determined by the vessels and nutritional conditions in that tissue. Rarely, however, such metaplastic bone is found to take an independent growth. We will, however, distinguish the various forms of what are not osteomas after laying down what constitutes a true osteoma and describing such.

The true osteoma may occur in connection with preëxisting bone (homoplastic), or apart, and in other tissues (heteroplastic). In the former case it may be superficial and derived from the periosteum, or may be within the bony substance (endosteal), and then originating either from (*a*) a misplaced area of epiphyseal cartilage, which takes an independent development, as other cell rests are capable of doing; or (*b*) from the medulla, in which case it exhibits no cartilaginous fore-stage. It may either be dense and ivory-like, or loose and spongy, but always, in the case of true osteoma, instead of there being gradual and imperceptible transition from the new-growth into the surrounding bone, there is central growth and expansion outward, so that there is produced a condensation of that surrounding bone, followed, as the tumor continues to expand, by progressive absorption, until, in the shaft of a long bone, one of these tumors may, even if itself of loose, spongy structure, eventually cause such thinning of the shaft that fracture ensues.

Tumors of this nature, endosteal, though rare, do occur. Another, more compact form, must here be included. Occasionally within the shaft of long bones, somewhat more frequently in the antrum of Highmore,

or other nasal fossa, again at the base of the skull in the region of the cribriform plate, there develop dense, indurated, bony masses. In such cases there is frequently the history of inflammation—thus, in the antrum, the growth most commonly proceeds from round the root of a tooth that has been inflamed or displaced, and so, at first, the condition in these cases would appear to be one of inflammatory overgrowth. But later the growth appears to be independent, and of a wholly different type, either from normal bone or inflammatory osteophytes, and, though such masses show more or less of a pedicle of attachment, the fact that cases are on record in which the nodules have been found free—and dead—in the antrum, would seem to show that, with continued growth, this pedicle of normal bone is liable to be absorbed.

Of the *heteroplastic osteomas*, the simplest type is the periosteal isolated tumor occurring free in the immediate neighborhood of a bone. Here, either congenitally, in the course of development, a portion of periosteum becomes displaced, and sooner or later takes on independent growth, producing a bony nodule, which it surrounds, or, as appeared to be the case in a youth, a patient of my colleague, Dr. Archibald, through injury a portion of periosteum became wholly displaced from the bone into the surrounding tissues, and eventually gave rise to an independently growing nodule. Such tumors of periosteal origin, as, also, some of the endosteal tumors, show no preliminary cartilaginous stage.

The other type is that of the ossifying chondroma, or true osteochondroma. We have shown that, whether by metastasis, or metaplasia, or as cell rests, chondromas may occur in the soft tissues. Here they may become the seat of calcareous infiltration (which is not true bone formation); or, on the other hand, by vascularization they may in their main bulk be converted into true bone. The growing surface remains cartilaginous, but within, true Haversian canals, and a marrow, red or fatty, become developed. Such osteochondromas may be met with also in connection with bone, originating from misplaced epiphyseal cartilage.

Here must be mentioned another true blastoma, the *osteofibroma*, or *fibro-osteoma*. We have once encountered a small specimen of this, by chance, in the medullary cavity of the femur, lying sharply defined, and shelling out without difficulty. The main constituent is a spindle-celled fibrous tissue, which, however, has the tendency to give origin to bony lamellæ and spicules. This form evidently originates from bone-marrow

The sharply defined nature of our specimen, despite its cellular character, showed that it was not to be included among the sarcomas. Other cases closely resembling this, but infiltrating and more cellular, must be classed as *osteofibrosarcoma*. But of the bone sarcomas we will speak later.

Let us repeat, *the true osteomas are rare* compared with the large number of cases which familiarly receive this name. These we must attempt to classify.

Osteomatoid.—All cases, in the first place, of localized or general overgrowth of the bones in which the growth is not defined from the normal bone, is not independent, and is of unknown cause (save that we may, in some cases, recognize congenital or inherited influences), must be classed under this heading. Here are to be included *hyperostoses* proper; among these:

1. Idiopathic general periosteal and endosteal *hyperplasias* affecting one or several bones. The long bones here are specially found affected, and, through the periosteal overgrowth, may assume remarkable forms.

2. *Enostoses*, localized and fairly circumscribed growths within bones, not so circumscribed and defined as to be independent of the surrounding bone.

3. *Exostoses*, processes of various grades rising from the surface of a bone, more particularly along muscular and tendon attachments. They may, however, be apart from these, as on the bodies of the vertebræ (where they are nodular, and often symmetrical, and so, evidently, of congenital origin). A special form is the *ivory exostosis* of the skull, small, button-like elevations of the cranial vault, which, by their intense hardness, are sharply demarcated. The periosteum over these is continuous with the surrounding, and, while the outer layers are singularly dense and compact, internally the growth passes imperceptibly into the underlying bony tissue. These cannot, therefore, be regarded as true osteomas. At the ends of the long bones may be found one or several *exostoses cartilaginea*. These arise either from the epiphyseal region or are terminal, and, like the joint surface, are covered with cartilage. They may thus be regarded as *ossifying ecchondroses*. Closely allied to these is the *exostosis bursata*, in which, in addition, a synovial covering, with synovial cavity and fluid, is present over the free end. Such appear to have developed originally from the cartilage at the edge of the joint. Their synovial cavity may communicate with that of the joint, or be free. Sometimes an extraordinary number of minute secondary synovial cysts are in connection.

In the second place, there are some conditions of bony growths apart from the skeletal elements which should, perhaps, be here included. Such, for example, are: (*a*) Bony masses occurring in tendons, and not connected with the bone insertion. Every transition occurs from the tendinous exostosis of varying length to these free masses. They grow with the organism, and then remain stationary, exhibiting no tendency to independent overgrowth. (*b*) Bony plates in the dura mater and falx cerebri. These are generally small and flat, and are best ascribed to a persistence of the primordial bone-producing property of the dura. More extensive bony development in the membranes of the cord are associated with chronic inflammation. (*c*) Penile bone formation, as seen in some animals and in certain African tribes, a congenital ossification of the connective tissue in the part (here, again, inflammatory processes may produce the condition when not congenitally present). (*d*) *Myositis ossificans*. Here we deal with an extraordinary and slowly progressive development of bone within

one set of muscles after the other, replacing the muscle tissue proper, and bringing about complete rigidity and fixation of successive portions of the body. Despite several studies of recent years (the condition having shown itself not to be so rare as was for long thought to be the case), we are still far from understanding the succession of events, save that it is generally accepted that it is *not* a myositis, not an inflammatory process. After having replaced the muscle, the bone shows no tendency to progressive growth. Provisionally this appears to be the place in which to note this condition, in immediate relationship to:

Metaplastic Ossification.—Here, as already noted in discussing metaplasia, we have in general an alteration of the structure of a part, most often brought about by inflammation, though it may also accompany senile changes in a tissue, and, following this, a development of true bone. We may here note in order the main examples: (1) The myositis ossificans above described, if due to general constitutional vice, is also a metaplasia; (2) ossifications in the adductors in cavalrymen, in the deltoids of [illegible], etc.; in both cases the result of irritation—in the one case, from repeated contusions of the muscles in riding; in the other, likely from carrying and firing the gun; (3) in the choroid, the eye; (4) in the brain (rare), apparently following upon inflammation; (5) in the spinal pia mater, as already noted, from leptomeningitis; (6) in the heart valves and arterial walls; (7) in the respiratory channels and lungs. Here several conditions are to be noted. In the trachea, besides ossification of the cartilages, there may be definite nodular submucous bony outgrowths, which in some cases are extensive, and apparently so independent that they may be classed as osteomas proper. Most often, however, they are in connection with the cartilages and perichondrium. It is where they are associated with this by a fine pedicle, which may undergo absorption, that independent growth is liable to occur. In the lungs there may be scattered, irregular masses, which develop from the bronchial cartilages, or a wholly different condition of ramifying, coral-like tubes, apparently the outcome of chronic peri-arteritis or periphlebitis, with laying down of bone in the overgrown and degenerating fibrous tissue; (8) in old pleural and pericardial exudates. Here we most often have calcification, but true bone may be later developed; (9) in various tumors, lipoma, fibroma, angioma, and even in malignant sarcomatous growths and cancer (carcinoma ossificans); (10) in the middle coat and deeper layers of the intima of the aorta. The variety of the growths in which this may occur and the variety of their sites make it impossible to regard the process in them as other than metaplastic. The same must be true in a specimen prepared by Dr. Klotz, in which the outer layer of a phlebolith from the prostatic plexus exhibited true bone formation.

ODONTOMA.

As with bone proper, so with the teeth; pure blastomas would seem to be rare, blastomatoid conditions the common overgrowth, not

Fig. 217

Odontoma. (Garretson.)

independent of the cement or dentine or alveolar periosteum. Yet true odontomata undoubtedly occur.

CHAPTER XIX.

TYPICAL HYLIC TUMORS—(CONTINUED)

BONE-MARROW TUMORS: MYELOMAS.

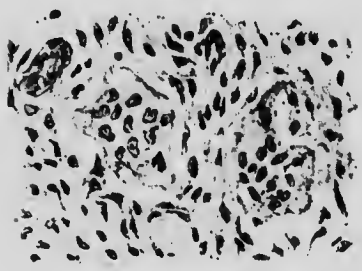
THERE is a remarkable—and debatable—class of tumors which, at first sight, morphologically resemble the atypical connective-tissue tumors; but although in them, as we so frequently note with other hylic tumors, there are transitions, and, from what is apparently a benign growth, we gain sarcomatous development, yet characteristically the members of this group are not malignant; they do not infiltrate other tissues; they do not form metastases; and, studying these neoplasms more carefully, we become convinced that we are dealing, not with kataplastic cell elements—with the growth of cells, that is, which have become undifferentiated—but with cells *which, when at their fullest development, are of relatively simple type*, with what are benign overgrowths of one or other of the constituent cells of the bone-marrow. On these grounds it is well to separate tumors so formed from the sarcomas proper; the evidence, we think, is sufficient to justify us in treating, and, what is more, the clinical characters render it eminently wise to treat, these tumors as a class apart, as typical, and not as atypical, growths.

The bone-marrow, it must be remembered, contains many different elements, and the genetic relationship of these elements is still a matter of active discussion. But these elements have, obviously, specific functions which are strongly impressed upon them, and persist through the life of the individual. On the one hand, we have the cells directly concerned in bone function and regulation, the osteoblasts and osteoclasts, or myeloplaxes; on the other hand, the remarkable series of erythroblasts, myeloblasts, and also lymphoblasts—of mother cells of the red blood corpuscles and leukocytes. The functions of these two orders of cells are wholly different, and, with recognition of the existence of the different forms, evidence has rapidly accumulated of late years that not only may there be overgrowth of one or other order, but even overgrowth of one particular form, while the apparently divergent facts that have been gained come very largely into line if we apply the same principles to these as to other connective-tissue tumors, and recognize three orders of growths: (1) typical blastomas; (2) blastomatoid diffuse overgrowth; and (3) atypical blastomas, either (*a*) of primary origin, (*b*) as secondary developments from typical blastomas, or (*c*) developing secondarily from blastomatoid overgrowth. These atypical developments come all under the heading of sarcoma, and

will in the main be treated along with other atypical hylic tumors. The other two conditions we may here briefly pass in review.

The Giant-celled Myeloma ("Giant-celled Sarcoma").—Giant cells—multinucleated cells—are common to, or may be met with in, almost all orders of tumors. Their characters differ. Von Hansemann recognizes three distinct forms: (1) The *foreign body giant cell* found in connection with necrotic and degenerating areas. This is identical in character with that already described as occurring in the tubercle, having a peripheral or polar collection of nuclei and central hyaline or necrotic substance. (2) *Parenchymatous giant cells.* The former class is of endothelial and leukocytic origin; here we deal with modifications of the cells proper of the tumor, brought about by irregular mitosis and lack of cell division, following upon nuclear division. Where this is the case the constituent nuclei are characteristically variable in size; often some are joined by bridges, or fibrils; others lobulated. Giant cells of this order may be found in cancers; they are especially common in endotheliomas. (3) *Myeloplaxes.* These differ from the first class in that the nuclei are distributed evenly through the cell body, and in the absence of central degeneration of that body, and from the second, in that the nuclei are well formed and of uniform size. They are present normally in the red marrow of bone, as osteoclasts in Howship's lacunæ, and are the characteristic constituent of the form of growth now under consideration; here they may be present in enormous numbers. Under pathological conditions they are developed both in the marrow and from the periosteum. What is their relationship to osteoblasts is still a moot point. Some regard them as derived from the adventitial cells of the bone vessels, and certainly, even in neoplastic growths, they appear to be intimately associated with fine capillaries; others as of endothelial origin. Ritter regards bone building through osteoblasts, and bone absorption through osteoclasts, as brought about by two states of one and the same order of cell. Kölliker held similar views; Pommer and Wegner have noted transition from osteoclasts into spindle cells and fibroblasts. (4) Yet another giant-cell, the sarcoblastic type, will be described later (p. 693).

FIG. 218

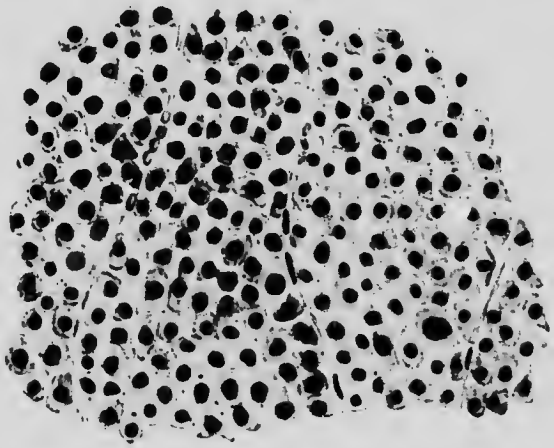


Giant-celled myeloma of bone. (After Ribbert.)

The giant-cell myeloma, then, has the following characteristics: It grows locally, most often in the shaft (marrow) of long bones, or of the jaw; it may also be of periosteal origin (as in the giant-celled epulis of the jaw); its growth is expansile, leading to absorption of the surrounding bone; it is abundantly vascularized; *it does not form metastases*, save in the infrequent cases in which it undergoes sarcomatous modification (see later); it does not recur on complete

removal, and, as recently shown, to prevent recurrence it is only necessary to remove the portion immediately involved, with very small surrounding zone; histologically, it exhibits a body formed mainly of short spindle-celled elements of fibroblastic type, somewhat irregular in shape, varying from the typical spindle to polygonal cells, and among these are abundant giant cells of the type described above. As in the fibro-osteoma (which is apparently closely related), so here, there is a tendency to the formation of bony lamellæ and spicules throughout the tumor, although the more abundant the myeloplaxes in an area, the less the amount of bone formation. A smaller, more round-celled matrix is the indication, we hold, that the tumor has taken on sarcomatous characters, and that metastases and recurrence may be feared.

FIG. 219



Section of myeloma of vertebra. × 600. (S. Saltykow.)

Myelomatosis (Myeloma Multiplex).—From this we pass to a condition that has recently attracted much attention. As indicating its general character, we cannot do better than quote Borst's[1] description:

"The condition always (according to Winkler) affects the red marrow (vertebræ, ribs, cranium), and this is converted into a dark-red or reddish-gray or grayish-yellow tumor mass. It is a *primary multiple process*, showing itself simultaneously in bones widely apart; a sharp limitation of the multiple growths is often impossible; these are at times soft and pulpy, at times more firm. The spongiosa and even the firm shafts of the bones become absorbed, so that the tumor masses may show themselves immediately under the periosteum, which may here and there be ruptured. Fractures are common, as are also giving-way and distortion of the vertebræ. What is remarkable is that the affection remains confined to the bony system; in pure cases there is no involvement of the lymph glands, no swelling of the spleen,

[1] Loc. cit., 1: 493.

no metastases in the internal organs. At times the progress of the disease is accompanied by intermittent fever and pains in the bones and joints. The blood in general is gravely altered; severe forms of anemia, pernicious anemia (Grawitz), and albumosuria are, to a certain extent, characteristic of the affection (Seegelken, Bence Jones, Nannyn, etc.)."

The condition, indeed, has been observed for many years, but under different names and with most diverse ideas to its nature (malignant osteomyelitis, myelogenous pseudoleukemia, sarcomatous ostitis, lymphadenia ossium). This clear presentation of its features demonstrates that the condition comes under our class of blastomatoid states. To speak of it as myeloma is incorrect if we respect our definition.

When we come to study the histology of these cases we meet with great variations in individual cases. Taking, first, the pure cases, it is noticeable that there is no overgrowth of the myeloplaxes, nor any indication of implication of the osteogenic marrow elements. The tumor cells are all such as are derivable by overgrowth from the cytoblastic elements of the marrow, are of the myeloblastic or lymphoblastic type; sometimes mixed, more often corresponding to one or other type, so that it is becoming recognized as possible to distinguish different forms of the affection.

It cannot be said that the exact relationship of these myeloid cells has been absolutely determined: some authorities refer to them as myeloblastic—and such may well be the case; others describe the form most commonly seen as composed of cells of the plasma-cell type with eccentric nucleus.[1] If we are correct in regarding cells of this last order as of lymphoblastic origin, then such cases must be classed as lymphomatoid rather than myelomatoid. It may indeed be that we have to recognize myelomatosis without leukemia and blastomatoid overgrowth of the lymphocytic elements of the bone-marrow without leukemia.

There are also impure cases: (1) in which the condition develops into a definite sarcomatous state, with metastases and infiltration; and (2) in which the lymphoblastic tissues and myeloblastic tissues in other parts of the body are, from the first, or become eventually, affected, and take part in the overgrowth, when we have myelomatosis complicating, or being complicated by, pseudoleukemia (Hodgkin's disease); (3) in Hammer's case, and possibly, also, in Baumgarten's, there was, in addition, extensive osteosclerosis and thickening of the spongiosa in all the bones; the former of these was of the first type, with eventual round-celled sarcoma; the latter of the second, with coincident involvement of spleen and lymph glands; whether here was an accompanying osteogenic myelomatosis must be left an open question.

Myelogenous Leukemia.—In the above cases while there is diffuse overgrowth of specific orders of cells of the bone-marrow, these cells do not become discharged into the blood to any marked extent. There are other conditions in which with similar diffuse overgrowth of the bone-

[1] See Christian, H. A., Trans. Assoc. Am. Phys., 22: 1907: 145.

marrow there is abundant discharge of the cells into the circulation, so that we obtain a condition of myelocythemia, myelogenous leukemia, or, as it is often termed, mixed leukemia. In this what is characteristic is the presence in the blood of large numbers of an abnormal element, namely, of large mononuclear cells with neutrophilic granulations, although there is at the same time a relative or actual increase in the number of eosinophiles; "mast cells" are apt to be increased in frequency and similarly normoblasts are often met with—*i. e.*, nucleated red cells. The ordinary red cells are reduced in number, the white cells enormously increased, until they may be more numerous than the red, and these myelocytes may form one-third or more of the total white corpuscles.

When the marrow of the bones is examined it is seen to exhibit a striking hyperplasia: often it is reddened. On examination the main elements present are the *myelocytes*—large cells with neutrophile granulation similar to those seen in the blood—so also there are nucleated red corpuscles (erythroblasts) and frequent cells, large and small, with eosinophilous granules. An associated anatomical character is the great enlargement of the spleen, causing this to be often spoken of as "splenomyelogenous leukemia." With Ehrlich we regard this not as a primary but as a secondary condition, due to accumulation rather than formation of the blood cells. In the liver and in the kidneys there are in some cases leukemic tumors due it would seem to active growth of the myelocytes outside the capillaries.

We have, briefly, the picture of an excessive growth of "leukoblastic" elements of the bone-marrow, at times confined to the bone-marrow, and at times—and it would seem secondarily—in other tissues of the body.

Chloroma.—In close relationship, in fact, as one member of this group, must be included chloroma. This is a form of growth characteristically multiple found in association with the bones of the face (orbit) and skull, affecting also the vertebræ and, more rarely, the ribs and bone-marrow, which, on first removal and examination, show many of them (not necessarily all) a striking greenish or greenish-yellow tint, which may tend to fade upon keeping the specimens.

The disposition of these tumors is strongly suggestive of periosteal or bone growths, and as such Chiari has regarded them; but, as Dock[1] pointed out, they show none of the elements found in ordinary periosteal tumors—no spindle or giant cells, and no tendency to bone formation. Their appearance is that of a lymphoid overgrowth, with a well-marked reticulum, in which lie medium-sized round cells. Still more suggestive is the fact, to which Dock particularly has drawn attention, that, associated with this condition, is a type of leukemia in which, as shown by Dock and Warthin,[2] the prevailing cells are of the large lymphocyte, or, more accurately, of the myeloblast type. We deal here, evidently, with an aberrant form of myelomatosis. In some cases a co-existent lymph-glandular tuberculosis has been recorded, but this bears no direct relationship.

[1] Am. Jour. Med. Sci., 106; 1893: 152.

[2] Medical News, N. Y., 1904.

There is still debate as to the nature of the pigment, which some find present in the form of highly refractible minute droplets or granules, others regard as universally diffused. Some (Chiari, Huber) hold it to be a lipochrome; others (Dock) can find no evidence of the presence of fat.

LYMPHOMA AND LYMPHOMATOSIS.

Although, inevitably, such a course leads us to consider various conditions on the borderland between the atypical blastoma and blastomatoid conditions[1] rather than states of typical blastoma, we here, naturally, pass from the bone-marrow to the allied lymphoid tissues and their overgrowths, and, doing so, have to admit that the time is not ripe for a full classification of this most complicated group of conditions; as, again, that our treatment of the problems involved can be but summary.

Nevertheless the work of the last few years has very materially illuminated what had been a very obscure subject. We would note especially the studies of Kundrat,[2] Löwit,[3] Sternberg,[4] Türck,[5] Yamaska,[6] Dorothy Reed,[7] and MacCallum,[8] and when to these we add a recognition of the existence of blastomatoid states, as here put forth, and apply this, we are inclined to believe that the different conditions fall into a natural grouping, even if we have to admit that there are transitional cases, intermediate between the various classes, along with other cases of relationships that are still uncertain.

The terminology of these lymphomatous states is, we admit, appalling —not so much the terms themselves as the diverse meanings given by different observers: pseudoleukemia, lymphadenoma, lymphosarcomatosis, to mention but a few, have very different meanings in the writings of different men. These terms we will not discuss. Rather we will lay down in the first place (1) that just as we recognize that the lymphocytes and what it is convenient to term the leukocytes (the polymorphonuclears and the eosinophile cells) have distinct origins, so it must be kept in mind that we have distinct if fairly parallel series of blastomatous and blastomatoid conditions, owing their origin to aberrant growth in connection with the tissues giving origin to these two orders of cells; (2) that just as upon analysis we determined that among the overgrowths of fibroid tissue a series of distinct conditions were to be made out from chronic inflammatory hyperplasia to the typical fibroma, and, eventually, to the fibro-sarcoma, so here we have an identical series.

[1] It will have been observed that similarly we recorded no typical as distinct from blastomatoid conditions.

[2] Wiener klin. Woch., 1893, Nr. 12.

[3] Lubarsch and Ostertag, Ergebnisse, 8 (7th year): 1902: 36.

[4] Ibid., 12 (9th year, Pt. 2): 1905: 360.

[5] Berlin. klin. Woch., 1901.

[6] Zeitschr. f. Heilkunde, 25: 1901: 200 and 313.

[7] Johns Hopkins Hospital Reports, 10: 1902: 133.

[8] Trans. Assoc. American Physicians, 22: 1907: 350.

Accepting these two postulates, the various conditions fall into a comprehensible order. To discuss them it is well to clear the deck by first casting overboard the conditions due to overgrowth of the "leukocyte" producing tissues (as distant from the lymphocyte). This we have already attempted to do. The leukocytes originate from the myeloblasts. We have seen that these myeloblasts have their seat in the bone-marrow: that this marrow contains specific cells of different orders, namely, osteoblasts (with osteoclasts) and myeloblasts, along with other cells which are not specific—lymphocytes (lymphoblasts) and connective-tissue cells (fibroblasts). Tumors derived from these specific cells we term myelomas, and of these we recognize the two main orders of the giant-celled myelomas and the various conditions due to overgrowth of the myeloblasts (and myelocytes), namely, myelomatoid or myelomatosis (myeloma multiplex), and what may be termed myelomatosis gravior, with escape of the proliferating cells into the blood, namely, myelogenous or mixed leukemia (in which the cells escaping into the blood possess granules and resemble myelocytes), and chloroma, in which the escaping cells are of the more primitive myeloblastic type without granules. We now can approach the lymphadenoid overgrowths proper. These are:

1. **Chronic Hyperplasia** (comparable with chronic inflammatory fibrosis). Some of the best examples of this are seen in connection with tuberculosis. In this connection there may be either (*a*) specific granulomatous change in the lymph glands with caseation, or (*b*) at times a diffuse enlargement of the glands without caseation, with marked fibrosis of the glands, prominence of large endothelial cells and diminution over large areas of the masses of lymphocytes. Along with other observers we have encountered cases showing distinct evidences of tuberculosis elsewhere with general firm enlargement of the mesenteric and other lymph glands without the presence in them of recognizable tubercle bacilli.

Such cases may be described as *paratuberculous lymphadenitis*. Cattle, more particularly, show this tendency to profound hyperplasia, suggesting that in them (and in those human beings exhibiting a like change) there is a constitutional tendency to excessive overgrowth of this tissue following upon the stimulus of certain toxins.

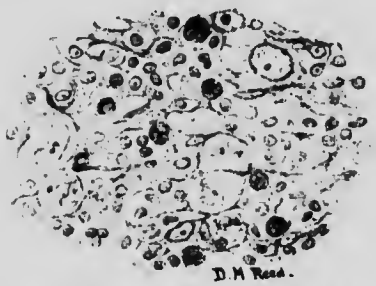
2. **Hodgkin's Disease** (comparable with cheloid). In the above cases we deal with a known irritant as exciting cause of the lymphadenoid hyperplasia. There is a condition of widespread enlargement of the lymph glands of chronic inflammatory type in which so far the exciting cause is not known, although many cases (although very far from all) regarded clinically as such have been found eventually to afford evidences of tuberculosis, and to have possessed similar histological features. These cases with unknown cause constitute Hodgkin's disease.

In general, the cervical lymph glands are first affected, becoming greatly enlarged, and consolidated into dense masses; then, progressively, the axillary, inguinal, retroperitoneal, bronchial, mediastinal, and mesenteric glands may show enlargement, and enlargement of the spleen makes its appearance. Later, the liver undergoes enlargement,

and at autopsy may show a diffuse lymphoid infiltration along the bloodvessels, notably the portal branches. The same is true in the kidney. In extreme cases the peritoneal and other serosæ, the submucosa of the intestines and other areas become also involved. *The lungs remain free. The blood shows no pronounced change, no advanced leukocytosis.* There is often an intermittent febrile or subfebrile state.

The histological characters are very different from those of leukemia. Taking first the enlarged groups of *lymph glands*, these show *no signs of infiltration*. In this we have a strong distinction from lymphosarcoma. The marked feature is the reticular and connective-tissue overgrowth similar to what is noticed in the tuberculous group. *There is a relative, if not actual, reduction in the lymphocytes and cells of the germ centres, a marked prominence of the larger cells of endothelial type, with often a marked abundance of eosinophile cells.*[1] The connective tissue, reticular and endothelial overgrowth is the marked feature. The same is true in the spleen. The organ is dense, fibrous. There is a remarkable increase in the connective-tissue elements of all parts, capsule, trabeculæ, vessel walls, reticulum of the sinuses, so that splenic pulp proper is greatly reduced, and the narrowed sinuses show endothelial overgrowth, or large of the cells, with loosening of the same. The lymphoid tissue along the vessels is present, but is not a marked feature.

FIG. 220



Section of enlarged lymph gland from a case of Hodgkin's disease, showing prominence of cells of large endothelial type, with occasional eosinophiles. (D. M. Reed.)

The appearances are different in the *liver*, *kidney*, and other regions where normally lymphoid tissue is little noticeable. Here it is the lymphoid cells that are the main feature. Some lymphocytes are always present in connection with the perivascular sheaths of the vessels. Now, around these vessels we find dense collections, but on examination these are found to be provided with a reticulum, and not to infiltrate the tissues, though they may cause atrophy of the constituent cells. Here we deal with a *lymphoid hyperplasia*. The same characterizes the subserous growth, if present. *The condition is not one of metastasis.*

The marked contrast between the involved normal glands and spleen on the one hand, and these secondarily involved organs on the other, strongly suggest that in the one we are dealing with reduction of the lymphoid elements, in the other with a compensatory hyperplasia. It may well be that in the early stage in the lymph glands there is

[1] To this Miss D. M. Reed (loc. cit.) has called particular attention.

similar lymphoid hyperplasia,[1] followed by exhaustion or atrophy, as the connective-tissue overgrowth progresses.

The picture, it will be seen, is wholly unlike that of malignant growth. *To speak of Hodgkin's disease as a form of lymphosarcoma or as a lymphomatosis is absolutely unjustified.* It approaches much more nearly to the results of chronic irritation.

3. Closely allied to Hodgkin's disease is a condition which has been described by Schottelius and by Gross,[2] and of which two cases have been studied at the Royal Victoria Hospital by my colleague Dr. Keenan, in which the earliest lesion has been an enlarged and apparently inflamed subcutaneous lymph gland tending to ulcerate, unaffected by ordinary treatment and in which, despite excision, there has been extension locally along the lymphatics with involvement of the related lymph glands, which on section resemble those of Hodgkin's disease. In one of these Professor Ewing, of New York, by intensive staining reported the presence of tubercle bacilli. These have been described as granulomatous lymphomatosis: more accurately they are granulomatous hyperplastic lymphadenitis.

4. In **leukemia**, on the other hand, we have what is characteristically a lymphomatoid condition, comparable in every respect with fibromatosis. Here we find localized *overdevelopment* of *typical lymphoid tissue*, the different constituents, reticulum, sinuses, and cells, being developed in due proportion. Now this is more restricted to the spleen or certain groups of lymph glands, now more widely developed, involving both spleen and glands, and also the lymphoid tissues of the bone-marrow. Eventually it may also, as in Hodgkin's disease, secondarily affect the liver and other organs, but the growth is not to the same extent as may be found in the latter condition. Of indications of inflammatory overgrowth the indications are slight; through distension the capsules of individual glands may become thickened, and they may become compressed into large consolidated masses, but the reticulum shows no corresponding overgrowth. So, also, in the spleen the trabeculæ may be somewhat thicker than normal, but in general this organ, despite its frequently enormous size, shows singularly little recognizable departure from the normal under the microscope, save that the lymphoid elements, the Malpighian bodies, are large and somewhat diffuse. As distinguished from malignant growth, the lymphoid hyperplasia respects boundaries and shows no signs of infiltration.

The main clinical and diagnostic distinction between this and the Hodgkin's type is that with this overdevelopment of otherwise normal lymphadenoid tissue there is the passage into the blood of excessive numbers of lymphocytes, whence the name of leukocythæmia (Bennett) or leukemia (Virchow). As already indicated, we believe in the existence of a group of cases which essentially belongs to this class (corresponding

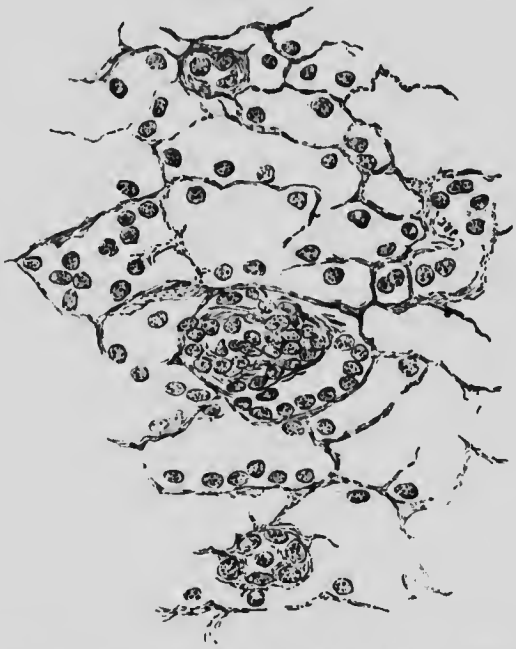
[1] This has been described by MacCallum and others.

[2] Ziegler's Zeit., 39: 1907: 405.

to that of myelomatosis without leukocytosis), namely, of lymphomatosis without lymphocytosis, or a pre-leukemic stage of leukemia. This may eventually develop into a true clinical leukemia, or, on the other hand, may develop up to a certain stage and there remain latent, with no further overgrowth; or, lastly, may slowly retrograde. Here, and not with Hodgkin's disease, must be placed some cases, at least, of idiopathic splenic tumor of children and adults.

5. **Typical Lymphoma** (comparable with typical fibroma). It is obvious that when lymphadenoid tissue is laid down so diffusely through the organism, it becomes a matter of peculiar difficulty to recognize a

FIG. 221



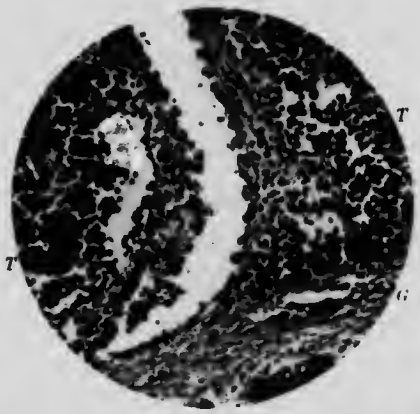
Lymphosarcoma, penciled to remove the cells in large part and show the characteristic stroma. (Le Count.)

typical lymphoma and distinguish it from mere localized hyperplasia of a preëxisting lymph gland. The fact that atypical lymphoma occurs indicates that the typical blastoma must also exist. We know of one such case recorded, that by Le Count. Kundrat likewise recognizes the simple local regionary lymphoma.

6. **Atypical Lymphoma.— Lymphosarcoma.**—When we recall that the lymph follicle contains tissues of more than one order—vessels and endothelium—along with the specific lymphocytes, it becomes evident that there may be several forms of sarcoma originating therein—spindle-celled, simple round-celled, etc. These scarce come into the category

of atypical lymphoma, save that it is almost impossible to state whether certain round-celled forms of sarcoma represent the most anaplastic and malignant type of lymphoma. Here we refer more particularly to two orders of tumors, well distinguished by MacCallum, both coming under the class of Kundrat's lymphosarcomatosis. The first order is encountered in the thoracic region, apparently originating most often from the remains of the lymphoid tissue of the thymus. It is a small round-celled growth, difficult to distinguish from the ordinary small round-celled sarcoma, but differing therefrom in the growth being *purely local and infiltrative*, spreading around the great cardiac vessels into the parietal pericardium, heart walls, and roots of lungs, involving the mediastinal and lymphatic glands, but not forming distant metastases—the spread, that is, is local and by the lymphatics not by the blood. The other originates as a primary lymphosarcoma of the intestinal submucosa infiltrating locally so as to enclose organs like the adrenal and pancreas and similarly spreading in the main by the lymphatics. The cells of this type are larger and there are interspersed phagocytes.

FIG. 222



Sarcomatous transplantation. Abdominal lymphosarcoma; section through two of the close-set small growths: *T T*, covering the surface of the liver *G*. (Martin.)

7. **Lymphosarcomatosis.**—Such tumors, however widely they infiltrate, are, I hold, wrongly termed "lymphosarcomatosis:" they are and they remain local. The termination—osis—is employed more correctly to indicate a generalized condition, and such multiple diffuse true lymphosarcomatosis is on record—what may be termed a malignant lymphomatoid state. Thus Göppert has noted the case of a boy of three years in which there was great enlargement of the thymus, enlarged tonsils and cervical glands, some enlargement of the spleen, enlarged liver and kidneys, and everywhere the affected areas exhibited infiltrating masses of small round cells. These were present also in the pericardium, renal pelvis, and periosteum. There was a slight leukocytosis.

It will thus be seen that these various conditions fall into three main

types: (1) proliferative lymphadenitis; (2) lymphomatoid (with and without leukemia); (3) lymphoma (typical, and atypical or sarcomatous).

The intimate relationship between the potential producers of the different cell forms of the blood, both in the bone-marrow and in the spleen, renders it obvious that there may be simultaneous involvement of the myeloblastic and lymphoblastic elements; indeed, Kundrat holds that myelogenous leukemia is always mixed celled. For practical purposes it is sufficient to recognize two types of leukemia: the lymphatic and the myelogenous, respectively.

LYMPHOMATOID CONDITIONS AFFECTING THE SPLEEN.

Splenomegaly, or Splenic Anemia.—The time is not yet ripe to make an assured statement regarding the nature and relationships of a group of conditions in which, for long years, splenic enlargement is the main symptom, unassociated with hyperplasia of the lymph glands. Osler distinguishes four types: (1) Simple splenomegaly, persisting for years without accompanying anemia. (2) Splenomegaly with marked anemia of a secondary type, associated with cutaneous pigmentation and liability to hemorrhages; these cases last from ten to twelve years, and then are apt to develop a secondary cirrhosis of the liver, with jaundice and ascites (Banti's disease). (3) The familial or infantile form (Frederick Taylor, Gilbert and Fournier, etc.) begins in infancy, affecting several members of the same family, and showing the same symptoms of Banti's disease, with associated stunted growth. (4) Gaucher's type of splenomegaly, with secondary anemia, in which the spleen presents what may be termed an endotheliomatosis, there being a very remarkable diffuse swelling and proliferation of the endothelium of the splenic sinuses, which dominates the whole picture. In Stengel's case this had advanced to the development of localized neoplastic growths in the organ. Here, also, the splenic enlargement and condition extend over many years. Intimately associated pathologically, though not clinically, is the condition of splenomegaly, not with anemia, but with cyanosis, and extraordinary increase in the number of erythrocytes up to 9,000,000 to 13,000,000 per cm. Osler[1] and Weintraub[2] have brought together and analyzed the cases.

Whatever the primary cause in the various conditions, histologically we appear to deal with a localized blastomatoid condition, now involving the splenic tissue in general, now the endothelium of the sinuses, and, in the last case, characterized, it would seem, by a continuance of, or reversion to, the fœtal condition of this organ; for in the fœtus, the spleen is one of the active seats of proliferation of erythroblasts and production of erythrocytes. Recent observations show that this capacity to give origin to red corpuscles is latent in the organ throughout life; that it may be stimulated into activity by extensive loss of blood, etc.

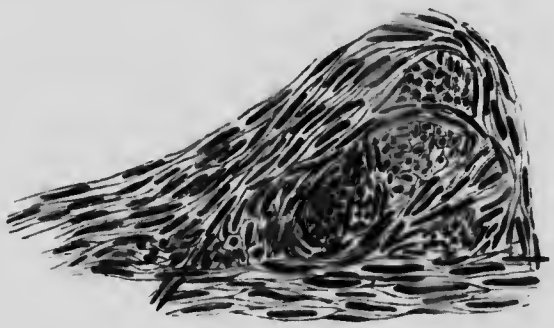
[1] Amer. Jour. Med. Sci., 126: 1903: 187 [2] Naunyn's Festschrift, 1905.

MYOMA (LEIOMYOMA).

The uterine fibromyoma, generally, from its appearance and characters, spoken of as the uterine fibroid, is the commonest of all tumors, and in most respects a most typical example of the benign typical blastoma. Possibly for this very reason we know less regarding its exact nature than we do of many of the rarer forms. And yet it has been extensively studied.

Gross Characters.—The tumors are most frequently multiple; if one large growth be present (and this may reach and exceed the size of an infant's head), careful examination will generally reveal other minute growths in the uterine muscle; or the whole body of the uterus may appear replaced by a collection of hard nodules, closely packed, and varying from just recognizable, pinhead nodules upward, the

FIG. 223



Section of portion of a pure myoma, showing the character of the nuclei and the appearance of the fibers cut transversely. (Perls.)

organ gaining a most irregular, nodose appearance. These tumors affect the body rather than the cervical portion, and may be either (*a*) interstitial, (*b*) submucous, or (*c*) subserous. In the last two situations they may, through progressive growth, become pedunculate.

Each individual tumor is to the naked eye sharply defined from the normal uterine tissue, though, while some shell out easily, others appear to be more intimately connected with the organ and, microscopically, are seen to have a more diffuse "capsule," the multiple small vessels as they enter being surrounded by fibrous tissue, which thus connects organ and tumor. On section, the appearance is characteristic, but here two types may be noted, between which is every transition: (1) the *pure myoma*, which is the softer, though still firmer than normal uterine muscle, and has a reddish-gray appearance (in the uterus this is not often noted in connection with small and apparently recent tumors); and (2) the fibroid proper, pale, almost white in color, and extremely dense, so that it cuts with difficulty. Unlike the fibroma, the

cut surface has a "watered-silk appearance," caused by the bundles passing in all directions, reflecting the light differently.

These are the characteristic forms, but we may also meet with the following variations:

1. Telangiectatic, the bloodvessels being widely dilated (rare).

2. Lymphangiectatic, the lymph vessels greatly distended; and here we can again distinguish between (*a*) the œdematous fibroid, with diffuse infiltration of serous fluid, and a spurious myxomatous-like separation of the tumor cells; (*b*) lymphangiectatic proper, with widely related lymph channels; and (*c*) cystic fibroids (see p. 655). Hemorrhages are rare.

3. Calcified, either surface layers, or central part, or the whole tumor, becoming converted into a dense stony mass, which can only be cut through by the saw. Associated with this, the microscope may reveal a preceding stage of fatty degeneration, as, again, of extensive hyaline degeneration.

4. Necrotic. Occasionally, through arrest of the blood supply, or through infection, a tumor may soften and undergo a colliquative necrosis.

Microscopically, we have every grade from a pure myoma to tumors in which no muscle tissue at all can be made out, but only bands of connective tissue—pure fibroma. To the beginner it is not always easy to recognize these two tissues; both run in bands, which are apt to spread and feather out. But, if the nuclei be studied, in bands which have been cut longitudinally, the distinction is soon made. Those of connective tissue and developed fibroblasts are spindle-shaped and relatively short; those of plain muscle fibers are larger, characteristically long, rod-like, and with blunt, rounded ends. So, also, cut transversely, the nucleus of connective tissue has a naked appearance; one observes round it no cytoplasm; the muscle fiber has a distinct body, and in well-preserved and well stained-specimens this appears roughly polygonal.

This fact that the small myoma is preponderatingly muscular, whereas the large is preponderatingly fibroid, indicates forcibly that, in the course of growth and aging of the tumors, there is a progressive development of the connective-tissue elements, with eventual atrophy and replacement of the muscular bands. The relatively small vascular supply, which must become progressively and proportionately smaller as the tumor increases in size, well accounts for this gradual effacement of the more highly differentiated tissue.

As a matter of experience, we would advise those desiring to demonstrate the structure of a typical myoma not to select portions of the largest and apparently finest examples, but to take a small growth —the smaller the better.

The tumors are essentially benign, showing purely local growth, and that extending, it may be, over long years. They may, however, set up, or be associated with, other uterine disturbances—menorrhagia and metrorrhagia, while a considerable number of cases are on record

of secondary cancer of the body of the uterus which may invade a myomatous tumor; so, also, of sarcoma, similarly infiltrating the growth.

There are those who deny that the myoma, as such, can undergo sarcomatous change, some on what we regard as the untenable ground that connective tissue only produces sarcoma; others on the equally untenable ground that fully formed plain muscle fibers cannot give rise to cells of the vegetative type, and that the sarcoma cells can only arise from the connective tissue of the tumor. Certainly, the fully developed muscle cells cannot; but, studying a series of uterine fibroids, we note a considerable variation in the size of cell, and length and shape of nucleus, indicating a series of transitions from the fully differentiated to the vegetative type of muscle cell. Sarcoma originating in uterine fibroids has repeatedly been recorded, and, while it may be that in some cases this originates from the connective-tissue elements, we see no reason why, along with Williams and others, we should not accept that some cases, at least, are of muscular origin. I have, indeed, recently encountered a case in which the transition from the muscle bands to bands of short spindle cells and from this to a diffuse development of short, almost oat-shaped cells was most striking.[1] Such cases raise a doubt as to whether the fibroid elements in the uterine fibroid may not in part, at least, be metaplastic, so great is the departure of these sarcoma cells from type, so near do they approach to cells of connective-tissue order.

This, however, does not detract from our statement that the tumors are essentially benign, nor does the fact, already noted, that some half-dozen cases are on record in which metastatic myomatous growths have shown themselves outside the uterus. The paucity of such cases must be contrasted with the many thousands of cases in which neither of these events develops.

Etiology.—What is the mode of origin of these tumors? To this no very satisfactory answer can be given. *We do not find them in the young;* nor in the child have there, to our knowledge, been noted anything of the nature of cell rests which could account for their later growth. On the other hand, we note a distinct family tendency to their development. Two possibilities are, therefore, present: either that there exist cell rests so inconsiderable as to escape notice, or that some constitutional condition favors the segregation of the tumor cells in late life. We see no reason why both conditions may not obtain, but at present there are no adequate data for coming to any decision.

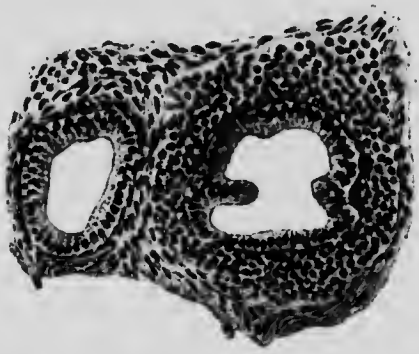
They may occur in both the single and those who have borne children. Pregnancy, therefore, cannot be regarded as an important factor. On the contrary, those who have borne children regularly and in number appear to be less liable than others, but here, again, no decision can be reached, for it may be that the presence of the tumors is the cause of the relative infertility of those with smaller families. At the same

[1] The condition was so diffuse that I am uncertain whether it should be regarded as a senile change or a sarcomatosis.

time it must be noted that the presence of myomas is not in itself incompatible with pregnancy.

Risger and Gottschalk, Lubarsch, Borst, and French pathologists in general regard the muscle fibers of these tumors as primarily originating from the muscular coats of the uterine arteries. They have reported cases in which, in small myomas, this relationship could definitely be made out. What is noticeable in all myomas is the relationship of the muscular and connective-tissue bands to the vessels, and a marked feature of the myoma, which renders it distinct from all other tumors that we can recall, is the frequent presence not merely of capillary vessels, but of arteries with well-developed muscular coat. Their presence must be regarded as supporting this view, which, if substantiated, renders it additionally likely that myomata may develop in later life from abnormal local overgrowth of what is not a cell rest. At the same time it must be kept in mind that other small myomas do not show this clear presence of arteries, and exhibit little more than a simple mass of aberrant plain muscle fibers.

FIG. 224



Gland acini included in a myoma. (After Ribbert.)

"Adenomyomas."—There is, however, an interesting group of myomas which, for a time, was held definitely to prove the cell-rest origin of myomas. These are the adenomyomas, wrongly so called, for more accurately they are diffuse myomas containing scattered gland tubules, that show no signs of active growth. To these von Recklinghausen's writings[1] have directed attention, and of late years they have been much studied. Such occur more particularly in myomas of the hinder wall of the uterus and below the angle of entrance of the tubes and in the wall of the tubes. But some cases are on record where these gland tubules have been seen in myomas of the body of the uterus. These tubules are lined by a columnar epithelium; sometimes they are distended into cysts, and often they have the characteristic appearance of a main channel, from which, on one side, several secondary tubules are given off more or less at right angles.

[1] Die Adenomyome u. Cystadenome der Uterus u. Tubenwandung, Berlin, 1896.

It was the last character which more particularly led von Recklinghausen to conclude that they represented included portions of the Wolffian body (paroophoron, or, more exactly, of the upper end of the Wolffian duct), the remains of which, in the broad ligament, frequently show this comb-like arrangement; to conclude, therefore, that the muscle elements of the tumor were overgrowths of the muscular coat of the included duct. This view cannot be accepted. The more the matter has been studied the more difficulties are presented by this view, though it still has its supporters. Most significant is the fact that, in the course of development, the Wolffian duct does normally enter into the uterus, but this not in the region where these "adenomyomas" are found, but in the cervical region, where myomata are strikingly rare. Others have pointed out, what impresses all who have studied any extensive series of uteruses, that processes of the uterine mucosa may extend and be found deep down in the muscle tissue. We have seen such more than half the distance between the inner and outer surface, and Ribbert has actually traced such sinus-like processes into an interstitial myoma; and seen that the tubules within the growth have all the characters of other uterine adenomyomas. In confirmation of this view, Cullen,[1] of Baltimore, has been able to trace this continuity in fifty-five out of fifty-six adenomyomas studied by him, and quotes cases in which the included ducts have been found to exhibit changes of the same character as those undergone by the uterine mucosa during menstruation and pregnancy. Such deep processes may also occur in connection with the intra-uterine portion of the Fallopian tubes. And lastly, Aschoff has called attention to the fact that in subserous myomas there may be peritoneal downgrowths which take on glandular characters. Our colleague, Dr. Goodall, has encountered an "adenomyoma" developing in the fundal portion of the uterine wall—a region in which, developmentally, the Wolffian duct could not enter. These facts are sufficient to show that these "adenomyomas" can be explained otherwise than by the theory of cell rests of portions of the Wolffian body, or Wolffian duct, or (as yet others suggest) of the Müllerian duct: they are diffuse myomas—if not "myomatoid"—with uterine glandular inclusions.

Myomas of Other Regions.—We have thus far only discussed the one form of myoma, and that because the uterus is far and away the commonest site for these tumors, and there they gain their greatest development. More rarely we encounter them in other areas, notably: (1) Other portions of the *genito-urinary system*, the walls of the Fallopian tubes, the broad ligament (in both these cases they may be "adenomyomatous," in the latter they may occupy the site of the parovarium); the round ligament (ditto), testes, prostate (rarely pure), kidney (often lipomyoma), ureter, mammary gland. (2) The digestive tract. Here, in connection with the non-striated muscle coats, they occur more frequently than in any other site outside the uterus. Usually small, they may in the stomach wall attain very large

[1] Adenomyoma of the Uterus, Philadelphia and London, 1908: 194.

size; usually single, some cases of multiple intestinal myomas have been recorded. Most often they project inward, and then may lead to obstruction or invagination or ulceration of the covering mucous membrane. Others, as in the case of a large gastric myoma described by our colleague, Dr. Nicholls, project into the abdominal cavity. The stomach and the intestines are more frequently involved than the œsophagus. One case is on record (Cohen) in which the tumor contained pancreatic lobules. (3) *Skin*. Cutaneous myomas are quite small, apt to be multiple. A rare case is on record of their appearance here in early childhood. Whether they arise from the muscle of the arteries or from the arrectores pili and muscular sheaths of the hair follicles is still an open question. The fact that when multiple on the skin, they are not found in other parts of the body, would rather favor the latter view.

TYPICAL HYLIC TUMORS OF MESOTHELIAL ORIGIN.

RHABDOMYOMA.

With rare exceptions, new growths of striated muscle fibers is found combined with growth of other tissues and sarcoma-like elements in tumors of the pluripotential, teratoblastomatous type, as, again, in teratomas proper. It is more particularly in the mixed tumors of the kidney, vagina, testes, etc., that we encounter more or less imperfectly formed striated fibers. Occasionally, however, we meet with pure rhabdomyomata, in general small and sharply encapsuled, and this in the kidney, genital tract, and other regions where mixed tumors may be found; but also in other regions, notably the heart muscle, and in areas where normally striated muscle is present—extremities, nates, orbit, etc.

In all these cases the fibers are of embryonic, imperfectly differentiated type; they may only show longitudinal fibrillation; or, if transverse striation is present, it affects only part of the fibers; in the other part, as in the developing muscle, are clusters or rows of nuclei, and, laterally or terminally, the fiber may be clubbed, without striation, and showing the nuclear clusters characteristic of sarcoblasts; or, lastly, large cells, with abundant cytoplasm and many nuclei of the perfect sarcoblastic type are present. These characters, coupled with the fact that, under normal conditions, the striated fibers show such imperfect regenerative powers, incline us to accept the prevalent view at the present time, that rhabdomyomas always arise from cell rests.

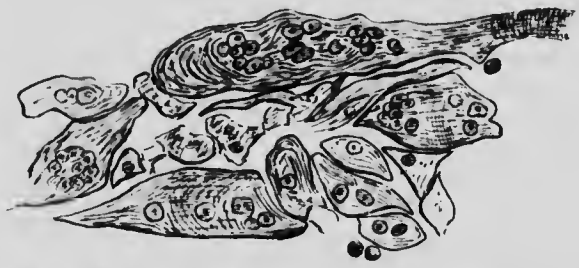
We encounter, in fact, cases in which these less differentiated stages are predominant; cases in which we have transitions toward the sarcomatous type. The difficulty in deciding whether we encounter true rhabdomyosarcomas is created by the fact that so often these tumors are of pluripotential type, and the vegetative cells seen may have originated, not from sarcoblasts proper, but from a still earlier type,

or from cells differentiated already toward the connective-tissue type. This, however, is to admit that sarcomas do originate from a forestage of the striated muscle fiber. There is, at least, one case on record, that of Störk,[1] of malignant rhabdomyoma (primary in the testicle,

Fig. 225

Imperfectly formed striated muscle fibers from a rhabdomyoma of the œsophagus. (Wolfensberger.)

Fig. 226



Rhabdomyosarcoma—giant-celled or sarcoblastic—from lateral muscle of trout. The tumor was almost wholly composed of these giant-cells, which here and there showed both longitudinal and transverse striation, more particularly in the relatively numerous elongated cells.

with secondary growths containing striated muscle elements in the retroperitoneal, mediastinal, and cervical glands). In others, while the primary growth has contained sarcoblasts and more highly differentiated elements, the metastases could only be described as pure sarcoma.

[1] Ztschr. f. Heilk., 22.

We have recently described[1] a pure rhabdomyoma, or rhabdomyosarcoma of this order, obtained from the red lake trout, in which the whole tumor was composed of cells of the sarcoblastic type, the majority multinucleated, some of the giant cells containing several score of nuclei; these giant cells had a tendency to be elongated and in parts showed definite cross-striation. The nearest approach to this pure type of "embryonic" rhabdomyoma in man is seen in a group of multiple myomatous tumors recorded in connection with the infantile heart muscle.

TYPICAL HYLIC TUMORS OF EPIBLASTIC ORIGIN.

NEUROMA.

Only such tumors as contain nerve cells are rightly to be classed as neuromata; if, for example, we find a tumor containing abundant nerve fibers—axones—but nothing that can be construed as even an imperfectly developed nerve cell body, we know full well that each of these fibers is in connection with some cell body *outside* the tumor, and that thus, so far as regards its nervous elements, the growth is not autonomous and independent of the rest of the organism; and that, therefore, the term *neuroma* is inapplicable. The recent researches into the histology of the nervous system has, therefore, materially reduced the number of tumors included under this heading; so much so that we find the true neuroma (or ganglio-neuroma)—as might be expected from the high degree of differentiation of the neuron—to be one of the rarest of tumors; the number of undebated examples can almost be counted on the fingers of the two hands.

Cases certainly exist, and they are of one order. Tumors, in one case as large as a child's head, have been observed, more especially in the abdominal cavity, and apparently in close connection with the sympathetic system—the cardiac plexus—which, upon microscopic examination, have been found to contain abundant cells of the type of sympathetic ganglion cells, with numerous processes histologically identical with the axones and dendrites of the nerve cell proper. These, without exception, are recognizable early in life, and date back to the embryonic period. They would seem, thus, clearly to be explained as due to developmental anomaly—to the segregation or displacement of a portion of the developing "neuroblast," which now takes on independent growth, the typical neuroblast cells proliferating and giving rise to nerve cells. Similar isolated tumors have been described in connection with the ependyma and the ventricles, evidently of like origin. We possess no instances of ganglion-celled neuromas of postnatal and irritative origin.

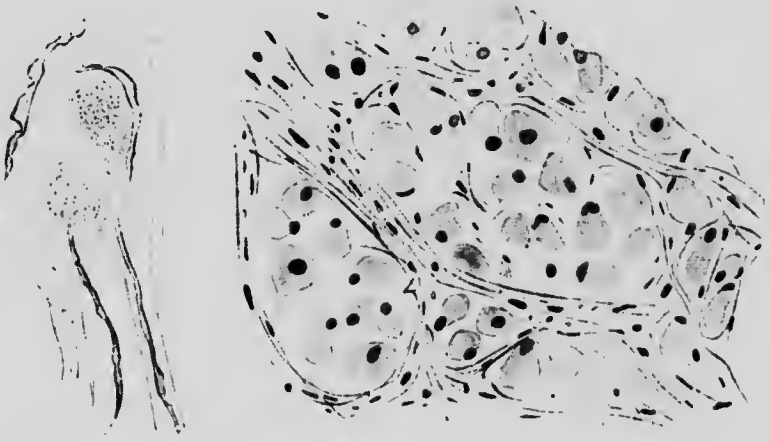
False Neuromata.—As already indicated (p. 658) under the headings of Neuroma, Plexiform Neuroma, Neurofibroma, we not frequently have recorded cases which should properly be classed as *fibromatosis*

[1] Adami, Montreal Medical Journal, 37, 1908: 163.

nervi vel nervorum. I have already described these in detail. Let me repeat that in these there is no independent growth of nerve cells.

A condition of a different order is the so-called *amputation neuroma.* It happens occasionally that, following upon amputation—more rarely after mere section or rupture of a nerve—the proximal end of one or more nerves becomes swollen to two or three times the diameter of the nerve, forming a firm, painful, bulbous mass. Sometimes this can be freed without difficulty, but frequently cicatricial fibrous tissue unites it to the surrounding tissues, making dissection difficult. Upon microscopic examination, the enlargement is seen to be composed of bundles of nerve fibers, often curving upon themselves, and passing in different directions, embedded in a dense overgrowth of the fibrous endo- and perineurium. Though the nerve bundles entering are, in general, in the main medullated, but little medullary substance can be recognized around the fibers involved in the growth.

FIG. 227



Cells from a benign and a malignant ganglioneuroma (a true neuroma) respectively, the former from the sacral region, the latter from the retroperitoneal region at the level of the pancreas. (R. Beneke.)

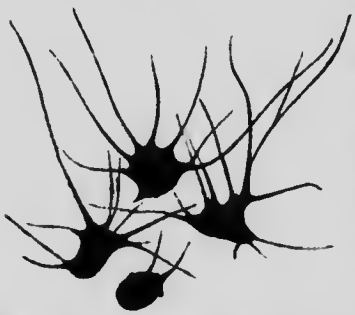
The process of events leading to this condition would seem to be an outcome and variation of what normally happens after section of a nerve trunk (see p. 575), but here, owing to absence of a proper channel of least resistance down which to advance, owing, also, to the formation of surrounding cicatricial tissue, the growing fibers turn upon themselves, and, together with the proliferated endoneurial tissues, form a definite enlargement, which ceases after attaining a certain size. What we have to deal with is, therefore, an *aberrant regenerative process,* and in no sense a true tumor formation. It nevertheless shows some relationship to the condition of fibromatosis for (1) the development does not follow all cases of amputation of a

limb (and so of its nerves); *i. e.*, it only occurs in certain apparently predisposed individuals; and (2) where once in an individual such an "amputation neuroma" has developed at the end of a nerve, and, on account of its painful qualities, has been removed, there is a distinct liability for a second tumor to form at the freshly exposed end of the nerve stem.

GLIOMA.

The other elements derived from the neuroblast, besides the neurons, is the glia, or neuroglia, formed of cells and singularly fine fibrils, which, together, give the stroma of the central nervous system its peculiar appearance. Compared with the neurons, these glial cells are small. They tend to be of oval shape, with a single nucleus and moderate amount of protoplasm, and, when teased out, show an extraordinary number of fine processes radiating from the body in all directions.

FIG. 228



Glial cells with multiple processes, from a case of congenital multiple gliomatosis of the brain. (Sterts.)

With regard to the nature and relationship of the fine fibrillæ which form a felting all through the stroma of the central nervous system, opinion has been divided. There has been a discussion similar to that regarding the relationship of the fibrillæ, yellow and white, of ordinary connective tissue. Weigert has laid down that these are not processes of the glial cells, but are independent derivations, formed and given off by the cells. Taylor[1] and Pusey,[2] employing Mallory's neuroglial stain, both found a definite connection between cells and fibrils. Bonome[3] has arrived at a similar conclusion, but holds that, in pathological conditions, this connection may be more intimate than normal, by which I understand that he takes the intermediate position, of regarding the fibrillæ as being found as processes of the cells which may later become separated, and so independent. By analogy with ordinary white connective tissue, this would appear to be the more likely relationship.

Tumors formed of these glial cells, with abundant or rare fibrils, are found only (*a*) in the brain, (*b*) along certain cerebral nerves (very rarely), and (*c*) in connection with the retina. The increased growth of neuroglia elements in connection with syringomyelia is, nowadays,

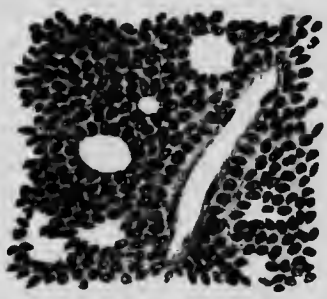
[1] Jour. Exper. Med., 2 : 1897 : 611.
[2] Trans. Chic. Path. Soc., 4 : 1899-01 : 44
[3] Virch. Arch., 163 : 1901 : 469.

generally regarded as hyperplastic rather than of the nature of true tumor formation—as a gliomatosis, and not a glioma.

Two varieties may be distinguished, the *hard* and the *soft*, the former found in connection with the ventricular walls, and projecting into the ventricles. These are well defined and easily enucleated; the latter are in the form of diffuse infiltrating growths, with no trace of a capsule, are very vascular, and peculiarly liable to be the seat of hemorrhages. In the brain, after death, their existence is indicated by the appearance of greater translucency than the surrounding brain tissue, and somewhat more bluish tinge, and by their more pulpy consistence; they often show signs of old and recent hemorrhages. The softness is due largely to the greater amount of glairy fluid in the matrix.

These soft gliomas are found only in connection with the cerebral hemispheres and corpus callosum, and may attain a very considerable size, gravely compressing and replacing the normal brain tissue. Neither the hard nor the soft form of cranial growth shows any tendency to metastasis.

FIG. 229



Section of retinal glioma, showing relationship of cells to vessels and formation of "rosettes." (Ribbert.)

Retinal gliomata, on the other hand, exhibit more evident signs of malignancy, both in their capacity to invade the surrounding tissue of other orders and to give rise to metastatic growths. These tumors originate as soft, grayish, finely nodular tumors projecting from the retina into the vitreous. If not detected and removed at this stage, the growing tumor may invade the sclera, and so extend into the orbit; or, after completely filling the bulb, may erode the cornea and project externally as a fungating mass. It may also extend along the optic nerve into the cranium. Histologically, appearances vary.

Retinal gliomas are only exceptionally—and then only in part—formed of typical glial tissue. Their structure, indeed, has led to considerable discussion as to their exact nature. In general, they are formed of small cells without processes, arranged characteristically in relationship to the vessels. The cells are grouped radially around the smaller capillaries, appearing to be in direct connection with the walls of the same, though, in the larger vessels, there is a layer of intervening connective tissue between the vessel wall and the surrounding cells. In the immediate neighborhood of the vessels the more or less radially disposed layers of cells stain well; farther away they tend to stain poorly, and to be broken-down and necrotic. The appearance thus, to some extent, recalls that of the perithelioma (or periendothelioma). There are, in addition, to be determined certain characteristic cell groups, or "rosettes"—collections of cells arranged radially around an apparent lumen, recalling the tubules of an adenoma or

glandular tumor, save that between the cells and the cavity proper there is a clear layer or membrane, from which occasional minute, conical processes project into the lumen proper. These characteristic cell groups led Flexner,[1] and subsequently Wintersteiner,[2] to conclude that the condition was epitheliomatous, and that the cells forming these rosettes were representatives of the layer of rods and cones—to hold, in short, that the tumors are of the nature of a *neuro-epithelioma*. But Graaf and Hartel have, independently, using the silver method of staining, shown that the tissue is of the nature of neuroglia, and Pusey, using Mallory's stain, has demonstrated glial fibrils extending from the cells of the rosettes to the edge of the lumen, some extending into it, and so forming the minute conical projections; these cells, therefore, are neuroglial; and similar rosettes have been observed in cerebral gliomata. These retinal tumors are, thus, true gliomata, but formed of less differentiated cells, so that if, as I urge, we employ the term sarcoma purely in a histological sense, it is admissible to speak of them as gliosarcomas.

Etiology.—In the newborn and in young children we occasionally recognize multiple small nodules, not well defined to the naked eye, but firmer than the surrounding tissue, which, under the microscope, are seen to be formed of glia, *with included nerve cells*. That these are found in the white matter as well as the gray points clearly to the fact that here we have to deal with developmental abnormalities—with inclusions, or overproductions of nerve tissue. It is in young subjects that we are specially liable to encounter gliomas. Further, as pointed out more particularly by Bonome, the existence of cysts lined by epithelium, in not a few examples of this condition, can only be satisfactorily explained on the assumption of developmental anomaly, either by lateral branching of the central canal and its epithelium, or by the inclusion of undifferentiated neuroblast at a very early period, which, in the process of growth, fulfils its destiny of producing epithelium of the nature of that lining the central canal.

There are, however, as Saxer has pointed out, other secondary cysts which may appear in cerebral gliomas, the results evidently of cell necrosis, and these may become more or less imperfectly lined by a layer of more cubical cells, which, at first sight, may be mistaken for an epithelium. As we have pointed out elsewhere (p. 564), this is not a true epithelium. It shows great variation, a basement membrane is wanting, and transitional stages can be seen between the surface and the immediately underlying cells of glial type.

CHORDOMA.

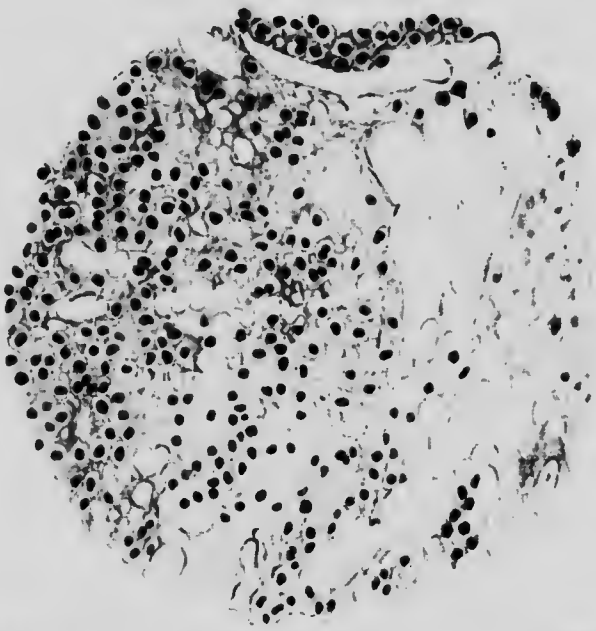
This is a remarkable form of tumor, first noted by Virchow, and regarded by him as cartilaginous; fully studied by Ribbert. Remains of the notochord are to be found in the intervertebral disks as small

[1] Johns Hopkins Hospital Bulletin, 1891: 115.

[2] Ueber Bau, Wachstum u. Genese d. Glioma Retinæ, Leipzig, 1897

collections of large vesicular cells separated by a homogeneous interstitial substance. As in cartilage, there are no vessels. They rarely form here anything that may be regarded as a tumor, but there is one site where a small tumor, never attaining great size, and formed by overgrowth of these cells, is to be found, and that, on careful examination, not infrequently—according to Ribbert,[1] in 2 per cent. of all autopsies. This position is the Clivus Blumenbachii at the spheno-occipital synchondrosis, corresponding to the original upper end of the notochord, behind the pituitary body. Here the growth, originating in the bone in the middle line, is apt to penetrate the dura

FIG. 230



Section of a chordoma. To the right the cells are of the benign type, not unlike in arrangement to those of cartilage; to the left through active multiplication the cells are taking on a more sarcomatous type and the growth is becoming malignant. (Fischer.)

mater and project as a mass the size of half a pea, often intimately attached to the basilar artery; so that, on removal of the brain, the fine pedicle in the dura is apt to rupture, and the tumor be found hanging to the artery. This little tumor is composed of tissue distinct from cartilage, and showing all the characters of notochordal tissue. From the presence of interstitial substance between the cells, on full consideration, we cannot, with Minot,[2] regard these cells as strictly epithelial, and must class the tumors thus formed as hypoblastic hylomata.

[1] Centralbl. f. Pathol., 1905.

[2] Adami, Jour. of Pathol., 1902: 216.

CHAPTER XX.

ATYPICAL HYLIC TUMORS.

SARCOMAS.

We have already of necessity referred on several occasions to the sarcomatous growths when discussing the type of form of hylic growth. Here, before writing of these extensively, it will be well, once more to lay down what we understand by a sarcoma. We repeat that the term has nowadays first and foremost a histological significance. (1) First and foremost a sarcoma is a richly cellular tumor of the connective-tissue type, the cells being of the vegetative, imperfectly differentiated order, or "embryonic;" and the component cells develop and present characteristically interstitial substance. This may be minimal and little beyond granular matter, but careful examination of different parts of a tumor will show that cells of identic nature show between them here and there such granular passing into definitely fibrillar interstitial substance. We have, that is, the hylic arrangement. (2) Such arrangement is not confined to tumors derived only from the mesoblast (whether mesenchymatous or mesothelial); it is characteristic of certain typical and atypical tumors of epiblastic and hypoblastic origin. *Therefore, certain atypical epiblastic tumors must also be regarded as sarcomas, and, as we shall show later, the actively growing tumors of transitional lepidic characters have also from this standpoint to be included as sarcomatous.* (3) Secondarily we have to give to tumors possessing these characters the clinical significance of infiltrative growth and the possession of malignant characters. But in doing this we must always keep in mind that malignancy depends upon more than the mere form of cell present: of two tumors composed of equally small round cells, one may exhibit rapid generalization, the other may be at most locally malignant. The tissue of origin, if it can be determined, should largely influence our diagnosis. At most, we can lay down that the more embryonic the type of cell the greater the presumptive evidence of malignancy, and that as between two tumors of the same origin the more vegetative the type of cell and the greater the departure from the adult cell standard, the greater is the malignancy.

All such sarcomas present certain features in common. They are not encapsulated, but exhibit a peripheral growth and invasion of the surrounding tissues. This invasion is along the tissue spaces and leads to progressive destruction of the preëxisting tissue, with general absorption of all that tissue save a supporting framework around the vessels and capillaries. Sometimes this is not so extreme, and so we obtain one

form of so-called alveolar sarcoma, in which the tumor cells are arranged in groups separated by well-marked connective tissue. We recall a case of Professor Delépine's in which infiltration of the diaphragm and replacement of the muscle fibers by advance of the sarcoma within the sheaths gave this appearance with singular clearness. But even in such cases examination of the primary growth, or of the central area of the tumor mass, shows that this appearance is only secondary, only the capillaries and vessels being eventually left, with a small amount of the preëxisting connective tissue.

The sarcoma cells, in short, *grow in the immediate neighborhood of the capillaries.* This is a marked feature of all sarcomas. We observe throughout the tumor that the vessels are composed of a single endothelial layer, immediately beneath which are the tumor cells. The capillaries may be widely dilated; in fact, another feature is the *abundant vascularity* of the growths.

While it is difficult to convince one's self over this point, it is generally accepted that there is a new formation of capillaries, and that the sarcoma cells grow along these, just as the fibroblasts appear to extend outward among the growing loops of granulation tissue; in fact, the close relationship between the sarcoma cells and the capillaries closely resembles that seen in granulation tissue. In certain small round-celled sarcomas we occasionally encounter channels, blood-vascular, that are bare of endothelium, as through here the blood makes its way directly between the tumor cells.

From these relationships it will be readily understood that (1) *hemorrhages* into the tumors are very apt to occur, and (2) that sarcoma cells are liable to become free in the blood stream, and that *metastases along the blood stream are characteristic of these growths.* Such metastases, it must be remembered, are not confined to the blood-vascular system; they may occur along the lymphatics, so that malignant enlargement of superficial and other lymph glands is not absolutely diagnostic of cancer.

Borst ascribes this liability to lymphatic extension especially to small round-celled sarcomas of lymphosarcomatous type. Our own experience leads us rather to the conclusion that, while undoubtedly sarcomas of that type show this tendency, all sarcomatous growths of the abdominal area, whether small round-celled, small spindle-celled, or mixed-celled sarcomas derived from pluripotential mixed tumors of one or other abdominal viscus, may form such metastases. We recall also a case in which, in an arm amputated at the shoulder by our colleague Dr. James Bell, Dr. Keenan found extensive osteosarcoma with bone formation in the axillary glands.

But extension by the blood vessels is undoubtedly the commonest process, and thus it is that secondary sarcomatous growth is peculiarly apt to show itself in the lungs. So also it must be noted that the growth may directly invade and grow along the blood vessels.[1] Apart from such

[1] This seems to be a feature of the not very common pure sarcomas of the kidney; both Wyler (Diss. Zurich, 1897) and Borst quote cases in which such growth has extended into the inferior vena cava, and so into the right auricle, and we have met

continuous growth, relatively large cell collections may become detached, and may even grow free within the heart cavity (as in a well-known case of malignant mixed tumor of the testis recorded years ago by Sir James Paget[1]), eventually gaining secondary attachment.

According to Ziegler, the sarcomas possess no lymph vessels proper, only occasional spaces and channels.

It will be readily understood that such rapidly growing tumors present abundant mitoses. Irregular mitoses, as also cell inclusions and so-called cancer or sarcoma parasites, which we must regard as a sign of degeneration, also occur, but not so frequently as in cancers. Indeed, the variety of degenerative changes is not so marked a feature as are the necrotic changes and death of the cells which affect portions of the growth, often associated with hemorrhages and pigmentation.

Forms of Sarcoma.—In accordance with what I have stated regarding cell differentiation and vegetative activity (pp. 125, 613), it will be recognized that lack of cell differentiation is to a very large extent accompanied by retention, or acquirement, of increased vegetative activity, and the student will be prepared to find that these rapidly growing malignant tumors of hylic type are composed of cells of the vegetative undifferentiated type. We now may be prepared to find that the stages of undifferentiation, or *anaplasia*,[2] in the different forms of tissue are not wholly identical. A glial cell, for instance, in its development never passes through a spindle-celled stage; thus, vegetative glial cells never produce a spindle-celled sarcoma; the mature lymphocyte is a smaller cell than the vegetative mother cell which produces it; thus, a lymphosarcoma formed of vegetative lymphoid cells may be of larger cell type than the adult lymphocyte, and, it also, is not of the spindle-celled type. Only cells which in the course of their (normal) development pass through a spindle-celled stage can give origin to spindle-celled sarcoma—connective-tissue cells, plain muscle fibers, etc.

And here a common misconception must be noted, that it is inconceivable that a typical, fully developed tissue, or a typical blastoma, formed of well-differentiated cells, should become converted into unripe sarcoma tissue. Birch-Hirschfeld laid it down that such an anaplasia is neither probable nor proved, and Ribbert and Borst reëcho the sentiment. Such an argument shows a want of realization of vegetative processes. Underlying it is the idea that the fully differentiated cell gives origin to the fully differentiated cell. The whole study of regeneration shows that this never occurs. Either there are undifferentiated mother cells, or cambium cells, normally present, from which the differen-

with a similar case; the specimen is in the museum at McGill College. MacCallum (Johns Hopkins Hospital Reports, 9) has reported a case in which a malignant tumor of the left testicle extended without a break along the left spermatic vein, left renal vein, and also along the left iliac veins, the growth passing into the inferior vena cava to above the diaphragm. According to our present knowledge this ought however, to be classed, from his description and figures, as a chorio-epithelioma of the testis rather than with the sarcomas proper.

[1] Also now regarded as a chorio-epithelioma of the testis.

[2] See p. 774.

tiated cell is developed, or, as in muscle and many other tissues, to become egetative the differentiated loses largely its specific features and passes back into the simple vegetative type. It is perfectly conceivable that in a highly developed tissue, or in a typical blastoma, certain cells can lose their specific properties and revert to a simpler stage; that as the regenerating muscle fiber reverts toward the sarcoblastic type, so the cells in rhabdomyoma, being unable to function, are therefore all the more liable to lose their functional differentiation and assume a vegetative sarcoblastic type. In this there is nothing improbable. According to the hereditary characters impressed upon them, according also to the surroundings in which they find themselves, so will such cells attain to a certain stage of differentiation. And so a tumor may show any stage, from the very lowest vegetative round-celled type up to the (not quite perfectly) differentiated tissue cell. Being under abnormal conditions and unable to function normally, the tumor cell can never, and never does, acquire perfect differentiation.

These vegetative or "embryonic" types of cell are simple and their range is comparatively small, from the small round cell, to that with larger amount of cytoplasm and rounded nucleus, to the oval cell, likewise with relative abundant cytoplasm and oval nucleus, and the spindle cell, still larger, with oval or even spindle-shaped nucleus and relatively less cytoplasm; though here we note a difference: we may have a small spindle-celled or a larger spindle-celled type of cell. In this way we distinguish the several forms of sarcoma, (1) small round-celled, (2) round-celled, (3) large round-celled, (4) oat-shaped cell, (5) small spindle-celled, and (6) large spindle-celled. We classify according to the predominant type of cell. Where, as in one order of growth, we find considerable variation in type we speak of (7) the mixed-celled sarcoma.[1]

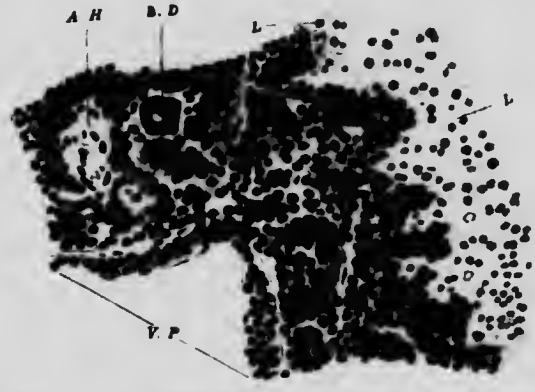
All these we may speak of as *pure* sarcomas. In addition there exist the *intermediate* sarcomas, in which the undifferentiation has not proceeded so far, so that some of the constituent cells attain a considerable degree of differentiation and tend to reproduce the tissue characteristics, whereas others are of the actively vegetative type. These are mixed-celled sarcomas in another sense. In this way we recognize the fibrosarcoma, osteosarcoma, chondrosarcoma. The terms *fibroma sarcomatosum*, *osteoma sarcomatosum*, etc., would more accurately express the nature of these tumors. It is from the study of these transitional forms that we learn to recognize the origin and relationships of the different types of pure sarcoma, for in them we see the different anaplastic stages exhibited by cells of one order. It cannot be said that this field has as yet been adequately worked; the finer details of the individual cell forms in these intermediate sarcomas need a fuller study, in order to afford adequate data for a sure recognition of the tissue of origin of the pure forms. We have thus far been satisfied to regard the sarcoma as an atypical connective-tissue tumor and leave it at that. The matter

[1] As noted (p. 676), I do not place the so-called "giant-celled sarcoma" here, but among the myelomas, the melanotic sarcomas are also considered separately (p. 759).

becomes one of practical and diagnostic importance once we admit, as we must, (1) that with a given tissue cell the more vegetative the type the greater the malignancy of the tumor, and (2) that the stages through which the cells of one tissue pass to attain full differentiation differ from those affecting the cells of another tissue, so that (3) tumors which superficially appear to be composed of cells of like size and arrangement, if derived from different tissues, may vary widely in malignancy.

The Small Round-celled Sarcoma.—The small round-celled sarcoma is in general the most malignant of all, or, concisely, the most intensely malignant and infiltrative growths with which we become acquainted are members of this class. The closely packed cells have deep staining, round nuclei with little cytoplasm; the interstitial reticulum is at a minimum; the arrangement of the cells immediately beneath the vascular endothelium is very characteristic. They are extremely vascular and

FIG. 231



Small round-celled sarcoma, infiltrating liver, advancing along a portal sheath: *V P*, portal vein; *B D*, bile duct; *A H*, hepatic artery; *L*, liver cells.

liable to exhibit hemorrhages here and there throughout their bulk. Metastases occur both through the blood stream and along the lymphatics.

They originate, it is generally held, from connective tissue in the most various parts of the organism, and the similarity they present in general to granulation tissue is striking. It is, however, possible that they represent the least differentiated, most actively vegetative stage in the development of all tissues.

Of the ordinary *round-celled sarcoma* nothing can be stated with definiteness, save that it also is actively malignant, but not to the extent that is the previous form. It also appears most often to originate from connective tissues Its cells, while small, are not strikingly so; their cytoplasm is more obvious.

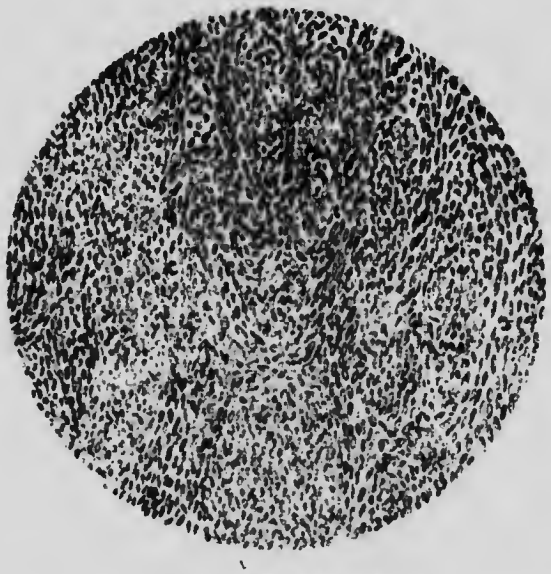
The Large Round-celled Sarcoma.—The large round-celled sarcoma shows, however, distinct difference in type, and we regard it as belonging

to another class. The cells impress one as being distinctly large and of the more "epithelioid" type; *i. e.*, with abundant cytoplasm forming a cell body not perfectly round, but rather variable in shape, now suboval, now obscurely polygonal; the nuclei tend to be suboval, paler, larger, and more vascular than those of the previous forms. The reticulum is more marked, and there is a slight connective-tissue stroma, nay, more, the peripheral portions of the growth are apt to take on an alveolar type. There is not the same extensive destruction and absorption of the tissue infiltrated as we note in the previous forms. Such tumors are often found in connection with striated muscle. It is at least possible that one group represents the most vegetative form of rhabdomyosarcoma, though more evidence is required upon this point. Another group of forms originates in the testis, with characteristically large cells, and derived

Fig. 232

Large round-celled sarcoma. (Ribbert.)

Fig. 233



Oat-shaped cell sarcoma. (Leo Loeb.)

possibly, as suggested by Hansemann, from the large interstitial cells of this organ (they thus are of mesothelial origin).

The Oat-shaped Cell Sarcoma.—The oat-shaped cell sarcoma is not very usual, but when encountered is a very characteristic form, because of the

regularity of the blunt cells with long oval nuclei which form the main mass of growth. We have not been able to satisfy ourselves that this form is characteristic of sarcomas originating from any particular tissue save that in one case as already noted (p. 689) we have possibly traced a plain muscle origin for this type.

The Small Spindle-celled Sarcoma.—The small spindle-celled sarcoma is, as the name implies, formed of relatively small spindle cells, varying in length from 10 to 20 μ (whereas in the large spindle-celled growths the cells are often from 50 to 80 μ long). The cell nuclei are oval or, like the cells, spindle-shaped, the cells collected in bundles with surrounding stroma, and these bundles appear to conform to or surround the capillaries of the growth. Here and there one notes often that some cells have produced definite fibrillæ, though this is the exception.

The appearance so closely resembles that of organizing cicatricial tissue that we have no hesitation in regarding this form as of connective-tissue origin, and, as a matter of fact, these forms are found in connection with connective-tissue areas, the corium, nerve sheaths, fascia, etc. Compared with the round-celled forms, these are much more benign. Metastases may occur, but are rare.

Fig. 234

Large spindle-celled sarcoma. (Ribbert.)

Large Spindle-celled Sarcoma.—The differences between this and the small spindle-celled form are very largely parallel to those between the large and small round-celled groups. Here also the nuclei are larger and clearer, often vesicular, and a variability is noted in the size and shape of the cells, as also in the terminal processes, which may be simple or forked. The tumors are found in connection with periosteum[1] (the large spindle cells of the giant-celled myeloma may here be recalled), fascia, and either the connective tissue of muscles or, it may be, from striated muscles themselves.

We refer here more particularly to a group of large spindle-celled sarcomas, in which, besides spindle cells of great length somewhat irregularly disposed, and possessing often two or it may be three nuclei, we encounter also large oval or irregularly shaped cells recalling the sarcoblasts.

Intermediate Types.—Fibrosarcoma.—It is singularly difficult to draw the line between the fibroma proper and what we would term the fibroma sarcomatosum, and this because the ordinary fibroma in general is more cellular than ordinary fibroid tissue. It thus becomes a matter of individual experience to decide when this cellularity is sufficient to label the tumor as fibrosarcoma, and so attribute to its malignant char-

[1] In this type of large spindle-celled sarcoma the cells, while large, are in general "stocky" and not of great length.

acters. A well-marked form may still be well encapsulated, but show abundant "naked" spindle cells along with cells, still spindle-shaped, that have attained to the stage of forming interstitial fibrillæ. Such tumors are often singularly rich in large dilated vessels, and are of soft consistency.

Myxosarcoma.—In such, while the main mass of the tumor may show a rather richly cellular myxomatous appearance (the individual cells presenting the characteristic processes), here and there are islands and masses of more closely collected round cells of fair size unprovided with processes: less differentiated cells, evidently more rapidly growing. Such tumors are apt to increase in size rapidly and to form metastases.

Liposarcoma.—A lipoma, after growing slowly for years, may take on more rapid growth, and with this on removal may show one or more areas of sarcomatous change, in which the fat cells become replaced by a richly cellular tissue. In one such tumor examined by us the cells and their nuclei were of an oval type. Rindfleisch would restrict the term to a class of cases in which a round-celled tumor of sarcomatous type shows throughout cells having the tendency to become infiltrated with fat in the form of larger or smaller globules.

As will have been gleaned from the general treatment of the subject, we wholly fail to see the propriety of this ruling, or that it accords with fact. The doctrine upon which it is based, of absolute fixity of properties on the part of tumor cells, is untenable. Once it is admitted that a metastasis, while retaining the same basal characters, may be of a simpler, more vegetative type than the parent tumor, it becomes illogical to hold that in that parent tumor the same process cannot occur and even be progressive until certain cells acquire the most undifferentiated characters.

Chondrosarcoma.—The various stages of undifferentiation are, indeed, frequently exemplified in a rapidly growing chondroma. We see there in the centre of an area unmistakable cartilage, though more cellular than is the normal tissue. At its edge we note the cells still more abundant, and here the chondriform interstitial tissue becomes replaced by a more mucoid matrix, and the cells become stellate. There is no sharp boundary, no island of cells possessing other properties, but a gradual transition from the more highly differentiated to the less differentiated—a reversal, we may describe it, of what occurs in the normal condition of cartilage. Passing farther out we have every transition to larger cells, still more closely packed, without processes, or at most of blunt spindle shape; a true, rather large-celled sarcoma, the cells exhibiting abundant indications of active growth.

The contrary view, that the tumor is from the first essentially chondrosarcomatous is incompatible with the fact that such tumors present, along with the development and vascularization of this sarcomatous tissue, evidence of progressive removal of the cartilage. As the vascular sarcoma tissue becomes formed, here and there it can be seen advancing into, absorbing, and replacing the previous cartilaginous substance. The

first stage has been that of cartilage formation, the latter that of sarcomatous modification.

Osteoid Sarcoma, Osteochondrosarcoma, and Osteosarcoma.—By these terms we distinguish three different types of intermediate sarcoma, exhibiting different grades of the ossification process.

The *osteoid sarcoma* is fairly common, and is, as regards malignancy, a true sarcoma, growing rapidly and forming metastases. In it we find areas which it is best to describe as intermediate between cartilage and bone. There is a homogeneous, cartilage-like matrix, but the cells in this, where single, resemble more bone corpuscles than cartilage cells; often there are several in one space, and where this is so they show all transitions to the sarcoma cells, surrounding thickly the osteoid lamella or mass. These cells are polymorphous, and away from the lamellæ giant cells occur. One cannot study such a tumor without being convinced that the osteoid tissue is an integral portion of the tumor mass, that it is the tumor cells which have produced and governed the deposit.

From this we pass to cases a stage less undifferentiated, in which there is deposit of calcareous salts in the lamellæ in certain areas; we are a stage nearer to true osteosarcoma. Other cases exhibit areas both of true cartilage and true bone; for these the name osteochondrosarcoma should be reserved, although the last-mentioned form is evidently very closely allied.

The *osteosarcoma* proper shows lamellæ and masses having the chemical composition of true bone. The histological picture may be, nay, generally is, imperfect—imperfect lamellation—and, while showing corpuscles, these have not the typical branching character. But, nevertheless, it must be regarded as true bone to the same extent as the fibers in a myoma are true plain muscle fibers. It is what von Hansemann describes as rudimentary bone formation. This may be present in irregular isolated spicules, or as a thin irregular spongy mass, well shown when the tumor is macerated; or, as in peritoneal osteosarcomas, as a series of radiating spikes, osteophytes, adherent to and apparently growing from the shaft.

It is interesting to note how the adherents of the fixity of tumor-cell properties theory dispose of this bone formation in these sarcomas. The presence of true bone as an actual intimate constituent of the tumor proper cannot be allowed. It is, according to Borst, following Rindfleisch, (1) calcified intercellular substance, and it is to be distinguished from (2) the true bone, the stroma-like remains of the bony tissue invaded by the sarcoma, or (3) a reactive inflammatory proliferation of the bone involved by the sarcoma. The benign ossifying forms, such as we see developing from the periosteum, cause superficial erosion of the shaft of the bone and a reactionary osteophytic inflammatory reaction. It is not explained (because it cannot be) how this inflammatory growth of the osteophytes is brought about; that, for example, each "osteophyte" is surrounded by a normal vascular tissue, with normal osteoblasts which deposit the new bone corpuscle and bone layers on the surface of the same, and so bring about increase in length. As a matter of fact, the

osteophytes are directly surrounded by the tumor cells, and the tumor cells, and they only, can give rise to the new-growth. As in normal bone, there is a layer of cells around the vessels which do not themselves undergo ossification, whereas away from the vessels these cells or their descendants become osteoblasts, so in this order of tumors the cells have not become so completely undifferentiated that they cannot still, in certain surroundings, manifest a certain amount of functional activity. Borst has to admit that in osteoid sarcomas the cartilage-like ground substance is a constituent portion of the tumor, and does not attempt to explain how the metastases in the lungs and elsewhere contain bony elements.

This group of osteoid sarcomas exhibit most often mixed sarcoma elements: spindle cells large and stumpy, polygonal cells varying in size, giant cells, the latter not so frequent, as a rule, in periosteal, superficial sarcomas as in central growths. Such central growths are apt to be expansive, causing absorption of the shaft and spontaneous fracture. With the growth there is still some periosteal bone formation on the surface, as indicated by the "egg-shell crackle" over them. In general they do not form metastases until the periosteum becomes ruptured and infiltration occurs of the surrounding tissues. In general, also, it may be laid down that the greater the development of osseous matter the less is the malignancy of the tumor. Thus the very "osteophytic" periosteal sarcomas of the long bones and face are only mildly malignant. The most malignant cases in our experience are those which show least bone and most cells of the small type.

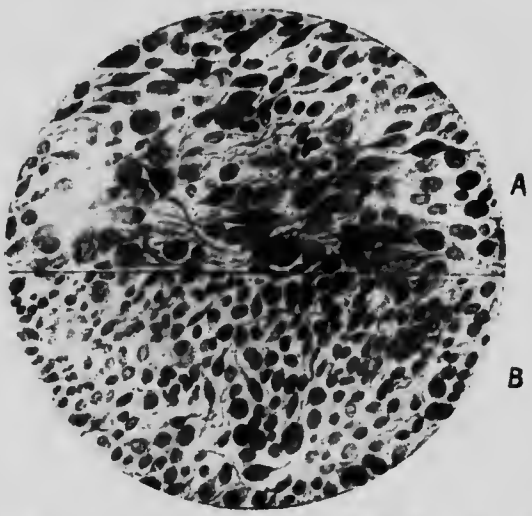
Lymphosarcoma.—This form we have already discussed. We will here only recall (1) that it is distinguished from the round-celled sarcoma proper by its more marked reticulum, well brought out by pencilling, or by washing the section in running water, and (2) that the larger-celled form (equivalent in size to the ordinary round-celled sarcoma) is of the more vegetative type. Such growths have a tendency to be local and infiltrative and to form metastases in the nearest lymph glands.

Leiomyosarcoma.—These again we have already noted (p. 689). It is probable that a group of spindle-celled sarcomas of the uterus and alimentary tract—possibly also of the genito-urinary tract—come under this category, tumors exhibiting moderately large spindle cells, variable in length, down to the blunt oat-shaped form.

Rhabdomyosarcoma.—The pluripotential tumors of the kidney and other regions are apt to take on this type, to exhibit, that is, large and very long, imperfectly formed muscle fibers, which may in part show transverse striation, others of long spindle shape showing only longitudinal fibrillation, large polymorphous and often multinucleated cells of the sarcoblastic type, and with these cells with one or two nuclei of the epithelioid type. Whether all the latter are of sarcoblastic origin remains an open question. The existence of this group renders it possible that a group of large spindle-celled tumors of muscle showing also great irregularity and some polymorphism may be sarcomata derived from muscle elements. (For the giant-celled form see page 693.)

Gliosarcoma.—We have noted this form in our discussion of the gliomas, and pointed out that (1) we regard the term as of perfectly correct usage (though we prefer the alternative Glioma sarcomatosum); (2) it is of most common occurrence in connection with the retina, and here is malignant, with infiltration, and liable to form metastases. The features of such a form are, briefly, that it is composed of small round-celled elements, in the main indistinguishable from those of ordinary small round-celled sarcoma. Careful investigation shows that some of these

FIG. 235



A. From the more typical portion of a glioma. *B*. Another region from the same growth of more malignant type, a true gliosarcoma. (Thomas and Hamilton.)

retain though imperfectly, the glial processes. The cells are especially well stained round the vessels of the tumor; *i. e.*, those at a distance are apt to degenerate. Here and there the peculiar rosette-like arrangement of the cells, characteristic of the glioma proper, is to be detected.

Greeff has even made out in these retinal tumors the existence of imperfect, undeveloped nerve cells, and ascribes the origin of these growths, we think justly, to cell rests of embryonic nerve tissue within the retina.[1]

[1] For reviews of the more recent literature upon individual forms of tumors the reader is referred more particularly to Lubarsch and Ostertag's Ergebnisse der allg. Pathologie, in which every other year or so there are afforded admirable studies upon neoplasia.

CHAPTER XXI.

PRIMARY LINING MEMBRANE, OR LEPIDIC TUMORS (LEPIDOMATA).

It has become the fashion of late years to speak of these as fibro-epithelial tumors. We doubt the utility of the term. It is true that there is always more or less of a fibrous connective-tissue stroma, but this is secondary, even though, through its variation in amount, it affords us to some extent a classification of certain forms, and although its presence is characteristic. But it exhibits no independent blastomatous growth of its own, save in the singularly rare cases which we shall have to note later. The essential part of all these tumors is the epithelial or glandular, or what we have termed the lining membrane element; it is this that takes on independent growth. For that growth the stroma, containing vessels, is essential, and, what is more, the very presence and activity of the "lining membrane" elements influences or sets up proliferative changes in the stroma, but these, at most (with the rarest exceptions), of an irritative, non-blastomatous type. These tumors, then, are best understood when we regard them as essentially of epithelial or lining membrane type. We can, as usual, divide them into the typical and the atypical.

PAPILLOMA

In these we have to deal with *outgrowths from surfaces presenting a covering layer of epithelium, whether squamous or columnar, and having a more or less pronounced connective-tissue core to each individual process.*

1. **Of Irritative Origin (Non-blastomatous).**—Here, again, we must remove a group of cases which, as their growth is obviously due to irritation, cannot be regarded as true blastomas, though, as these are papillary tumors, the name papilloma still adheres to certain of them.

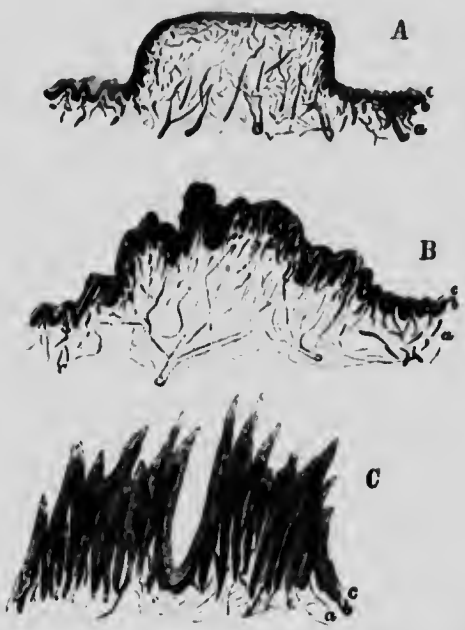
(*a*) **Warts.**—In these we deal with overgrowth of a collection of papillæ of the corium, covered by a common, thickened, and somewhat hypertrophied epiderm. They would seem to arise from irritation, are commonest in childhood, and have a marked tendency to disappear eventually. Some ascribe to them a definite infective origin, and clear evidence has been brought forward of transmissibility of the condition.[1] This may, however, indicate mere trans-

[1] Jadassohn, Verhandl. d. deutsch. dermatolog. Kongr., 1898; Lanz, Deutsch. med. Wochen., 1899; Nr. 26.

plantation, although, as Lanz was able to produce them upon the tip of his finger by rubbing it over the wart of a patient, an infective origin appears the more likely.

(*b*) **Molluscum Contagiosum.**—This is a definitely contagious skin disease affecting the face and head, the hands, and other parts of the body, which presents itself first in the form of small red elevations, which grow into warty elevations, continually breaking down in the centre and discharging whitish, cheesy matter. The growth is not so much superficial, according to Kaposi, as deeper, affecting the epithelium of the sebaceous glands, or (O. Israel) the hair follicles.

FIG. 236



The various grades of warts and cutaneous papillomas. (Perls.)

The surface layer, indeed, may show little hypertrophy; only, therefore, from its warty appearance does the condition come to be considered here. Characteristic bodies are found in the affected epithelial cells, regarding which there has been much debate as to whether they are parasitic protozoan forms or merely cell degenerations—or both.

In a somewhat similar condition affecting the head and comb of the fowl, it would seem evident that there are parasitic organisms present and setting up the disturbance. The consensus of opinion at the present time tends rather toward the degenerative view regarding the molluscum corpuscles; they are classed with the cancer bodies (see p. 925).

The Pointed Condyloma.—This projecting epithelial overgrowth occurs more especially as a multiple development upon the external genitalia—vulva, vagina, penis—or, again, in the anal region, or, more rarely, in the mouth.

It presents itself as a warty, nodular, sometimes mulberry-like, or even cauliflower-like growth, the outer wall of which is formed of thickened, overgrown, squamous epithelium, lying upon a stock of hypertrophied connective tissue, vascular, or very often showing small-celled infiltration. There is always a history of irritative discharges bathing the part, and in almost all cases in man one of chronic venereal disease to be gained. It is deserving of note that, while themselves of a benign type, they may eventually become the seat of epitheliomatous developments. On the other hand, if in the early stage the source of irritation be removed, their growth is apt to be arrested. If left, the growth becomes progressive and independent, and may attain an extraordinary extent, with abundantly branching processes, as upon the penis, where it may completely encircle the glans. We here deal with a borderline condition.

FIG. 237

Condylomata of the vulva. (Orth.)

Cutaneous Horns. — We occasionally encounter these, more often in the old than in the young—very slowly developing processes of true horny matter, often of bizarre shape, projecting from one or other region (most often of the scalp and face), and movable, their bases being soft.

They represent a condition of hyperkeratosis, or excessive development of the keratinous matter, an overdevelopment of the horny layer of the skin, coupled with a failure of the scales to peel or be rubbed off, so that they accumulate and form these masses. But as the horn grows in length it is to be noted that the underlying skin papilla, or papillæ, become elongated, to form a vascular core, passing almost to the end of the growth. An overgrowth of the epithelium appears here to be the primary event, but as the process in the older areas appears to be self-limiting, the cells throughout the whole thickening of the epidermis becoming keratinized, and the stratum Malpighii almost completely disappearing, it is difficult to regard this as a true blastoma.

In reference to the relationship between inflammation or irritation and papillomatous growths, two interesting conditions have to be noted—coccidiosis and the disturbances caused by the ova of the worm Bilharzia.

Coccidiosis.—In the ordinary rabbit bred in captivity it is very common to find in the liver a variable number of rounded, whitish nodules, some hardly visible to the naked eye, others reaching the

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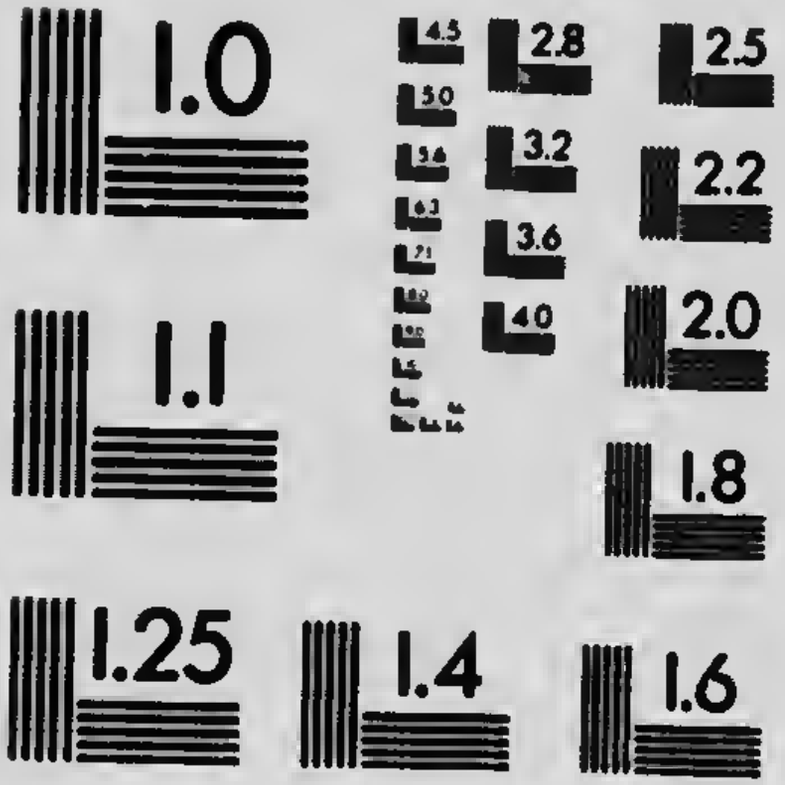

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size of a pea, and even larger, and distributed along the branches of the bile ducts. When large, these are soft and not unlike small abscesses, and when the soft material is removed from the centres of the nodules, a cystic cavity is left, with a papillomatous wall.

Upon examining these under the microscope, it is seen that we have a very remarkable condition of dilatation and proliferation of the bile ducts. The surrounding fibrous tissue is considerably increased, and the overgrowth of the epithelium is such as to form numerous fine papillary projections; in fact, the appearance is very much that of a cystadenoma.

If, now, we examine still more carefully, many of the individual columnar cells of this epithelium are seen to contain inclusions, and these inclusions cause the cells to be, many of them, greatly enlarged.

FIG. 238

Section of portion of the wall of a coccidial cyst in the liver of a rabbit: *a*, fibrous capsule; *b*, proliferated epithelium of bile duct, with papillomatous outgrowths; *c*, coccidia free in lumen.

If we follow the series of stages, at first little can be made out beyond that there is an indefinite body in the cell substance; but, as this grows, it gains a definite wall of double contour, and takes on a somewhat oval shape. Outside the body, kept in a moist condition, sporulation takes place, and four spores are produced, in each of which there develop two somewhat crescentic germs. These germs become amœboid, and in this motile state are evidently capable of entering the epithelial cells of a second host, there to repeat the life history. According to Delépine, they may be found frequently affecting the cells of the duodenum of the rabbit, and it is supposed that here the motile forms are elaborated, pass up the bile duct, and into the liver, and, again, either directly or through a second generation, enter the epithelium of the bile ducts.

A remarkable part in this disease is that the presence of these small animal forms within the cells leads to a very marked proliferation

resembling what we find to occur in tumors proper of the adenomatous type. What is further of interest is that there is no spread of the growth apart from the presence of these coccidia, and that there is apparently no general disturbance set up in the vast majority of cases. Again, the presence of these parasites does not necessarily lead to necrosis and death, but rather to proliferation of the cells. As Delépine remarks, "the parasite appears to be almost entirely devoid of any marked irritating properties; its presence leads to a setting up of irritation which only slightly exceeds physiological stimulation, and a result of this slight irritation is an excessive growth and multiplication, with hardly any increase of death among the cellular elements."

Recently Tyzzer[1] has made a study of coccidiosis in the rabbit. He points out that the parasites attack only the epithelial cells, and that at the termination of the process of growth of the parasite the cell is reduced to a sac containing the parasite, having on one side a darkly stained crescent, representing the degenerated nucleus. Ruptured cells are found from which the parasites have been set free. Degeneration and destruction of epithelial cells thus follow their invasion by parasites. But, adds Tyzzer, "numerous mitoses are seen in the epithelium, and, where the infection is not overwhelming, proliferation is in evidence. The epithelium is markedly thickened and its cells are crowded." His opinion is that the formation of the papilliform projections is to be explained by hyperplasia of the connective tissue, which pushes through defects in the epithelial layer; that both epithelium and connective tissues are stimulated to increase, and that the epithelium proliferates in an attempt to repair the defect in its continuity. For myself, I am more than doubtful whether the epithelial overgrowth is so particularly in relation to previous destruction, or to the papilliform projections of the connective tissue. It is often generalized all around a dilated bile duct, and irregularly of several layers. We have here a case, that is, in which irritation of low intensity, acting in a more concentrated form, leads to cell destruction; where less concentrated it leads to cell proliferation; where overgrowth both of the epithelial cells and of the neighboring connective tissue is initiated by the coccidial products, the interesting and remarkable feature being that the irritation here leads to localized overgrowth of epithelial elements. In this we have a condition unusual in ordinary inflammation, and more like what we see in epithelial tumors or adenomata. There are, however, two features which would seem to distinguish these coccidial growths from tumors proper: first, *the continuance and further growth is directly dependent upon the continuance of the coccidia*, so that we frequently come across evidence of old cicatrized areas, showing no coccidia, or containing them in the encysted and resistant stage, the epithelium having undergone complete degeneration; and secondly, unlike true adenomata, showing

[1] Journal of Medical Research, 2; 1902

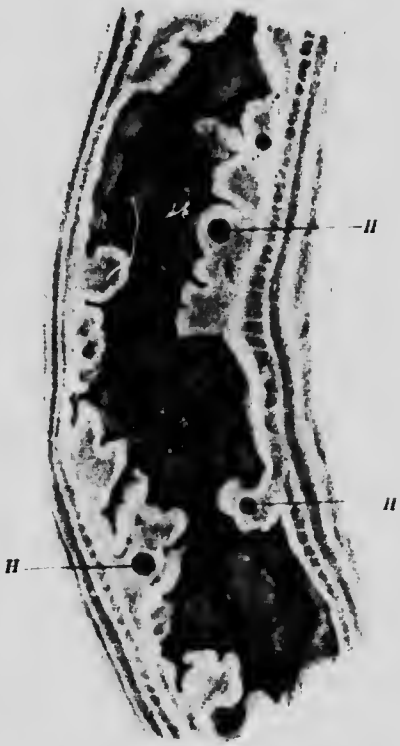
cystadenomatous change and atypical epithelial proliferation, *we never meet with evidence of metastasis.*

Therefore, while coccidiosis is interesting and of importance as indicating the existence of irritants which lead to epithelial overgrowth, it cannot be quoted as affording us examples of true tumors or blastomata of parasitic origin. At most, it can be adduced as one of the intermediate stages between inflammatory and blastomatous conditions,

Fig. 239

Ova of Bilharzia (schistosoma) hæmatobium, to show *a*, terminal; *b*, lateral spikes. (Perls.)

Fig. 240



Bilharziasis of the rectum, to show papillomatous overgrowth of the mucosa: *H*, cavities filled with blood. (Looss.)

and as an illustration that irritation of low intensity, insufficient to cause cell degeneration, may lead to proliferation of specific cells.

Bilharziasis.—There is, however, another condition of new-growth due to parasites which appears, from all descriptions, to be definitely blastomatous. It is possible that further and more minute studies will demonstrate recognizable differences, but for the present I do not see how we are to distinguish tumors of this order from tumors proper, save in that here the direct inciting cause is known. We refer to the rectal and vesical growths initiated by the ova of the Bilharzia.

The parasite is extremely common in Egypt and Abyssinia; the adult female, when mature, shows a predilection for the portal veins, more especially for those of the pelvic area. Here the eggs are discharged, and, passing into the smaller veins, mechanically, through the agency of their terminal spikes, they penetrate into the surrounding tissues. More particularly are they found in great numbers in the mucous coats of the large intestine and rectum and in the walls of the bladder, a considerable number making their way out, passively, into the cavity of the bladder and into the gut—inducing thereby conditions of hematuria and melena. This passage out of the ova induces chronic

overgrowth of the rectal mucosa and the vesical epithelium, so that the mucosa of lower portions of the rectum becomes greatly swollen, in fact, papillomatous, and the same is true of the inner coat of the bladder. What is more, numerous cases are on record in which this condition of chronic proliferative inflammation has given place to definitely cancerous growths.

We spoke of the assumption of malignant properties in cases of fibromatosis, as in epiphenomenon. It might be said that the same is the case here. The difference in the two is that here we recognize the presence and influence of a continuously acting irritant, which eventually, in a certain proportion of cases, if in action for a sufficiently long period—possibly, also, in those having a special predisposition—leads to something beyond mere inflammatory changes—leads to an aberrant progressive and excessive tissue growth, with the proliferation of atypical tissue cells invading the surrounding tissues and, indeed, capable of forming metastases.

A point of not a little interest is that, while the ova are abundant in areas of chronic proliferative inflammation, T. Harris found them absent in the definitely cancerous areas. In other words, while they appear to start the cancerous process, once it is started they do not appear necessary for its continuance. This absence, I am assured by Professor Symmers, who has extensively studied the condition, is not by any means constant.[1]

2. **Blastomatous Papillomas.**—(*a*) **Soft Papillomas.**—These grow from mucous membranes, and in general afford the most satisfactory examples of the form of tumor which develops in direct continuity with, and clearly from, a normal epithelial membrane. What is the direct cause of the cells in one particular locality taking on excessive growth is not easy to say. Even if, as is often the case with intestinal papillomata, we gain a history of previous inflammation or of dysentery in cases of so-called colitis polyposa, of gastric ulceration in gastritis polyposa, why in some individuals these conditions set up the overgrowth we can, at the most, suggest. But these matters we will discuss later. Of these papillomas we may have every form, from a simple nodular protuberance of the mucous membrane, either sessile or subpedunculate, such as we often meet with in the intestine, up to a brush-like mass of delicate long processes, such as may be present in the bladder.

Such growths show themselves in the nasal passage, the stomach and intestines, gall-bladder, urinary bladder, ureters, pelvis of kidney, and uterus. They show a framework or stock of connective tissue, which follows faithfully the branching of the growth, and is distinctly vascular. A transverse section of one of the finger-like processes of the many branching forms exhibits usually a central artery, with vein, or veins, surrounding a soft connective tissue somewhat infiltrated, and outside this the epithelial layer. That epithelium is apt to show

[1] See also Symmers, "Festschrift" by the pupils of Professor D. J Hamilton, Aberdeen, 1907

abundant mitoses. At times it is highly differentiated and very typical; in the intestines it may exhibit abundant goblet cells. But often,

Fig. 241

Papilloma of bladder to show the long, finger-like papillomatous outgrowths. (Ribbert.)

Fig. 242

One of the fine processes of a papilloma of the bladder more highly magnified to show the central fiber core or stock with vessels.

especially in the more exposed parts of the growth, it is modified. A papilloma of the bladder, for instance, may exhibit an undifferentiated

Fig. 243

Intracystic papilloma of breast. (Orth.)

round-celled epithelium, resembling a proliferation of the cells of the lower layers.

(*b*) **Intracystic Papillomas.**—Another group of papillomas, the intracystic, is found developing in cystic adenomas, filling up the cysts with branching and complicated masses of epithelial processes. Such we find, notably, in connection with ovarian cystic growths and mammary adenomas. More rarely we encounter these in cystic growths of the kidneys and bile passages. As in the other form, these intracystic growths possess a connective-tissue stock—though it is interesting to observe, in ovarian adenomas, that the *first* stage of papillary overgrowth presents itself as a folding outward of the layer of columnar cells, suggesting that by this means the increased number of cells accommodate themselves; in this first stage nothing beyond basement membrane is present in the fold. *The connective tissue and vascular growth into the process is secondary.* These grow into the space offered by the outward projection of the epithelium. This must be regarded as the mode of development of all papillomas, even of the most complicated and many branching forms, such as we encounter in the bladder.

Not infrequently these soft papillomata become the seat of cancerous growth, with increasing proliferation and accompanying changes in the character of the cells. In certain areas the cells grow inward, instead of outward, and proceed to infiltrate. A study of papillomas exhibiting the early stages of the change is most instructive (Hauser). To this we shall refer later.

ADENOMA.

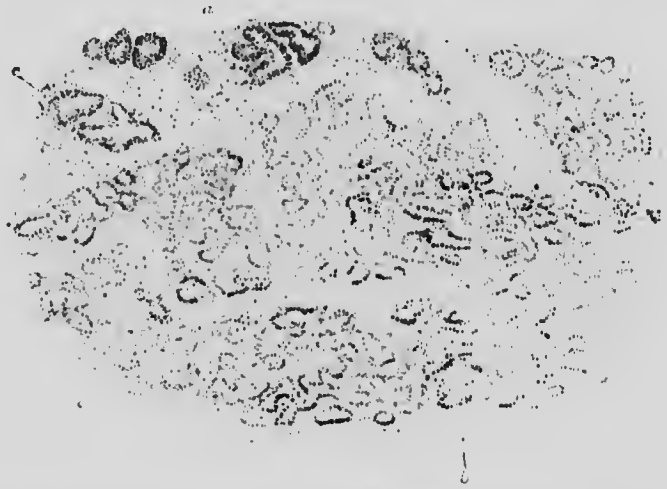
By adenoma we understand a growth composed of relatively typical glandular epithelium, arranged, that is, according to the manner in which it is found in the mother tissue; if that tissue be composed of glandular acini, with definite lumina, there the adenoma is likewise in the form of acini, with lumina; if, as in the liver, the acini are formed of solid cell masses, then the adenoma is of solid cell masses without lumina; if developing from duct epithelium, then the adenoma partakes of the character of duct epithelium. The form exhibited by the different varieties of adenoma is thus capable of very considerable variation; each has to be considered in relationship to the tissue of origin. Nevertheless, certain features are common to all.

Exhibiting relatively slight anaplasia, such growths of secretory cells are apt to retain some power of secretion. Adenomas of the digestive tract still exhibit goblet cells and discharge mucus; of the thyroid, many still form colloid; of the liver, still produce bile; and, as such growths are independent, where contained within the tissues and encapsuled they are incapable of discharging their secretion, which is apt to accumulate and, distending the constituent tubules, to form cysts—*cystadenomata.*

Here we immediately encounter the great crux in the study of this order of growths; although histologically of the same grade of development, of two tumors of the same organ one may become cystic, the other not; some tumors are sharply encapsuled from the mother tissue, and, in fact, may lie heterotopically, far removed; others, while

apparently equally encapsuled, but within the mother tissue, clearly (as in the so-called adenomatous hypertrophy of the prostate) retain through their ducts a communication with the body of the gland from which they have developed, and are still able to discharge their secretions. This is notably the case in the polypoid adenomas of the digestive tract, the nasal cavities, etc. From the frequent communication and direct connection with the surrounding normal tissue it is impossible by any means at present at our command to make a separation between adenomas of this order and conditions of localized glandular hyperplasia, in which, likewise, the communication with the exterior is not arrested. Given two sections, for example—one from a case of diffuse chronic fibroid induration of the mammary gland of known irritative origin, another taken from the centre of a localized encapsulated

FIG. 244

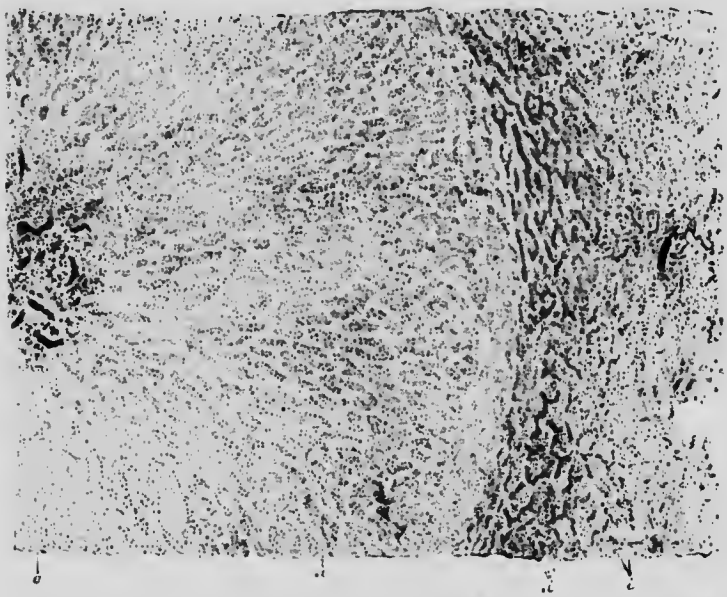


Adenoma of bile ducts, formed of acini resembling those of normal bile ducts. (Wätzold.)

fibro-adenoma of the mamma of this type, and it is frequently impossible to determine which is which. The same is notoriously true in the liver. We meet with a succession of cases from simple diffuse regenerative hypertrophy, as after acute yellow atrophy, through others in which, as in cases of cirrhosis, the regeneration, while regular, is more localized, confined to separated islands—or peninsulas—of liver lobules (regenerative hyperplasia); to others, in which nodules of liver tissue exhibit an expansive growth, and, growing, cause atrophy of the surrounding liver cells, a definite boundary of capsular nature distinguishing these growths from the rest of the liver tissue. Histological examination of such tumors shows the cells of typical character, arranged in typical masses, but these masses are not arranged into lobules. The same is true even lower down in the scale, in the regenerative hypertrophy of

cirrhosis, but here it becomes even more pronounced, and from these cases we proceed, again by almost imperceptible transition, to others in which the cell growth is more and more irregular and atypical and locally malignant, columns and processes of the tumor cells infiltrating and spreading into the surrounding liver tissue, causing atrophy of the normal cells, the two forms being easily distinguishable by the deeper staining of the nuclei of the invading cells. Cases giving like histories will present one or other of these stages. It is true that by no means all cases of portal cirrhosis exhibit regenerative changes, and that of those which do present them, a very small percentage exhibit the adenomatous type, still fewer the cancerous type of change. There

FIG. 245



Adenoma of liver, formed of columns of cells (*c*), causing compression of surrounding normal liver tissue (*d*). (Wätzold.)

are, obviously, individual differences in reactive and regenerative powers, and these differences—in other words, the tendency or absence of tendency to excessive cell growth—is an all-important factor in determining whether a given insult to the tissues leads merely to an orderly regeneration or to tumor growth. But it is equally clear that simple irritative and regenerative hyperplasia, adenomatous growth, and carcinoma, are stages which can be manifested in succession by the same tissue; that the differences are those of degree and not of kind.

We have, in short, conditions which are largely parallel to those to which we called attention in connection with hylic growths, and here we may make the like distinction between conditions of adenoma

proper (independent encapsuled growths), adenomatosis (not properly encapsuled), and irritative and congenital glandular hyperplasia.

It is interesting to observe how the upholders of the unmitigated cell-rest theory, those who hold that all tumors arise from cells congenitally displaced, dispose of these cases. The facts have to be admitted, and are; but the straightforward explanation cannot be accepted. Judgment is suspended, and we are advised that it is necessary to be very cautious; it is suggested that the adenomas of the liver, for example, are not truly adenomas, the cancer not true cancer, and this, although they conform to all the usual postulates; that the irritative adenomas of the digestive tract are not true adenomas, although in the next paragraph, it may be, their liability to become the seat of malignant growths is acknowledged. It is pointed out that there are adenomas which, being heterotopic, can only arise from displaced cell masses; that occasionally, in the liver, for instance, we encounter homotopic masses sharply encapsulated, and it is urged that, therefore, invisible and insignificant congenital displacement of cells is at the bottom of all these cases; or, driven farther back, that, although duly placed in the tissues, certain particular cells have from the first had a congenital weakness toward overgrowth. This, it will be seen, is coming very near to our point of view. The cell rest is cast overboard. No sign of it can be seen in simple regeneration of the liver, and equally none in adenomatous hyperplasia of the same.

Is it not more rational to take the view that, while cells (in cell rests) which have never attained full differentiation may, with relatively slight stimulation, take on independent and blastomatous characters, nevertheless fully differentiated tissues have not wholly lost the same power? We see that in inflammation these cells can revert to the undifferentiated vegetative stage and atypical arrangement. Why not accept that under these conditions the same cause that sets up independent growth in cell rests, may set up independent growth in cells produced from differentiated tissues?

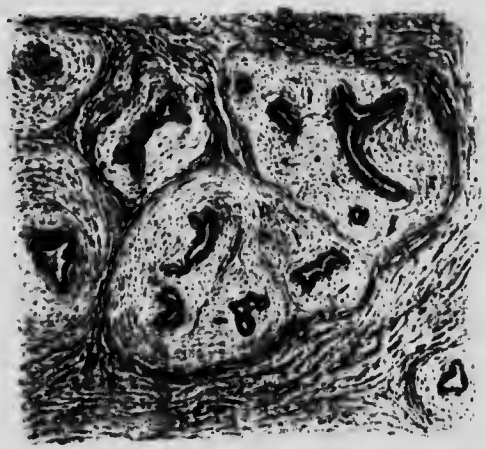
We shall have to call attention to a like order of phenomena when we discuss the cancers.

Regarding the structure of the adenomas, it is necessary to say a few words. As with the papillomas, so here, the stroma is an essential part. The most typical adenomas show a well-marked basement membrane between the cell layer and the underlying stroma; where growth is rapid and becoming atypical this may be absent. With their growth, also, we must recognize that, while gland cells and stroma are essential to one another, the former are the dominant agents; the growth of the stroma follows that of the epithelium. The appearances seen in ovarian adenomas (see p. 719) can only be explained along these lines. So, also, it is evident, from the results of transplantation of adenocarcinomas in mice, *it is the transplanted gland cells that form the new tumors, the stroma being furnished by the new host.* The process by which the one tissue follows the other, so as to form an essential whole, is very remarkable. The growth of the stroma, with its

accompanying vessels, must be regarded as reactive, as of a chemotactic nature.[1]

It may well be that this reaction on the part of the normal tissue is a factor in the arrest of adenomatous and cancerous growths. Two orders of conditions have to be recognized. If, on the one hand, a given cell, entering a tissue, induces no reaction, its proliferation becomes arrested after attaining a certain point, because no vessels and stroma enter into the cell mass. If, on the other hand, an excessive reaction is produced, then the connective-tissue overgrowth cuts off the nutrition of the developing new-growth. In other words, as we have already pointed out, the development of a blastoma is the resultant of two factors, the proliferative capacity of the invading cells and the reactive properties of the organism.

FIG. 246



The so-called fibro-adenoma of the mammary gland. The glandular acini and ducts are prominent and show some irregular overgrowth of the epithelium, but the main feature is the development of connective tissue both peri-acinous and interstitial, the latter not sharply defined. (Ribbert.)

We notice that the amount of stroma in the different forms of adenoma varies very greatly; it may be of the very slightest, little more than a network of vessels, with their supporting connective tissue; it may be so dense as to be the main feature in a growth. Then we speak of a *fibro-adenoma*—although, from the above considerations, *fibroid adenoma* (adenoma fibrosum) is seen to be the more correct term.

Let us now attempt to classify these allied conditions, calling attention briefly to the more important forms.

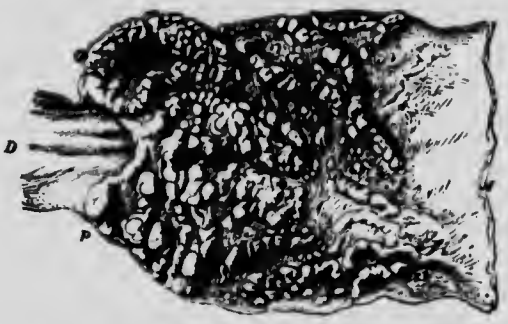
Congenital Glandular Hypertrophy.—This may affect any glandular organ, though what is perhaps the most remarkable example occasionally is met with in connection with the mammary glands.

[1] For a study of the mode of formation of the stroma in adenocarcinomas of mice, see Bashford, Rep. Imp. Cancer Committee.

These, with the development of puberty, may take on enormous growth, and be a source of so much disfiguration as to demand excision. If not removed, it is found that they function normally and excrete milk. If removed, as in a case of my colleague, Dr. Bell, which came under my examination, they are found to be composed merely of an excess of normal mammary gland tissue.

Irritative Hyperplasia.—This in general is marked by an enlargement of the gland, in the main due to increased fibrosis—as in chronic interstitial mammitis. With this, however, there may be some glandular overgrowth of the same order as that which we note affecting the epithelium in chronic ulceration when also the glandular elements, the sebaceous glands more particularly, may undergo actual hyperplasia. Indeed, the growth at times may be so extreme as to simulate tumor growth. Similar irritative hyperplasia leads to marked overgrowth of the mucous membrane of the digestive tract at the edge

FIG. 247



Multiple adenomatous polyps (adenitis polyposa) of stomach: *D*, duodenum; *P*, pyloric ring. (Orth.)

of an old ulcer, and of this, again, the same is true. It is being increasingly recognized that *prostatic hypertrophy* comes into the same category, that the prostatic adenoma, so called, is not a blastoma proper.

Here, also, though forming a different class, is *regenerative hyperplasia*, such as occurs in the liver after acute yellow atrophy and cirrhosis (p. 720).

Adenomatosis.—We would confine this term to the conditions often, but not necessarily, multiple, in which, while maintaining organic connection with the surrounding tissue, portions of a glandular tissue or surface become the seat of exuberant irregular adenomatous overgrowth, with evident disturbance of function. No sharp line of demarcation can be drawn between this and the preceding class. Under this heading come the multiple adenomatous polyps of the alimentary canal, some of the adenomas (fibro-adenomas) of the mammary gland, the multiple adenomas of the liver, advanced cases of prostatic hypertrophy, and uterine adenomas. From their general properties we are inclined to regard the multiple adenomas of the

thyroid gland and ovarian adenomas and cyst-adenomas as belonging to this group, although regarding the last we shall have more to say when discussing the transitional lepidomata.

It must be emphasized that the transitional lepidomas also afford adenomatous growths; we think it better to discuss them as a separate class.

Adenoma Proper.—Here, finally, we include all the sharply demarcated and completely encapsulated benign glandular growths. Their number, compared with the examples of adenomatosis, is relatively small, and the main members will be noted when discussing the transitional lepidomas. So far as we can see, these must, one and all, be regarded as originating from cell rests. The only case regarding which we have doubt is a sharply defined and extremely typical adenoma of the sudiparous glands of the wrist which came into our hands, in which, however, the absence of any cystic enlargement suggested that it must have possessed a communication with the exterior. When the cell nest is formed of glandular tissue which normally communicates with the exterior, the complete encapsulement, coupled with but slight anaplasia, must (we are inclined to think) inevitably result in cyst formation; with progressive growth of the epithelium lining these cysts, papillary projections occur into the cyst cavity (intracystic papilloma), and may almost completely fill them. Absence of secretion, as in some bile-duct adenomas, indicates either origin from non-secreting duct cells or a further grade of anaplasia.

Here we would include the well encapsuled cystic adenomas of the mammary gland, whether situated within or separate from that organ, certain isolated adenomas of the liver and pancreas, and detached adenomas of the thyroid. The large and important group of adenomas of Wolffian duct origin together with renal and suprarenal adenomas come under the heading of transitional lepidomata.

THE ATYPICAL LEPIDIC GROWTHS.

EPITHELIOMA AND UNCOMPLICATED CARCINOMA.

We may satisfactorily consider together the atypical growths from epithelium and gland tissues, and that because the properties of the two orders are the same; indeed, the most atypical members of the two groups can with difficulty be distinguished; all are true cancers. In all we meet with a greater grade of undifferentiation, or anaplasia of the constituent lepidic cells, than is noticeable in the adenomas and papillomas, though, at the same time, we cannot but recognize that forms showing *histologically* a relatively slight degree of anaplasia may, nevertheless, be as malignant and as liable to form metastases as are more anaplastic forms—or even more so, so that here we possess some notorious examples in apparent—nay, actual—contradiction to the general rule that the extent of anaplasia is the index of malignancy.

The most pronounced example of the contradiction is seen in the

condition of *rodent ulcer* proper, which Krompecher—we hold unfortunately—has rechristened *basal-celled carcinoma*.[1] Ordinary epithelioma is prone to form metastases in the lymph glands. Here we deal with an epithelioma of the most aberrant and anaplastic type, which, nevertheless, for long months, and, it may be, years, continues to grow and locally infiltrate and destroy the surrounding tissue, which, nevertheless, characteristically does not form metastases—which possesses local and not general malignancy. As we note later, this assignment of these growths is not accepted by all. Under this category comes also the large group of *adenocarcinomas*, which some would term malignant adenomas. Carefully analyzed, it seems to us that here the exception is more apparent than real. While these growths are of the adenomatous type, showing well-formed gland tubules, with lumina, etc., compared with benign adenomata of the same order the arrangement is seen to be less typical. More particularly a basement membrane is found very largely absent; here and there, instead of a single layer of cells, the acini show several layers, and some are simple solid cell groups without lumina. In other words, of the adenomas of the same origin, one benign and the other malignant, the latter is the more anaplastic. Yet it has to be admitted that of these glandular tumors certain forms, showing relatively little evident anaplasia, have powerful infiltrative tendencies, with capacity to form metastases.

These examples, as before noted, we cannot explain. It has been suggested that gland cells which, under normal conditions, actively produce proteolytic and other enzymes may, when they take on blastomatous growth, then elaborate and discharge enzymes whereby they easily overcome the resistance of the neighboring tissues. This, however, does not appear to explain all cases.

Thus, then, *we regard as cancer all cases in which there is infiltrative, and apparently independent, growth of epithelial or gland cells into the surrounding tissues, and this whether of only slightly atypical or markedly atypical cells.*

Relations of Specific Tumor Cells and Stroma.—As with the adenomas, so here, the primary tumor element is the gland cell; it is this that makes its way into the tissues, and, doing this, sets up a reaction on the part of that tissue. Such reaction is often very well marked at the growing edge of these tumors, best, perhaps, in the epitheliomas. We observe that there is set up a reaction of a distinctly inflammatory type, with marked small-celled infiltration. More study is needed of the form of cells exhibited in this process, but some clearly are leukocytes, and such leukocytes may be seen to penetrate into the masses of cancer cells, to accumulate especially in areas where such cells have undergone necrosis, and, what is more, either actively to penetrate or to be taken up by the tumor cells, forming a definite order of *cell inclusions*. Probably both events occur, for while, on the one hand, we may find well staining masses of leukocytes occupying

[1] Krompecher, Der Basalzellenkrebs, Jena, Fischer, 1903.

the site of previous cells, in others, more especially at the growing edge, the included leukocytes stain badly, and are evidently undergoing disorganization.

There are thus indications that the actively proliferating cancer cells feed upon the tissues of the organism; and it would seem that by phagocytosis, as by extracellular ferments and preparatory solution, the cancer cells replace the preëxisting tissues, using them as foodstuffs.

Such process, however, has its limits. Often we can note that, the growing cells making their way into lymph spaces, those spaces still present their endothelial lining, and the vessels with surrounding connective tissue of the infiltrated area are retained to form the stroma

FIG. 248

Early adenocarcinoma of the rectum, to show the marked difference in staining powers between the cancerous (*a* and *b*) and the unaltered epithelium (*d*). (Petersen.)

of the advancing growth. Such stroma may, indeed, itself proliferate under the stimulus of the tumor cells, just as we noted in the case of adenomas, and there may be new-growth, not only of new simple connective-tissue elements, but of even higher forms. Thus, in secondary cancer of bone, such as frequently follows prostatic cancer, the stroma may exhibit not only remnants of the old bone lamellæ of the area invaded, but what is obviously new-formed bone.

Thus, according to the extent of the reaction, so do we distinguish three forms of cancer: (1) *medullary*, when the cell growth is abundant and predominant, the stroma inconsiderable; (2) *scirrhous*, in which the development of the stroma and its overgrowth is the most marked feature, the cancer cells in such cases being small and compressed;

and (3) *carcinoma simplex*, in which neither element can be spoken of as taking the upper hand. Only very rarely, indeed, does the stroma overgrowth pass beyond the irritative stage and assume an independent blastomatous type, leading to the production of the true *carcinoma sarcomatodes*.

At the growing edge the cancer cells are characteristically hyperchromatic, their nuclei stain deeply, they are of the intensely vegetative type. Cells of the same order may be found also in the centre of a growth, with mitotic and other indications that the growth of these tumors may be expansive (from within) as well as peripheral. But frequently we note that, more particularly in the deeper portions of a growth, the cells show evidences of extensive degeneration, and the degeneration varies, often, according to the mother tissue from which a cancer is derived. Thus, fatty changes are common in mammary gland tumors (recalling the active part taken by the normal cells of the mammary gland in passing on absorbed fats into the milk), mucoid degeneration common in tumors derived from the stomach and intestinal epithelium (in evident relationship to the normal function of the goblet cells of the mucous membrane).

Cancer Bodies.—There exists, in fact, a very remarkable series of localized degenerative changes in cancer cells that have been the cause of active controversy for now close upon twenty years; nor can it be said that the controversy is as yet at an end, although the main body of pathologists of all countries are now of the opinion that these appearances are degenerative, and not parasitic. For some years, however, the parasitic theory of cancer had active and enthusiastic supporters. We shall have to notice the various arguments in support of the parasitic theory when discussing the etiology of tumors.

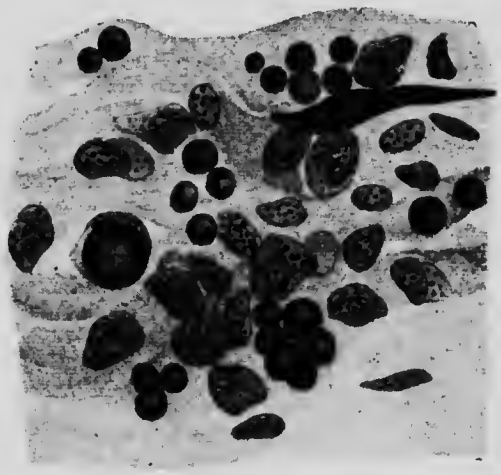
Here we need only refer to these particular changes. They are of two orders—intercellular and intracellular. The first we may dispose of rapidly.

These are the so-called "*Russel's bodies*," small, hyaline, spherical bodies of varying size, the mean size being that of a red corpuscle. They stain an intense red with fuchsin, and thus are easily recognized. From the fact that they often lie in little groups attached one to the other, like vegetative yeast cells, Russel, of Edinburgh, who first called attention to their frequent presence in malignant growths, was led to regard them as blastomycetes. Their presence, however, is not confined to malignant conditions; they may be encountered in a great variety of inflammatory states, and are now accepted generally as examples of hyaline degeneration; whether of red corpuscles of cell substance or of segregated albuminous matter is still a matter of debate.

The *intracellular bodies* assume a variety of forms. There may be a single rounded homogeneous mass within the cell pushing the nucleus to one side; or, like bodies may have a metachromatic central part; or they may be surrounded by a clear space in the cytoplasm; or show a peripheral ring or case, with different staining powers; or this peripheral ring may exhibit an obscure radiation, or present

processes connecting it with the cytoplasm; or, again, a large, rounded, central body may be surrounded by a ring of smaller globules; or a ring or sphere of these globules may surround a poorly staining space; or, throughout the cytoplasm there may be scattered abundant small

FIG. 249



Russel's bodies, stained with fuchsin, highly magnified, from epithelioma of the lip. It will be seen that the majority are extracellular. (Klien.)

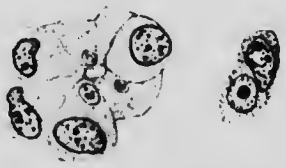
bodies of the first type lying in apparent vacuoles. Lastly, Sjöbring has described a large amœboid, gregarine-like form, at times within the cells, at times free and intracellular.

As will be seen from this rapid review of the main forms described, they are very various, nor have any two observers quite corroborated

FIG. 250

Intracellular bodies of the type of Russel's fuchsin bodies from a case of cancerous leukoplakia in cells of the plasma-cell type. (Krompecher.)

FIG. 251



Cell inclusions in cancer cells — the supposed parasites. It will be seen that the bodies are to the inner side of the cell toward the lumen: in the position that is of modified secretory products. (Greenough.)

each other and the rest regarding what are truly parasitic, what are to be regarded as cell degenerations. As here set forth, it will be seen that the series of forms reads something like the description of the successive stages of maturation of an intracellular protozoon—of the

malarial organism, for example—with progressive enlargement and continual production of peripheral spores, which may, when set free, continue to grow within the parent host; or it may be that several small forms invade a cell at once. And, as such sporozoon forms, they were regarded by Ruffer and Metchnikoff, Sjöbring (first papers), Plimmer, and many other observers. Celli and the Italian school, from the result of experimental inoculations, were led to regard them as blastomycetes—yeast-like bodies. Gaylord has taken an intermediate position, and regarded the bodies (such is the impression we have formed from reading his papers) as presenting both animal and vegetable characteristics.

Fabre Domergue was the first to call attention to the fact that these bodies have the same reactions as degenerative products within the cells, and Pianese, as the result of a most thorough and elaborate investigation, in which he first studied very thoroughly the microchemical staining reactions of mucin, hyalin, amyloid, keratin, and other matters, the products of cell degeneration, carried these observations much farther, and showed that all the forms described corresponded in their staining reactions with one or other of these forms of degeneration; as also that while by selection it was possible to recognize sharply defined and globular bodies in some of the cells of a given cancer, other cells in the same sections show matter giving like reactions, but diffused or so irregular in its disposition that there could be no question regarding its paraplasmic and non-parasitic nature.

These observations of Pianese have never been refuted; nay, more, Borrell and Farmer, Moore and Walker,[1] Greenough,[2] Borrel,[3] and several recent workers have recognized the close similarity between these presumed cancer bodies and the products of nucleolar discharge into the cytoplasm, comparing them more particularly to the changes undergone by the "archoplasm" of developing sperm cells of mammalia. (See Appendix C, p. 922.) It is, of course, possible that there may exist one cycle of intracellular bodies which cannot be explained in this way, but so far that cycle has not been determined, and other considerations, to be noted later, show that no one specific agent can be ascribed as cause of malignant growths in general, or of glandular or epithelial cancers in particular.

Mode of Extension.—While sarcomas exhibit a predilection to extend by means of the circulatory system, cancers show a predilection for lymphatic extension. This does not mean that they also cannot form metastases along the vascular channels; a growth may penetrate the wall of a large vessel and its cells be "seeded" in the next capillary area; thus, we have seen pancreatic cancer invade the splenic vein and cause an extraordinarily diffuse secondary growth in the smaller portal veins in the liver. But in general the cells infiltrating the lymph spaces of a tissue find their way thus into the lymph channels, and

[1] Proc. Roy. Soc. B., 76: 1905.
[2] Jour. of Med. Research, N. S., 8: 1905: 137
[3] Bullet. de l'Inst. Pasteur, 5: 1907: 497.

then, either by continuous growth along those channels or by becoming detached, are found in the group of lymph glands draining the region affected. In this way, after proliferating here, some cells may be carried to the next group of glands in communication, so to the thoracic duct, and so eventually into the jugular vein and vascular system.

Site of Origin.—Often we can come to no conclusion as to the first stage of a malignant growth; it has become too extensive before death ensues. But even in these cases, in the majority of cases it is evident that the condition originated in a single limited area of an organ. If the growth has an external situation, we see that it develops at a single point. Most often (though not always) this is the case with cancer of the breast, and the appearances in other organs point generally in the same direction. This does not, however, mean necessarily that a cancer represents the progeny of a single cell. This matter has been studied by Hauser, and more fully by Petersen.

Petersen employed the ingenious means originated, by the embryologist, Born, of taking serial sections, plotting out each elaborately by means of the camera lucida upon a wax slab, cutting out the parts representing the stroma, and building the slabs one upon the other.

It has thus been demonstrated very clearly that, though in sections the alveoli of cancer cells appear separate, all are connected in series. The growth is like a bush of branching processes. But while in some cases there is a single root, or centre, very often it is pluricentric—a fact which indicates that at the same time several cells in the same region may take on aberrant growth.

Here, as with the adenomas, we have to conclude that these malignant growths may originate either from cell rests or from hitherto functioning cells. The best illustration of the former condition we have met with is, it is true, in a transitional lepidoma, a case of Professor Aschoff's, in the museum at Marburg, in which the one adrenal shows a large infiltrating adenocarcinomatous growth, the size of a child's head, the other, a well encapsuled benign mass, the size of a cherry, a segregated mass of adrenal tissue, which has developed up to a certain point and then remained stationary. The clearest examples of carcinomatosis are afforded by intestinal papillomata. We have already called attention to the irritative origin of several of these growths. They frequently pass on to a malignant stage. Hauser[1] has shown, we think convincingly, that if a series of such papillomas be examined some manifest what must be regarded as the earliest carcinomatous modification.

The cells of certain of the follicles, which otherwise are quite typic are, some of them, seen to have a lessened mucin production; othe show no signs of such production, are smaller, with more deeply staining nuclei, and exhibiting a tendency to form not one, but two and more cell layers. With this the follicles become larger, irregular, form lateral projections and bridges with neighboring follicles, while others form solid processes projecting evidently through the basement

[1] Ziegler's Beitr., 33: 1903: 1.

membrane into the underlying tissue. We have ourselves noted a like series of changes in the same condition.

Occasionally several primary growths are encountered. Sometimes, as may happen in the breasts, one being the larger and noted before the other, it is a question where the smaller is not secondary, due to metastasis from the first. In other cases, as in primary carcinomas of the liver, this cannot reasonably be advanced. These belong to the same category as the multiple epitheliomatous growths of chimney-sweepers, workers in paraffin, and following upon the use of arsenic (J. Hutchinson). The most striking example of the condition is found in adenomatous and adenocarcinomatous growths in the ovary. Here, practically always, both organs are involved. There may be no secondary growths found elsewhere at operation, and only the one organ may appear to be involved, but, if the other be left, it may require subsequent removal, and then presents the same type of disturbance.

So, also, more frequently than is usually recognized, the one individual may exhibit two or more distinct forms of primary growth in different parts of the body. Rarely are these both, or all, malignant; most often we have one malignant and one or more benign tumors, uterine fibromas, or thyroid adenomas, along with epithelium or cancer of one or other organ. But occasionally we encounter two different types of cancer in organs remote from one another. To these cases we have already referred (p. 638).

While one group of these cases (multiple malignant adenomata of the alimentary canal, hepatic "carcinosis," and the occupation epitheliomas) comes under the heading of carcinomatosis, the other group as evidently suggests a general tendency to aberrant growth on the part of the tissues, and is best explained as the outcome of vices of development and multiple development of cell rests.

We have here a condition of affairs curiously parallel with what we observe in infection. There, also, most frequently we recognize a single focus of origin, though in other cases there may be more than one, but these in general simultaneous, or almost simultaneous. And if in these cases we conclude[1] that the growth of the bacteria in the one focus sets up a general reaction of the organism, so that its resisting powers are raised, and the same species of microbe, gaining entrance elsewhere, is successfully resisted, so it may be the general rule in cancer, that once the cancerous process has developed at one focus, the diffusion of the products of the new-growth causes a general reaction, which, not sufficiently strong to arrest the process once actually started, is, nevertheless, sufficiently powerful to prevent the manifestation of like tendencies on the part of other tissues. This, indeed, has been shown to be the case by the experiments of Sticker, Gaylord and Clowes, and Ehrlich.[2] Sticker showed that a mouse with inoculated cancer was immune to secondary inoculation, but the immunity disappeared soon after the primary tumor had been removed.

[1] See Adami, Brit. Med. Journ., 1905, i: 1133

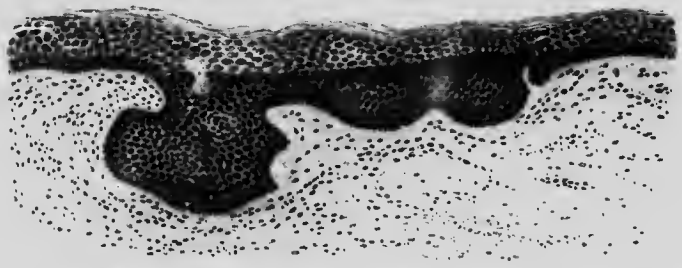
[2] See p. 779

The subject of cancer is so large and so important that much more might here be said. We will, however, proceed now to call attention to some of the more important forms. In describing them, we may have occasion to call attention to matters of importance as bearing either upon etiology or properties of these growths in general.

EPITHELIOMA.

The epitheliomas originate always from a squamous epithelium, and are, as such, in the main of epiblastic origin. It must, however, be remembered that hypoblastic lining membrane may also be of the squamous type, and may also give rise to epitheliomas, *e. g.*, the œsophagus; and as the skin glands of epiblastic origin can give rise to glandular cancers, it is evident that no broad distinction can be made between epitheliomas and gland cancers along the lines of regarding the one as of epiblastic origin and the other of hypoblastic. According to its relationships and its functions, so does a given lining membrane develop either into the squamous cell or the columnar or cylindrical type; and according to the type of the mother tissue so is the type of the malignant growth developed from it.

FIG. 252



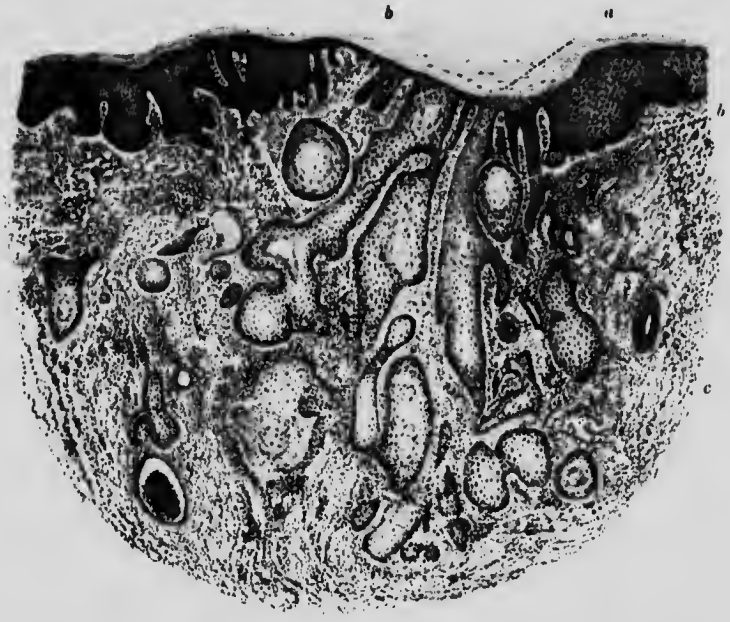
Epithelioma: earliest stage of cancerous metamorphosis and proliferation of cells. (Petersen.)

Characteristically, the squamous-celled epithelioma presents solid columns of cells passing in various directions and cut in sections, now longitudinally, now transversely, lying in a relatively abundant and moderately vascular stroma. As already noted, this stroma is apt to show considerable small-celled infiltration. In the most typical members of this group the epidermal characters of the growth are very marked. There is an outer layer of closely set cells with deeply staining nuclei, representing the Malpighian layer. Within this there may be several rows of prickle cells, which, as the centre of the mass is approached, become indefinite and flattened, and eventually keratinized. Thus, the centre of a process may be formed of concentrically arranged, flattened, and keratinized cells, taking on the eosin stain strongly when hematoxylin and eosin is the stain employed. Such concentric bodies constitute the *epithelial pearls*.

The formation of these pearls is understood if we imagine, instead of a solid downgrowth of epithelium from the surface, a follicle-like downgrowth of skin. Such would exhibit keratinization of the oldest cells farthest away from the Malpighian layer. When the process is solid, these oldest central cells show still the same tendency toward keratinization.

In less typical growths the outer Malpighian layer is not so distinct, and, as von Hansemann points out, the mitoses, instead of being in the main confined to it, occur more irregularly through the whole mass; the prickle-cell elements, also, are not so distinct. In the true rodent

FIG. 253



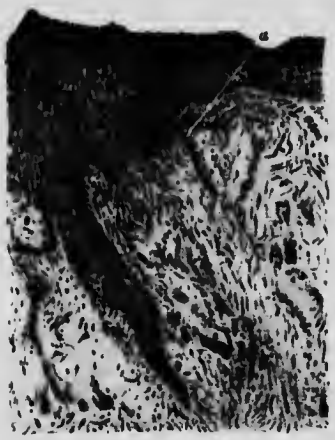
Early epithelioma of tongue, to show (*a*) region of origin by downgrowth from preexisting epithelium; *b, b*, epithelial pearls; *c*, small-celled infiltration in surrounding tissue. (Petersen.)

ulcer occurring in the upper part of the cheek, below or at the angle of the eye, and sometimes a little farther out over the zygomatic area, the cell masses are still more atypical. Epithelial pearls are wanting; the constituent cells are rounded, polygonal, or even spindle-celled in appearance. Nor are the cell masses so sharply defined from the stroma, so that some observers (Braun) have classified these growths as alveolar sarcomas, or endotheliomas, and Borst still holds that the characters and region of growth show this to be the correct view. Careful study seems to show that the processes originate definitely in connection with the overlying skin (though Borst urges that the junction is secondary). The region of development of this particular form of

tumor is curiously limited, and, as noted (see p. 726), while of a very amplastic type and exhibiting considerable, though slow, local malignancy, these tumors rarely form metastases.

Krompecher, recognizing that all conditions classified as rodent ulcer do not belong to the type, has labelled this form *basal-celled carcinoma*, on the mistaken ground that, as it shows no prickle cells or keratinization, it is derived wholly from the basal, undifferentiated cells of the rete Malpighii. But this is so, also, for all epitheliomas. In the more highly developed forms the prickle cells present do not arise from preëxisting prickle cells, but also from the basal mother cells. It is the stage of undifferentiation, or anaplasia—the capacity or incapacity to develop beyond a certain point—that determines the form of the cells.

Fig. 254



Portion of edge of a rodent ulcer.

Fig. 255

Part of the same at *a* more highly magnified to show assumption by the epithelial cells of a spindle-shaped type. (Krompecher.)

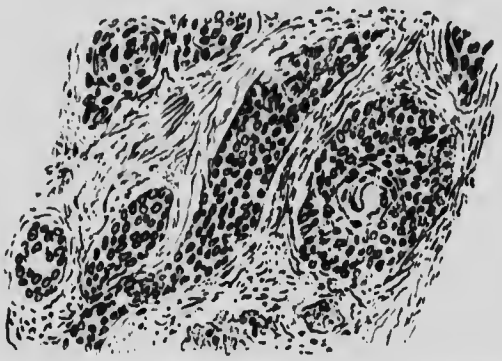
There are certain differences to be made out in the appearance of the tumors, according to the region of origin. Skin and tongue epitheliomas are apt to give the most well-marked pearls. Œsophageal growths in general show them poorly developed, just as normally in the œsophagus the keratin development is not marked.

The more rapid the growth, the deeper the infiltration, the more atypical is apt to be the growth; we have encountered metastasis of a very malignant epithelioma of the tongue which it has been impossible to distinguish from those of a medullary round-celled cancer.

Then it must be noted that squamous-celled epitheliomata occasionally present themselves primarily in regions which normally show a columnar epithelium; such have been recorded from the larynx, lung, bronchi, stomach, gall-bladder, uterus. There is still dispute regarding

these. As the result of chronic inflammation, all these organs may show metaplasia and development of squamous epithelium. And to this metaplasia several would ascribe these epitheliomatous growths. Others point to the fact that occasionally islands of squamous epi-

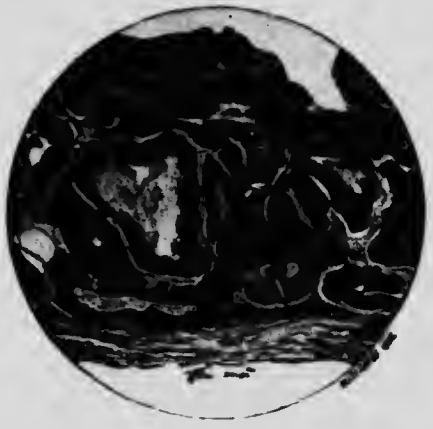
FIG. 256



Aberrant squamous epithelioma of gall-bladder. (Von Hansemann.)

thelium are found (in the uterus, for example) where there has been no history of previous inflammation, and these they ascribe to congenital displacement. There is, however, no possible neighboring

FIG. 257



Epithelioma of the antrum of Highmore with degeneration and liquefaction of the centre of the cell masses, producing large pseudolumina. (Krompecher.)

organ that could afford squamous epithelium to the gall-bladder. Others point out that the tumors arising in these organs, in the gall-bladder and uterus, at least, are not typical epitheliomata; that they show no epithelial pearls, and nothing corresponding to a Malpighian

layer. This we hold is the case: *they are not typical epitheliomata, but, also, they are not tumors of the type ordinarily arising in these organs* —not adenocarcinomas, but solid cell growths. Were we dealing with cell rests, they should afford tumors true to type.

We would scarce expect acquired characters to be so tenaciously preserved as those of primary endowment, but clearly, in these cases, the metaplasia has modified the nature of the resulting tumor. To the importance of this conclusion I shall revert (p. 776).

Lastly, an abnormal form of epithelioma is to be noted, in which, instead of epithelial pearls, degeneration occurs in the centre of the large epithelial cell masses, whereby false lumina are produced, giving the growth a transitional appearance. We have come across this form in man, and once in the horse, in connection with the antrum, the pharynx, and the œsophagus. Krompecher includes this as one of the types of his *carcinoma basocellulare*. Similar appearances are sometimes to be encountered in secondary growths from gland cancers, *e. g.*, from the stomach.

GLAND-CELLED CARCINOMA.

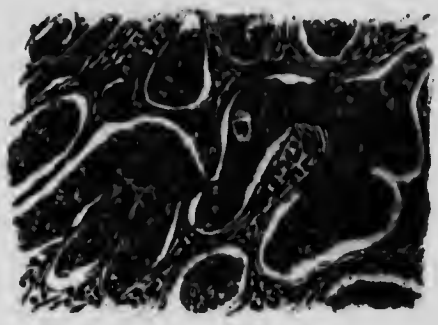
According to the structure of the mother tissue, and the stage of anaplasia, so do we encounter a series of forms of uncomplicated carcinoma. From mucous membranes which, normally, are provided with simple follicles lined with a cylindrical epithelium, as again from ducts, like the bile duct, and from tubular glands, we are apt to obtain cancers which, in some parts at least, exhibit a tubular arrangement. From acinous glands we may gain cancers whose alveoli have a more solid type and grape-like arrangement; from the liver, alveoli formed of solid irregular strands. On the other hand, with greater anaplasia all glandular organs may give rise to growths formed of solid cell masses. Once again the cancer has to be judged according to its region of origin; what in the one case is a relatively typical form of growth, in another may be most atypical. In general, however, we may distinguish certain main types.

1. The *adenocarcinoma*, including forms of highly glandular type, and differing but slightly, as we have noted, from the simple adenoma (the so-called malignant adenoma) (see Fig. 259), and others in which only here and there the alveoli possess lumina, with cells arranged around them with some approach to the arrangement seen in the parent gland, the rest of the alveoli showing solid cell masses with, it may be, several imperfect small lumina scattered through, or only *pseudolumina* (produced by cell degeneration), or altogether devoid even of this distant imitation of the normal glandular arrangement.

2. The solid-celled carcinoma, departing still farther from type, in which the alveoli are formed of an aggregation of cells without sign of orderly arrangement—cells either large, full, and rounded, or irregular in form, polygonal and compressed. More particularly in the latter type we may make the further classification (see p. 727) into the (1)

medullary forms, formed of large cell masses, with little stroma, and that very vascular; (2) ***scirrhous***, with abundant stroma, compressing the cells, and showing alveoli formed of few individual cells, and those compressed and small; and (3) carcinoma simplex, the intermediate form.

FIG. 258



Carcinoma simplex. (Ribbert.)

A yet further classification of the adenocarcinomas may be made according to the tissue of origin into:

(*a*) ***Cylindrical-celled carcinomas*** arising from mucous membranes, *e. g.*, the less atypical cancers of the alimentary tract, corpus uteri, and, in part, of the cervix uteri (for here there may also be squamous epithelioma, Fallopian tubes, gall-bladder, and portions of the respiratory

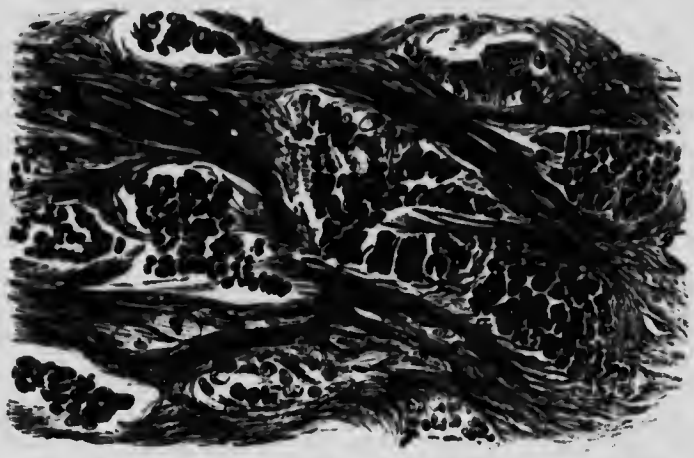
FIG. 259

Medullary cancer. (Ribbert.)

passages (nose, trachea, bronchi). In all these there is a columnar-celled epithelium of one or more layers, in all a distinct tendency not merely to infiltrate, but to grow outwardly into fungating polypoid masses; in all, again, so long as the adenomatous type of growth is preserved, some liability to formation of goblet cells and continued formation of mucin.

(*b*) *Duct carcinoma*, arising from ducts provided with a more or less cubical epithelium, in which, again, the less atypical forms present characteristically alveoli, recalling the characters of these ducts. Such

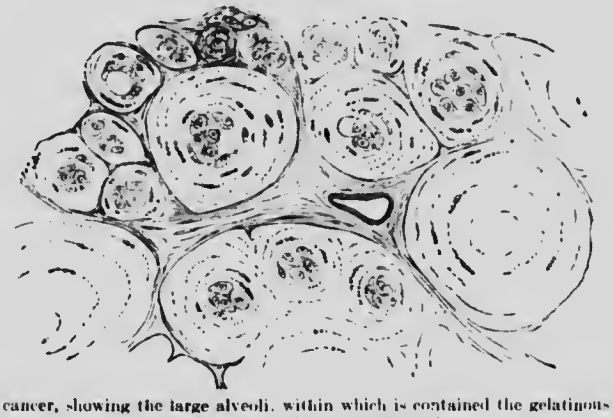
FIG. 260



Scirrhus of breast. The cells are compressed and degenerated and the stroma relatively abundant. × 250.

we may get in the liver, from overgrowth of the smaller bile ducts. This is the most characteristic form of primary cancer of the liver, and may, indeed, represent not so much a growth of these ducts as an

FIG. 261



Colloid cancer, showing the large alveoli, within which is contained the gelatinous colloid material. × 300. (Rindfleisch.)

anaplasia or reversion of the liver cells primarily affected to the earlier stage of their development. In the mammary gland occasionally we meet with cancers in which the ducted appearance is predominant.

(c) *Gland cancer*, reproducing imperfectly the structure of the component acini of the glandular tissue of origin. Such, according to the tissue of origin, may be composed of more tubular alveoli (C. tubulare), or of grape-like acini (C. acinosum), as in adenocarcinoma of the pancreas and of the prostate, or of follicles tending to be separate (C. folliculare), as in cancer of the thyroid and of the ovary.

We may meet with a combination of these forms; thus, in the mammary gland we meet with all possible combinations of duct, tubular, and acinous cancer, with, in addition, another form, which has here to be noted, the cystadenocarcinoma.

The organs and parts which give rise to these various forms of adenocarcinoma may, it must be remembered, give rise also to the more atypical and undifferentiated solid-celled cancers.

Degeneration.—What we have said regarding the degeneration affecting the adenomas applies here also. We may note particularly:

1. The tendency that superficial cancers have to undergo extensive ulceration. This applies especially to the cancers of mucous membranes (as, indeed, also, to the necessarily superficial epitheliomata). The new tissue is of a lower order not under the governance of the nervous system, cannot control its blood supply, and so is capable of offering little resistance to insults and infective agents.

2. The extensive mucoid and "colloid" degeneration that this same order of cancers may undergo, especially those of the digestive tract, leading to the development of what is termed *colloid cancer*. The cells of an adenocarcinoma, while still retaining the power of forming mucin, may, nevertheless, be unable to excrete it properly, with the result that it becomes heaped up in the cells to such an extent that they become greatly distended and eventually die. Whole alveoli may be found composed of the more or less inspissated and fused cell bodies—and the growth, filled with this modified mucin ("colloid"), presents a remarkable, massive, translucent appearance. So extreme may be the condition that only here and there, upon careful search, may alveoli be found showing relatively healthy cells, and affording a clue to the nature of the change.

Metaplastic Glandular Cancer.—Just as we noted that from a columnar celled surface occasionally a squamous epithelium is found to arise, so, but much more rarely, do we get indications of the opposite process. The majority of the cases so far recorded must be regarded as the results of tissue disturbances and cell rests. But Schridde has pointed out recently the normal presence of islands of columnar epithelium in the œsophagus, having a common origin with the surrounding squamous epithelium, and this would seem well to explain the occasional occurrence of a columnar-celled cancer in this organ. And Enderlen has noted the frequent conversion of the many layered vesical epithelium into a definite columnar-celled type in cases of ectopia vesicæ, and in one case has seen this metaplastic tissue give rise to a definite adenocarcinomatous condition (see pp. 588 and 736).

CHAPTER XXII.

THE TRANSITIONAL LEPIDOMATA (MESOTHELIOMAS AND ENDOTHELIOMAS).

It will be recalled that we classed together as a main group of lepidic tissues all those lining-membrane tissues of mesothelial and mesenchymatous origin, derived secondarily, that is, from the mesoblast, and suggested that tumors developed from these be placed in a separate class, as the secondary or transitional lepidomata. Of these, upon consideration, it will be seen that we can make four groups: (1) the tumors arising from the developments and vestiges of the Wolffian and Müllerian ducts; (2) those arising from organs which, while they come into intimate relationship with these, nevertheless, as regards their essential constituents, are of separate mesothelial or mesoblastic origin (ovaries, testes, kidneys). With this group may be included the adrenals; (3) other mesothelial tumors derived from the serous surfaces, and (4) the endothelial tumors.

1. UROGENITAL DUCT TUMORS.

We make these separate classes because the urogenital duct tumors occupy a position by themselves. Whether, as we have hinted, these ducts gain a secondary lining of hypoblast or epiblast, or whether, from their singularly early differentiation, the properties of their mucous membrane are more fixed, certain it is that the tumors derived from them are most often of pure lepidic type—true adenomas and true carcinomas—with little tendency, so far as we can see, to take on secondarily hylomatous (sarcomatous) development. Thus, in the uterus, we have pure adenomatoid or cancerous growths, indistinguishable in this respect from the adenomas and cancers of the digestive tract. The same is true in the prostate.

We have encountered a tumor of the prostate, certain portions of which, submitted to other well-known pathologists, were diagnosticated by them as possible alveolar sarcoma. Examination of all parts of the growth showed that in the body of the organ itself the appearance was that of a typical adenocarcinoma. As the growth infiltrated the bladder wall, and grew freely into the vesical cavity, the cell growth became most abundant, the stroma correspondingly diminished, until there developed a collection of large alveoli filled with moderately large, round cells, the alveoli being surrounded by thinnest of vascular stroma. The growth thus was still a cancer, though of the extreme medullary type

The same holds for tumors of the Fallopian tubes, and, if we mistake not, for here our experience is very limited, for those of the ureters, vas deferens, and vesiculæ seminales. It is thus, also, for the interesting series of tumors which arise in the various developmental remnants of, more particularly, the Wolffian ducts in the female.

So far as we can see, few or no observations exist upon tumors originating from the corresponding remains of the Müllerian duct in the male (from the prostatic sinus or uterus masculinus, and the sessile hydatid of the epididymis). When these remains take an aberrant growth, their tubes being blind, they inevitably produce cysts—cystadenomata and cystocarcinomata. It is still a matter of debate among the embryologists to what extent the tubules of the primitive kidney (pronephros or Urniere) are contributed by the Wolffian tube itself; to what extent they are formed by the nephrotome, or mesoblastic blastoma; and by the pathologists how far ovarian and testicular growths are derived from components of the primitive kidney which take part in the development of those two organs. It is impossible, therefore, at the present time to make a positive embryogenetic differentiation of the tumors affecting these two organs. While tumors of the broad ligament are regarded as largely due to Wolffian duct remains, there is a conflict of opinion as to the part played by the Wolffian duct remnants in the development of ovarian cystadenomata.

2. TUMORS OF THE OVARY, TESTIS, ADRENAL, AND KIDNEY.

In the primitive kidney (Urniere), while the Wolffian duct provides the distal, collecting portion of the tubules, the glomerular epithelium and the main portion of the tubules are of mesoblastic origin; the same, following Balfour and Sedgwick,[1] is nowadays more and more accepted for the kidneys—that here the glomeruli and convoluted tubules are of mesoblastic (mesothelial) development. In the development of ovary and testis, not the Wolffian duct, but the primitive kidney, intimately connected as it is with the duct, is similarly involved, along with the germinal mesothelium.

This much may be said with regard to all these organs, that while in all four we may encounter pure adenomas showing no tendency to reversion, in all we encounter a remarkable series of transitional tumors, tumors in certain areas definitely of adenomatous type, in others, formed of solid cell masses which are not truly adenomatous, because, on employing Mallory's stain, we find that here and there connective-tissue fibrils are present between the cells. These portions are of the nature of alveolar sarcoma, and, on careful study, we can make out the transition from the truly adenomatous to the alveolar sarcomatous areas. And from these latter areas we may pass to regions of purely sarcomatous type, round, or even blunt spindle-celled. The

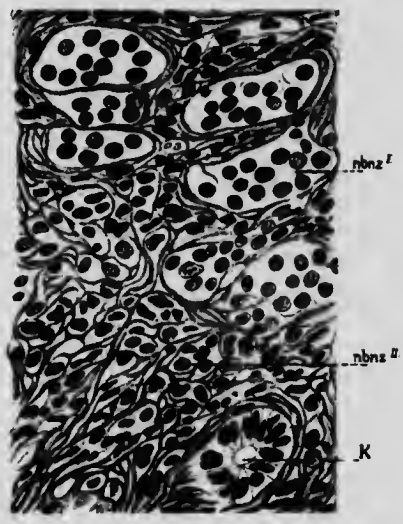
[1] See p. 787 for a fuller study of the embryogeny of the kidney.

picture is an extraordinary one, wholly at variance with the older views of the "sanctity" of sarcomatous and carcinomatous properties. Here, absolutely without any manner of doubt, a tumor shows transition from carcinomatous to sarcomatous characteristics. The condition has been regarded as inexplicable, has been labelled carcinoma sarcomatodes, or sarcoma carcinomatodes, has been treated as a never-do-well member of the family, and too often left out of account in general discussions upon the family relationships of neoplasms. Some have thought to dismiss these cases by the ruling that mesoblast cannot form true gland tissue and true adenomas or carcinomas; that wherever, as in the kidney, we obtain typical gland tubules, these must be of epiblastic or

Fig. 262

Hypernephroma of kidney, section from same tumor shown in Fig. 263. In this portion the growth retains the columnar arrangement characteristic of adrenal cortex, the columns of cells (*nbn*) being separated by a capillary network, *Bdg*.

Fig. 263



Transition from adenomatous to sarcomatous type of growth: *nbnz*^{I}, adenomatous overgrowth of solid columns or masses of cells of adrenal type; *nbnz*^{II}, transition to sarcomatous arrangement; *K*, a kidney tubule involved in the growth. (Debenardi.)

hypoblastic origin; others have denied the transition. But the fact is there that such transition occurs, and is to be found in tumors of just these organs, as, again, in the endotheliomas, to be presently mentioned.

Adrenal Tumors.—More particularly in the ovary and testis, as above noted, and to a less extent in the kidney, we at the same time may encounter tumors of fixed type, showing no signs of transition. These (possibly, as we suggest, originating from the more stable Wolffian epithelium) introduce an element of confusion. There is an organ free from constituents of this nature, and in it we find the most unequivocal examples of the transitional tumors in question. We refer to the adrenal bodies.

These are formed of two constituents, which in the lower vertebrates (*e. g.*, selachian fishes) remain permanently separate, but in the higher vertebrates become joined. The medulla originates in connection with the sympathetic system; the cortex, it is now generally accepted, from mesothelial elements closely related to those which originate the cortex of the primitive and the permanent kidneys.

From the medulla we obtain grayish tumors, never attaining any good size. These have been studied more especially by Marchand, who has demonstrated that they are amyelinic ganglioneuromas—true neuromas; that they contain rudimentary ganglion cells and non-medullated fibers, and, in short, must be regarded as developed from cell rests of sympathetic constituents. At times tumors are noted containing characteristic homogeneous pigmented cells, the so-called chromaffine cells, which are present in the normal adrenal medulla, and also are in relationship to the sympathetic system, for tumors composed of those elements have been described in connection with the solar plexus. The cortical tumors are of wholly different order. It is of frequent occurrence to find accessory suprarenals.

These are portions in general composed only of cortical tissue, either lying separate in the adrenal capsule, or outside it, or even as isolated, capsulated little nodules within the adrenal tissue. Or, again, these have become adherent to and inclosed within the liver during development, or, more often, to and in the kidney. As Marchand has pointed out, the ovary, also, and the testis may carry down with them portions of adrenal tissue in their descent. In the rat, for example, such accessory adrenals are constantly found adjoining the ovary and testis.

Such accessory adrenals contain typical cortical tissue, columns of cells lying in a meshwork of capillaries, the cells containing abundant droplets of what appears to be fat, along with others of the nature of myelin. It is not infrequent to find that one or more of these, whether homotopic or heterotopic (under the kidney capsule, for example), which have undergone hypertrophy, so as to be as large as a cherry. It is difficult, perhaps, to know whether to speak of this as hyperplasia or as an adenomatous condition; the fact that they are isolated from the normal tissue, and have grown, despite want of normal relationships, must, we think, place them among the benign adenomas. Others evade the difficulty by terming the condition *struma suprarenalis*, just as like nodules in connection with the thyroid are also labelled struma—a convenient word, which means simply "nodular swelling." But, in addition to these, we may have much larger growths, often as large as a child's head, developing in connection with the adrenal.[1] Studying them, we find the remarkable series of transitions noted. In some the growth throughout retains the character of the normal cortex, and is of adenomatous type. We have solid columns of cells, lying in a meshwork of capillaries, the cells much larger than normal, densely

[1] As also, rarely, in the liver. See Pepere, Arch. de Méd. exp. et d'Anat. pathol., and White, C. P., and Mair, Jour. of Pathol., 12: 1907: 107.

filled with fat and fat-like globules and glycogen (the last a constant constituent of the growing adrenal). Here and there may be giant nuclei, or cells with three or four nuclei, but the type of structure is well preserved. In other tumors of this type we encounter an occasional definite tubule, a column of cells possessing a lumen. Such tumors we must regard as adenomatous.

The existence of lumina is common in the cortex of the bird's adrenal, and is occasionally met with in the otherwise normal adrenal of mammals. It is a further support for the view now held that the adrenal cortex is of like origin to the renal cortex, derived from the same order of cells, and for the contention that these tumors are adenomas.

But other tumors exhibiting in the main these characters show in various areas a development of more irregular cell masses. The cells in those masses become smaller, less fatty, the nuclei more deeply stained, and in one and the same section we may have every transition, from the adenomatous, through the alveolar sarcomatous, to the diffusely sarcomatous appearance, with the appearance not merely of round, but also of irregular spindle cells. What is more, as well shown by the early case studied in our laboratory by Dr. Woolley, a tumor of the adenomatous type in the adrenal may furnish metastases of purely sarcomatous type. The same has been noted by Jores and Askanazy, the latter noting also that after removal of the adenomatous tumor the recurrence was sarcomatous.

It is but necessary to glance over modern literature to see what confusion exists regarding these tumors. Some speak of them as alveolar sarcomas (Beneke), others as angiosarcomas, or among the peritheliomas; others, again, as carcinomas (Ribbert); others, not to commit themselves, as hypernephromas (*hypernephros*, the suprarenal), hypernephroid tumors (Lubarsch), suprarenal epitheliomas (Marchand).

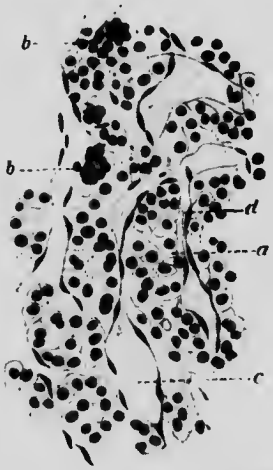
The same doubt as to their exact nature extends to the tumors developing from heterotopic adrenal tissue, notably in the kidney (*hypernephroma* or *struma suprarenalis aberratæ*). Grawitz was the first to recognize the relationship between a group of large and eventually malignant tumors which affect the kidney, most often after the fortieth year, and the frequent adrenal cysts in this organ. His views are now very generally accepted, though there is still debate as to whether all the tumors included by him and others under this term are truly of adrenal origin, and whether the cortex of the kidney itself, being so closely allied to its origin, may not give origin to tumors of like order.

We are of opinion that this latter view must be accepted, that whereas, aberrant adrenal tissue is, from its heterotopic nature, more prone to become blastomatous, and whereas, it may well be that a large number of the kidney tumors of this type are hypernephromas, others are "nephromas." We certainly encounter typical tubular or cystic adenomas of renal origin, and know now that what we once regarded as the conclusive demonstration of adrenal nature, namely, the presence of glycogen (Lubarsch), is of little diagnostic value. A very large number of embryonic tissues, as, again, of freely growing

tumors, contain glycogen in their cells. When a tumor of the kidney shows a special liability to form tubules rather than solid cell masses, we would suspect a renal rather than an adrenal origin. Not to enter exhaustively into the subject, we would say that the two organs are embryogenetically so closely related that *tumors arising from homologous tissues must possess closely related characters.* Where, as is most frequent, but by no means constant, one of these growths arises from the upper pole of the kidney, there the probabilities are that it is of adrenal origin.

Certain other properties of these more malignant tumors as a group remain to be noted. They are apt to be extremely vascular; the cells lie in close contact with the capillaries, with, as a rule, little connective-

Fig. 264



Section of portion of a hypernephroma of the kidney. A characteristic area showing columns of clear polygonal cells: *a*, lying in immediate apposition to the endothelium (*d*) of the capillary sinuses (*c*). At *b*, areas of infiltration and degeneration.

Fig. 265

Section from another portion of the same tumor, more highly magnified, showing tubular arrangement: *a*, swollen translucent tumor cells surrounding a definite lumen *b*, capillary *c*, fat droplets in tumor cells. (Buday.)

tissue stroma; the vessels are apt to be greatly dilated. Thus, hemorrhages are frequent, and necrotic areas, and infiltration of the cell masses, which may gain thus pseudolymina, the cells in immediate connection with the vessels retaining their vitality, the central cells of a column or mass undergoing necrosis and becoming replaced by blood so that an endotheliomatous appearance may be produced. So, also, not only are metastases mainly, as in sarcomas, by the blood stream, but both in the adrenal and in the kidney the tumors are curiously apt to grow in continuity along the veins into the inferior vena cava.

If a convenient term is required for all this order of tumors, the transitional adenocarcinomas of adrenal, kidney, ovary, and testis, we have, from embryogenetic considerations, suggested the term *mesothelioma.* Briefly, a mesothelioma is:

1. A tumor arising from such tissues or portions of organs as, being of mesothelial origin, possess in the adult state lepidic characters.

2. When typical, and growing slowly, it is of pure adenomatous type.

3. When atypical or more anaplastic, and growing rapidly, it reverts first to an alveolar sarcomatous type, and later to a structure, or want of structure, which renders it indistinguishable from a round or even a short spindle-celled sarcoma.

4. The tumor, when it takes on this undifferentiated type, affords metastases of sarcomatous order. The primary growth, in general, if studied, exhibits indications of the successive stages through which it has passed, from the adenomatous to the sarcomatous form of growth.

I would recall that in the chapter upon Classification (p. 647 et seq.) there is given what, to me, appears to be a reasonable explanation why this order of tumors has these particular properties.

3. MESOTHELIOMAS OF SEROUS SURFACES.

Occasionally on the pleural surface, more rarely in connection with the peritoneum, and still more rarely in connection with the pericardium, there is encountered a form of tumor which, from all the attendant circumstances, is of primary origin at these sites. They are flattened, nodular tumors, spreading locally over the serous surface, causing what at first sight appears to be extreme inflammatory thickening, of the nature of a localized hyaloserositis; but in general, on microscopic examination, they are found of a distinctly cancerous type. A relatively abundant fibrous stroma contains elongated acini, lined with irregular, swollen cells, large and sometimes almost cubical, resembling the curiously epithelioid type of cells we encounter in some endotheliomas. In parts these are flattened, lining long narrow spaces, and then they recall endothelioma proper. In one case that came under our observation it was possible to follow the cells covering the peritoneal surface directly, first into more solid cellular downgrowths into the omental tissue, and thence, apparently, into the lymph spaces of the part. Sometimes, in place of a single layer of tumor cells, we encounter more solid masses, and in one case (in the pleura) we have noted a transition into the alveolar sarcomatous type.

Taking into consideration all these characters, it is difficult to regard these tumors as other than mesotheliomata, originating from the endothelium (or epithelium, whichever term be preferred) covering the serous surfaces, that cell layer being of mesothelial origin.

Here, again, there has been great debate as to what these should be called, some regarding them as endotheliomatous, others (Ribbert) as true carcinomas. Histologically, they most often present a strikingly cancerous appearance. In certain early vertebrate ancestors, as pointed out by His, the body cavity originates as an invagination of the hypoblast; there is no sign of such invagination in the higher

vertebrates, in whom the serous cavities seem clearly to originate by a splitting of the mesoblast and formation of a lining mesothelium.[1]

4. ENDOTHELIOMA.

Of those tumors in which overgrowth of the lining cells of vessels is the most prominent feature, we distinguish naturally two groups: the *hemangio-endotheliomas*, originating from the lining membrane of bloodvessels; the *lymphangio-endotheliomas*, from that of the lymph vessels. The two groups present many features in common, nor is it always easy in tumors of large size and long establishment to determine with which form we have to deal; but even in such cases, in one or other part of a tumor we may encounter vascular spaces lined by one or more layers of tumor cells, which, if they contain blood corpuscles, are clearly of blood capillary nature, if free throughout from formed contents, must, *per exclusionem*, be regarded as lymph spaces.

Ribbert objects that no proof is afforded of the nature of these tumors by finding vessel spaces lined by cells approximating in type to those of the tumor. We cannot but feel that the objection is hypercritical. While, with him, we agree that it is contrary to experience to find that the normal cells in the neighborhood of a tumor take on, progressively, blastomatous features, the other possibility has to be admitted, that proliferating endothelial cells replace the normal cells in their outward extension. How, indeed, otherwise does he, or are we to, explain the continued enlargement of these tumors? For grow they do, and such is their structure that the growth cannot be central. We see such a process occurring in the uterus in pregnancy, when the fœtal syncytial cells absorb and replace the endothelium of the maternal blood sinuses, and it is in full harmony with all we know concerning cell properties that such tumor cells, when in relationships which more nearly approach the normal, should themselves exhibit characters most nearly approaching the normal.

Typical Endotheliomas.—We find some little difficulty in treating the growths, and that because, under this heading, it is customary to consider only the growths of an atypical type. Following our custom, we think it necessary to call attention first to typical growths. These, along with a collection of what are not blastomas at all, have usually been discussed as a class apart, and this by modern writers, who, nevertheless, admit that they are of the nature of benign endotheliomas. We refer to the *angiomata*. These, then, we will first take into consideration.

5. ANGIOMA.

We cannot but conclude that the majority of so-called angiomas, or tumors having vessels as their main constituent, are spurious blastomas, whether formed of bloodvessels (“*hemangiomas*”) or of lymph

[1] See Miller and Wynn, Jour. of Pathol., 12: 1908: 267, for bibliography of these conditions.

vessels ("*lymphangiomas*"); *they possess no power of independent growth.* Mere dilatation and filling of vessel spaces with fluid is not growth, even if preceded by aplasia and followed by atrophy of the tissue proper to the part. And in the majority of cases the evident increase in length of the vessels (such as must occur in *cirsoid aneurysms*) or thickening of the walls of the individual dilated loops (such as we see in *cavernomas*) is apparently not in excess of the physiological requirements. We find, that is, no evidence of proliferative capacity, at most a widening of preëxisting vessels, either of congenital origin, and ascribable to a primary want of co-ordination in the growth of the vessels of a part and of the tissue or cells they should nourish, or of postnatal origin, due to alteration in blood pressure of the nature of local venous obstruction, as, for instance, in the multiple capillary telangiectases, which can be produced in the liver by partial obstruction and stenosis of the hepatic vein—*hemorrhoids* are of this nature—or due to local atrophy of the cells of a restricted area in an organ, the capillaries undergoing what we may speak of as compensatory dilatation. We do not mean to imply that true angiomatous blastomas are nonexistent; as we shall point out, they exist, only, compared with the spurious form, they are distinctly rare.

Here once more we must dwell on the meaning of words. A cell rest or inclusion within a tissue is not a blastoma so long as it lies latent and is not growing; similarly, a mass of tissue which, owing to developmental defects, is aberrant in structure is not a blastoma so long as it strictly respects physiological laws and at most grows coincidently with the rest of the organism. Independent growth is the test of what constitutes a tumor of this order. Does this mean that we are to remove most of the conditions now included under the heading of angiomas, and place them under the class of, say, telangiectases? Frankly, this would be the better course; it would make for precision. We must be governed here by our conception of the meaning of the word *angioma*. If that is to be taken as meaning simply a swelling composed of bloodvessels, then all these remain as angiomas. If we restrict it to mean a tumor, due to the independent growth of vessels, they must be cast out of this class. To provide a class for them Albrecht has suggested the term *Hamartoma*.[1]

BLOOD-VASCULAR TUMORS ("HEMANGIOMAS") WHICH ARE NOT BLASTOMAS.

1. **Obstructive Telangiectases.**—The type example of such is the *hemorrhoid*, or pile.

The hemorrhoidal veins of the anal region communicate, it will be recalled, with both the main and the portal venous systems. Situated, as are these veins, immediately beneath the surface, and so, poorly

[1] Apparently from ἁμαρτια = error, *i. e.*, due to developmental defects.

supported, obstruction to the onward passage of the blood in either system is liable to lead to a dilatation of the capillary loops and smaller veins.

Similar capillary telangiectases are not infrequent in the liver; notably they occur in connection with the nutmeg liver (chronic passive congestion), as, again, upon the nose and cheeks of elderly individuals, apparently secondary to localized fibrotic change and venous obstruction; while venous telangiectases (*varices*) are also common, and due, if not to obstruction, at least to giving way of the walls against the weight of the column of blood (pampiniform plexus, superficial veins of the lower extremities—*varicose* veins, etc.). In like manner, weakening of the arterial wall, so that it is unable to withstand the internal blood pressure, leads to the production of:

2. **Aneurysms.**—Of these, one variety has been the cause of debate whether it should be regarded as angioma, namely, the *cirsoid* aneurysm. This is evidently congenital, may show itself at birth, but sometimes only "grows" rapidly in adult life. The favorite seat is the scalp, where the worm-like pulsating arteries beneath the skin give a very characteristic sensation. The dilatation of the vessels may lead to erosion of the skull. The condition, we hold, can only be ascribed to a congenital weakening of the arterial wall, relative to the blood supply and blood discharge.

We had occasion to examine one such some weeks after it had been reduced by ligaturing the carotid on the same side. The case was that of a young adult, in whom, from being inconsiderable, the aneurysm had rapidly increased. We found practically nothing. There was no evident increase, in our sections, in the number of arteries of the temporal region which had been involved; at most, a condition of fibrosis, and that not of recent type.

It has been argued that in these conditions there is a condition of angiomatosis, because on ligature or removal of such cirsoid aneurysms they are liable to recur. In face of this finding we can only conclude as above, namely, that there is a constitutional weakness of the arterial walls, coupled with inadequate discharge, and so with relative and local increased pressure an artery and its branches becomes widely distended. A like cirsoidal aneurysmal condition occasionally follows trauma.

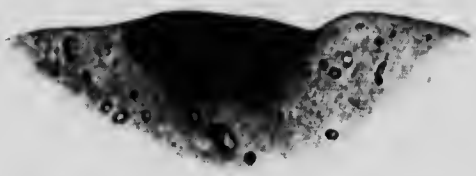
3. **Congenital Telangiectases.**—(*a*) *Telangiectatic Nevi:* Some nevi (pigmented moles) are purely cutaneous overgrowths, with collection of subcutaneous melanin-containing cells; others are yellow, and of the nature of xanthoma; the majority contain, in addition, dilated capillaries, or may, indeed, be areas of simple telangiectasis, such as the ordinary "birthmarks." An extreme grade of the same condition is the blue nevus, which may be extraordinarily extensive, affecting the whole side of the face, or even larger areas.

At Manchester, as a student, we assisted at the autopsy of an adult, a patient, if we remember aright, of the late Dr. Dreschfeld, in which the whole head and neck were involved. The skin was purple, the

face a collection of coarse nodules. At Marburg, an infant, upon which Professor Aschoff performed the autopsy, showed the whole lower half of the body involved.

The frequent association of the telangiectasis with congenital pigmental disturbances in the same area indicates strongly that here we are dealing with a vice of development. We find two grades; in the

Fig. 266



Cavernoma of liver. Gross appearance. (After Ribbert.)

simple birthmark (N. flammaus) it is obvious that we are dealing with a capillary dilatation; such may also be found in bone, muscle, and (rarely) brain. In the *blue nevus* the vascular spaces are apt to be of greater size, sometimes septate, showing where, by pressure atrophy, neighboring spaces have fused into one, and there is a more cavernous appearance. Some authorities regard these as of venous origin, and speak of venous telangiectases. We are inclined to regard them as of capillary origin, the thickening of the walls and the surrounding fibrosis, which give the walls the venous appearance, being regarded as of the nature of overgrowth through pressure—strain hypertrophy.

Fig. 267

Section of small cavernoma of liver, showing the cavernous and communicating vascular spaces, from which the blood has been removed. (Ribbert.)

(*b*) *Cavernoma.*—From these cases we pass imperceptibly to the cavernoma. These cavernomas are one of the commonest abnormalities to be met with in the liver, where they most often are small—from the size of a pea to that of a hazelnut—but, rarely, may be of great size—as large as an orange, and larger. They are to be found in the livers of young as well as of elderly individuals, and evidently a considerable proportion are of congenital origin, though probably some are acquired through localized atrophy of a group of liver cells and compensatory dilatation of the capillaries of the part.

Examined microscopically, they are found to be formed of large, irregular, distended, and communicating blood spaces, lined by endothelium; the walls between these are relatively thick and fibroid. They may contain groups of pigment particles, suggesting, when present,

possible previous liver cells which have undergone atrophy, but of persistent liver cells there are none in the affected area. There is a liability to thrombosis in these cavities, indicated by the presence of recent blood clot, or organized blood clot, and fibrous bands; or, again, of calcification and formation of phleboliths.

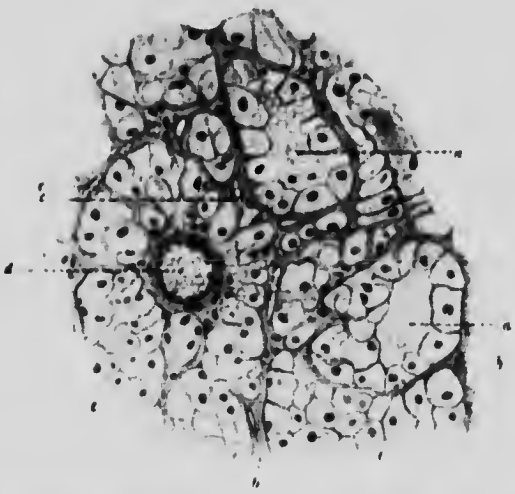
Here, also, we deal apparently with what are capillary ectases. As we have noted, some are obviously of congenital origin, and it is suggested that they are due to a vascular branch not becoming clothed with, or not entering into connection with, liver cells; while Ribbert and others have called attention to the fact that the spaces do not communicate with the surrounding capillaries, and cannot be injected through the hepatic vein. We have noted these 20 times in 1400 complete autopsies, more frequently, in proportion, in adults and elderly people than in the young, and so are inclined to regard some, at least, as due to localized atrophy of liver cells. They show absolutely no signs of independent growth.

TRUE TYPICAL BLASTOMATOUS HEMANGIOMAS.

Angioma Simplex.—There are, however, true hemangiomas in which we encounter what can only be regarded as a progressive new development of capillaries. The slightest grade is seen in what are otherwise simple capillary angiomas, characterized by no pronounced ectasis. Some there is. But what is the marked feature is that the endothelium is very prominent; not only are the cells relatively large, with much cytoplasm, but they are two, and it may be more, layers thick. The appearance is not that which would be given by contraction of dilated capillaries in the process of preparation; there has been a definite overgrowth. Such cases have been recorded from the skin, the chorion, and muscle. A definite tumor is thus formed, composed throughout of these proliferating endothelia tubules. This we may speak of as the true benign hemiangioma. A more advanced condition is seen in what Ziegler termed, we think unfortunately, *angioma hypertrophicum*, for there is more than hypertrophy—there is a true blastoma formation. In this, while some of the capillaries have the appearance noted above, in others the endothelial overgrowth has become so extensive that solid columns of cells are formed, and, what is more, these appear to be budding or projecting into the surrounding tissue. Save that the capillary tubes are the prominent feature, the condition is scarcely removed from what is characteristic of the hemangio-endotheliomas. A full study of a case of this nature, which, while benign, afforded metastases, has recently been published by Borrmann.[1] In fact, it will be seen from this description that we regard the angiomas proper as *typical* endotheliomas; that we regard the capillaries alone as giving rise to the condition, and see, in the capillary endothelium, the one

[1] Ziegler's Beiträge, 40: 1907.

FIG. 268



Section from a hemangio-endothelioma of bone: *a*, large vascular spaces filled with erythrocytes and surrounded by large, clear, cubical endothelial cells, which in parts, as at *c*, form solid masses; *b*, stroma; *d*, larger and *c*, smaller bloodvessels. (Driessen.)

FIG. 269

Section from a case of hemangioma simplex, exhibiting progressive enlargement and extension (Borrmann.)

primary factor in new vessel growth. All other conditions come under the heading of telangiectases.

Next may be included, possibly, a remarkable and rare form, whose nature, we believe, was first recognized by Ziegler. This has its seat in the skullcap, and presents itself as a sharply defined nodular growth, composed of large blood-filled spaces, with little interstitial tissue, each lined by a relatively large and very regular cubical epithelium. This form is most nearly related to the hemangio-endothelioma of bone and kidney, but differs in the remarkable regularity of its gland-like endothelium, and not infiltrating, sharply defined character.

We encountered this form once many years ago, before we knew much regarding endothelial possibilities, and shall not easily forget how it mystified us. The epithelium had an obviously glandular appearance, and the cavities were as obviously filled with blood.

Ribbert denies that vascular endothelium ever takes on such epithelial type as is seen in tumors of this nature, and so excludes them from the class of endotheliomata. In so doing he forgets the swollen epithelioid character that the endothelium may take on (along with increased proliferation) in various forms of inflammation, notably in endarteritis affecting arterioles. There the cells become strikingly epithelioid.

LYMPHANGIOMA.

Here we have an exactly parallel series of cases to those observed in connection with the bloodvessels. The majority of cases termed lymphangioma are strictly lymphangiectases. These may be wholly apart from any other form of growth, or, like capillary ectases, may accompany various forms of tumor.

In the preceding section no reference was made to what we have called attention to elsewhere, namely, the frequent occurrence of dilated capillary spaces in every form of overgrowth, which, more particularly in the connective-tissue group, may afford indication of actual new formation of vessels. When such occurs, it is strictly subordinate to the growth of the tumor, and in no sense independent, save in the hemangio-endotheliomas, so that to speak of an angiofibroma, etc., is incorrect. "Telangiectatic fibroma" expresses more accurately the condition. The same is true in respect to the frequent occurrence of dilated lymphatics in tumors; the condition here is subordinate, and, indeed, may occur in company with the former. When independent of other new-growth, these lymphangiectases may be either inherited or acquired. We thus distinguish three grades, although between them there is every transition.

1. **Simple Lymphangiectasis** (**"Lymphangioma Simplex"**). (*a*) *Congenital.* One or several lymphangiectatic areas may be present in the skin, slightly protuberant, sometimes breaking through, and then "weeping" persistently (lymphorrhœa). Like "mother's marks," they are most frequent on the face and neck, the frequency in both cases

suggesting some slight vice of development in connection with the closure of the fissures present in these areas during development. The affection may be confined to the papillary layer of the corium, or may extend more deeply. On section, the tissue presents abundant moderately dilated and cylindrical lymph channels, lined with endothelium, lying in a fibrous, somewhat cellular stroma.

(*b*) *Acquired.*—Of allied type is the condition seen in filarial (tropical) elephantiasis. Here we have definitely to deal with lymphatic obstruction as a cause of the development of the condition, and it is worthy of note that, as we have pointed out elsewhere, the obstruction leads to surrounding connective-tissue overgrowth. We do not think it necessary, with Ribbert, to assume that there is an essential connection between the lymph channels and the surrounding connective tissue to account for the fibrous overgrowth seen in so many cases of lymphangiectasis. It is a secondary result of the expansion and "lymphœdema."

2. **Cavernous Lymphangiectasis** (**"Lymphangioma Cavernosum"**).—This corresponds to the cavernomas, only, in place of blood, the wide, irregular chambers contain lymph. Under this heading we have some remarkable congenital conditions: *macroglossia*, in which children are born with relatively large tongue, which may continue to enlarge after birth; *macrocheilia*, similar enlargement of the lip; congenital elephantiasis (E. lymphangiectatica). When occurring in the mesentery, these cavities have milky, chylous contents. Here, also, we find extensive overgrowth, with fibrosis of the parts between the dilated lymph spaces. The conditions are all congenital, and we must conclude that there is obstruction to onward flow of the contained fluid, due to some abnormal relationship of the different vessels.

3. **Cystic Lymphangiectasis** (**"Lymphangioma Cysticum"**).—The most extreme and remarkable examples of this condition are encountered in the neck, causing the condition known as *cystic hygroma*—multiple large clear cysts, either below the ear or, more commonly, in the submaxillary region; or, again, below the level of the larynx, and extending to the supraclavicular region; usually unilateral, and forming a large, tense, fluid swelling, which may extend outward to the shoulder, or deeply beneath the sternum. The tumors are formed of a collection of large cysts, lined by endothelium, containing clear lymph, and having fibroid walls. Many of the large cysts appear to be absolutely closed off, not communicating with their neighbors. We must suppose that, with increasing distension, there has been a valve-like closing of the channel of which they are a dilatation, that the endothelium has grown *pari passu* with the dilatation, and that this endothelium has secretory powers. The mere force of the lymph flow cannot explain such extreme development; we have to assume active excretion, which, indeed, is indicated by many other considerations and actual experiments (Heidenhain) (see also p. 792).

This condition must be distinguished from *cervical hydrocele* brought about by secretion into one of the persistent cervical ducts or fissures.

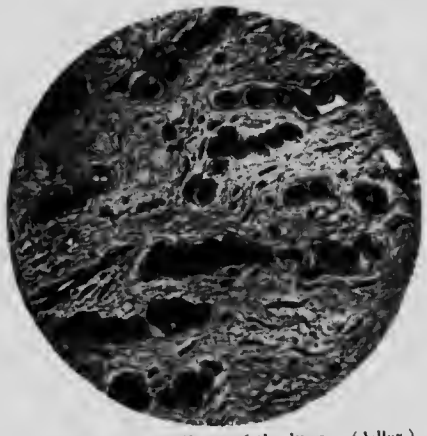
Such consist of one cyst, and are lined, not by endothelium, but by squamous or columnar and sometimes ciliated epithelium.

An allied form is the *sacral hygroma*, one variety of the congenital sacral tumor (p. 219), in which, again, from imperfect lymph discharge, there develop congeries of relatively large, lymph-containing cysts. In uterine myomata occasionally we meet with a like condition.

4. **Lymphangioma Proper.**—From these telangiectatic cases we pass to what must be regarded as true lymphangiomas. Here let us repeat that the mere existence of growth of lymph channels, *pari passu* with other changes in tumors, but subordinate to the main tissue overgrowth, must not be considered as lymphangiomatous, even if actual budding of new channels be observed, as noted by three or four observers.

Borst describes and figures a localized lymph-vascular nodule observed by him in a lipoma, composed of a close collection of apparently new lymph channels. We have noted a somewhat similar condition in

FIG. 270



Lymphangio-epithelioma of the lung. (Adler.)

normal, but very fatty, appendices epiploicæ, and have regarded it as a latent lymphoid nodule. Whereas, in the normal state, such can be detected only with difficulty, in acute peritonitis each appendix is found to contain an easily recognizable and typical lymph follicle.

The cases that we would regard as true lymphangioma are characterized by a notable proliferation of the lymphatic endothelium. In some cases of congenital simple lymphangiectasis in the young, this is to be observed here and there; in older individuals the same is not observable. Thus, it may be questioned whether, in the former case, we were dealing with a true blastomatous growth. Schwalbe has described a case in which, in addition to the marked proliferation, he found solid endothelial cords being produced, and even solid processes, as of advancing new formation. Here we seem to have the transition to a lymphangio-endothelioma.

Possibly the lymphangioma tuberosum multiplex of Kaposi comes under this heading: multiple small nodular cutaneous appearances in the adult, which, on section, are found to be due to dilatation of a group of lymph spaces in the cutis, each of which shows marked endothelial proliferation and is filled with a jelly-like matter, due, according to Beneke, to a hyaline degeneration of the proliferated endothelium, and, according to the same observer, there is here a pronounced new budding of lymphatics.

ATYPICAL ENDOTHELIOMAS.

Hemangio-endothelioma.—Of this form of growth quite the most frequent and characteristic example is that developing on the inner side of the dura, over the skullcap, where it forms smaller or larger sessile or rounded nodules; or from the membranes at the base of the brain, where it may either form a large nodule, or take on a spreading growth. More rarely, it may originate within the sheath of the optic and other nerves.

The appearance of a favorable section of such a growth is very striking. The whole field may be found composed of a collection of whorls of concentrically disposed cells. Between these whorls, and not sharply marked off from them, is a somewhat cellular stroma. The cells composing these whorls are flattened, the centre of each whorl is not close packed, but rather loose, and with careful examination, or good fortune, here and there may be seen a whorl that has a lumen containing red blood corpuscles. Elsewhere, where the section has been transverse through the component whorls, they have an oval appearance, or may be elongated and curved. In some cases there is a fair amount of cellular fibrous tissue separating the individual whorls; in others the whorls exhibit hyaline change, and their central cells become homogeneous, fused and translucent; while frequently we encounter the further change of deposit of calcareous salts in these degenerated areas, so that the specimen has scattered through it small calcareous nodules. Tumors in which this calcareous change is marked have been given the name "*psammoma*." These psammomas, and they are not uncommon, are, so far as we can determine, always of endothelial origin. There may be multiple small tumors of this nature scattered under the dura, or in the choroid plexus. In other cases, and these more particularly where there is a more rapidly spreading growth, the picture is not so clear; only in some parts of the section can these whorls be made out, and then somewhat indefinitely; elsewhere, and not sharply defined from the previously mentioned areas, we have the appearance of a moderately small-celled sarcoma—a diffuse round-celled growth.

The appearance is most satisfactorily explained as due to localized overgrowth of the capillary endothelium, at first in the main concentrically, so that the capillary becomes enlarged by the deposit of layer

within layer of these endothelial cells. But, as we have had repeatedly occasion to note, the capillary is formed merely of endothelium, and growth may thus be outward as well as inward. Ribbert figures an early endothelioma of the optic-nerve sheath, showing this outward growth. We have encountered the like appearance in the same region. It is in this way that, with more active proliferation, a more diffuse sarcomatous growth is developed.

Ribbert, with whose views on this group of tumors we find ourselves largely in disagreement, regards these tumors as developed from the endothelium covering the dura mater and pia arachnoid space. He does not explain why a growth from such a primarily covering endothelium should take the remarkable form of cells concentrically disposed as though along a series of vessels, as, indeed, serial sections show is their arrangement. We are prepared to find that tumors exist of the order he describes corresponding with the pleural and peritoneal mesotheliomas, but this is not the common type.

Fig. 271

Portion of an endothelioma of the dura mater, showing the characteristic whorled arrangement of the tumor cells and at a a concentrically arranged calcareous deposit or psammoma body. (P. Ernst.)

As a rule, it would seem that this form is relatively slow growing, in the main causing death by pressure upon the brain substance. We have, however, found it extensively spreading over the surface of the brain, and in a case where the optic nerve was also affected, have found recurrent nodules of alveolar sarcomatous nature developing in the orbit after extirpation, whereas the cranial growths showed still the endotheliomatous type.

Atypical Lymphangio-endothelioma.—More often, in other regions of the body, similar whorled cell masses of endothelioid type show no relationship to blood capillaries, and must be regarded as originating from the endothelium of lymph channels. These, equally with those just described, when exhibiting more active growth, show areas of round-celled, sarcomatous type; indeed, the greater part of the tumor may appear sarcomatous.

Perithelioma.—A striking form of tumor is occasionally encountered exhibiting capillary channels cut in various directions and lined by recognizable endothelium, around each of which capillaries is a collection of cells, many layers deep, arranged radially. The individual cells are not specially elongated, but the arrangement in rows at right angles to the capillary axis is most characteristic. The general opinion is that these cells gain their origin from the lymphoid endothelium of the perivascular space—that thus these tumors form one variety of lymphangio-endothelioma.

Apparently those cells farthest removed from the central bloodvessel are the oldest. Whether from this cause, or from their more remote position, they are liable to exhibit degenerative change, and more particularly to undergo hyaline change. To such modification of a perithelioma it would seem that we owe the most typical form of *cylindroma*—tumors formed of a collection of hyaline tubes, or cylinders, cut in various direction, having a central dilated capillary vessel, surrounded by a zone of round cells.

FIG. 2[illegible]

Section of a perithelioma of Luschka's or the coccygeal gland. (Von Hleb-Kozanka.)

MELANOMA.

We have purposely left to the last the consideration of a series of tumors regarding which there is still hot debate and violent conflict of opinion. While, as will be seen, we take a definite position on one side rather than the other, believing that the facts brought forward up to the present turn the scale in that direction, and that it is wiser to present positive opinions, we confess that our inclination is to treat the matter as still open.

Pigmented moles are, as everyone knows, a very common minor malformation. Most individuals, if we mistake not, are possessed of one or more. In the adult these exhibit no very clear histological picture; in the child their structure is more definite. They consist of a fibrous stroma immediately beneath the epidermis, in which are situated clusters of cells of fair size, irregularly polygonal, and containing brown pigment. *In the slighter cases these cells are noted to encircle closely the vessels.* The condition is notoriously congenital. The mole represents an area in which there has been some vice of development. The specific cells are of a peculiar order, peculiar, not

to these moles, but to the skin, and (to a less extent) the mucous membranes, as, also, the choroid coat of the eye, where they are most abundant. These pigment-bearing cells are known as *chromatophores*.

In the ordinary skin of the white man they ca not be clearly made out, save in the anal region and the pigmented areola of the nipple. In animals with deeply pigmented skin they are most abundant, and are to be seen not merely in the corium, but between the cells of the deeper layer of the epidermis. They are characterized by possessing two or more long, rather coarse processes tending to be branched, and relatively abundant cytoplasm, in which are pigmented granules of melanin, a pigment differing from hemoglobin in being iron-free and relatively much richer in sulphur (see p. 891). That the cells of the pigmented mole possess these properties can be demonstrated, according to Ribbert, by examining a teased-out preparation. In sections they appear merely polygonal.

Whether these moles should be termed definite benign tumors—melanomas, or, with some, melanofibromas—is at least debatable. Though to the naked eye they appear sharply differentiated, under the microscope their connective-tissue stroma passes imperceptibly into the surroundings. Nor, although clearly due to some vice in development, can we with absolute precision speak of them as cell rests. The appearances indicate more the excessive development of what is a constituent of the normal skin rather than a dislocation—a constituent which, for some reason (possibly increased vascularity, for these moles are most often nevoid), has taken on the active heaping up of pigment. Here we should explain that everything indicates that the chromatophore is a cell which has the capacity to take up or manufacture melanin, but which, however, is not always melanin-containing. But the cell relationships are here disturbed.

In the choroid coat of the eye, and from the skin, frequently originating from such moles, we gain the development of highly malignant melanotic tumors. It is interesting to note that in the eye similar aberrant cell clusters have been noted, either in the iris (in areas showing coincident tumor growth) from the choroid, or even in and upon the sclerotic, as though in this latter case, in the course of development, a portion of the ultimate choroidal tissue had been pinched off. Virchow has described a primary growth from the brain membranes, which often show some pigment cells. And primary growths have been recorded from other regions, more particularly the liver and gall-bladder. We confess to having had considerable doubt concerning the primary nature of these growths until recently our colleague Dr. Duval showed us his material from what is clearly a small primary growth originating beneath the mucosa of the common bile duct.[1]

These tumors are very striking; according to the amount of pigment they contain, they may be coal black, or various shades of brown, or, on section, show pigmented areas, while the rest of the growth is

[1] Montreal Med. Jour., 37: 1908: 270.

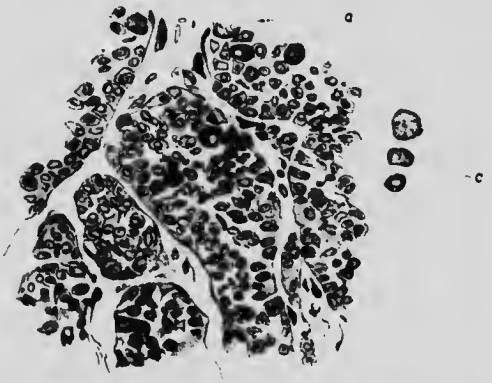
colorless; or the primary growth or some of the metastases may be colorless, while other growths are heavily pigmented. As a rule, they grow rapidly, and are nearly always fatal within three years, often the period is but a few months; there are, however, exceptions of cutaneous melanomas of slow development over many years. The original tumor does not often attain any great size, but metastases are extraordinarily abundant. No other form of tumor affords so many obvious metas-

FIG. 273

Pigment containing cells from a spindle-celled melanoma. (Ribbert.)

tases, and these both by means of the bloodvessels and the lymphatics, so that the nearest lymph glands are apt to be involved, along with the liver (a specially favorable seat for abundant and relatively large secondary nodules), the lungs, practically all the viscera, including the brain, heart, bone-marrow, the coats of the intestine and the serous membranes. As usual, the muscles show little involvement.

FIG. 274



Section from an alveolar melanoma or chromatophoroma of the great toe. The cells in general are here seen to be free from melanin granules, but these are present in occasional cells both of the tumor (*a*) and of the stroma (*b*). At *c*, some of the melanin-containing cells are drawn separately.

When we come to examine various cases histologically, we find a marked divergence in the characters of the various tumors, and this whether a series be examined originating from the eye or from the skin. It is regarding the translation of these appearances that there is such active difference of opinion. We meet with two main types: the first, more common within the eye, composed of relatively small spindle cells; the second, more common in cutaneous growths, formed

of large epithelioid cells, with or without obvious large spindle forms, and these tending to be arranged in alveolar masses surrounded by a fairly abundant fibrous stroma. The first, in general, shows not the slightest sign of alveolar structure.

In both forms the pigment, contained as small brown granules, within the cells, varies considerably in amount; in some cases it is so densely packed that nothing can be seen of nucleus or cell structure; in these, and in cells containing less amounts, it is present also in the long cell processes. As a rule, in the tumor cells themselves the individual pigment granules are slightly rod-shaped. In the spindle-celled type we encounter densely pigmented globular cells without processes, in which the granules are more rounded and conglomerated. These Ribbert regards as dead cells which have undergone contraction. So, also, in the stroma we see cells containing irregular rounded pigment granules. In both forms we may encounter what are the cells proper of the tumor, wholly devoid of pigment; indeed, Ribbert, as the result of his studies, goes so far as to lay down that all sarcomas of the uvea and interior of the eye (excluding the gliosarcomas) are of the one origin, whether pigmented or unpigmented. In both, but more particularly in the alveolar form, there may be more pigment in the stroma than in the tumor cells proper.

Ribbert lays down that when this is intracellular in the stroma it is still within the same order of cells. This we are inclined to doubt. Certainly there is not the same sharp distinction between tumor cells and stroma as we meet with in ordinary cancers, but when we see that, in advanced cases, leukocytes and the endothelial cells lining the vessels take up the pigment, we cannot deny the same properties to the connective tissue and wandering cells of the stroma. And when, as frequently is to be noted, the tumor cells degenerate and form areas of softening, so that cavities full of a black fluid appear in the growths, then leukocytes pass into these areas, take up the pigment, and, judging from appearances, deposit it in the stroma.

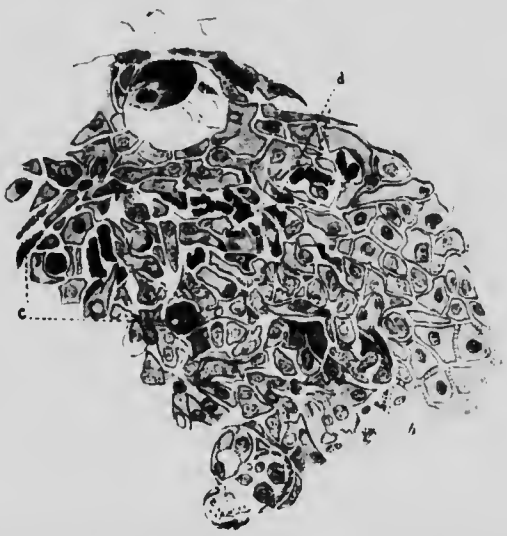
So extensive may be these degenerative processes that free pigment passes into the blood (*melanæmia*), and may be discharged into the urine (*melanuria*), besides tinging the tissues in general.

As to the meaning of these two forms of melanotic growth, two opinions are possible: (1) that they are distinct, and that there is a connective-tissue type of growth producing the spindle-celled type, a cancerous form which is the alveolar type; and (2) that they are both produced by one order of cell under different conditions, or at different stages of vegetative activity. There are still those who hold to the former view, but the existence of transitional and combined forms, and the fact, as pointed out by Ribbert, that teased-out specimens of the spindle-celled form afford cells with long and branching processes of the same type as those afforded by the other form, renders this view untenable. We must conclude, therefore, that cells of the same type give origin to both, and these cells are the *chromatophores*, that particular order of cells which, in the normal skin, may be pigment-containing.

But what is the nature of these cells, and what their origin, that they can give origin to tumors of varying type? It is round this question that the controversy ranges itself. Some years ago Unna, in his extensive studies upon the pathology of the skin, first brought forward the view that the cells which give rise to cutaneous melanomas are of epithelial origin, and this view has from many quarters gained adherents.

It must be recalled that the cells of the rete Malpighii contain pigment —melanin—and this in colored races in easily recognizable quantities. Prior to 1889 there was no doubt regarding the epithelial origin of melanin; in that year Aeby called attention to certain pigmented cells, now known as chromatophores, lying in the corium and between the

FIG. 275



Section taken through epidermis parallel to surface, or somewhat obliquely, over a small cutaneous melanoma, showing typical prickle cells, as at *b;* others oval (*c*) containing a few granules of melanin and others apparently of the same order as at *d*, densely filled with melanin granules.

cells of the Malpighian layer. These are stellate cells of connective-tissue type, and he, not unnaturally, concluded that they act as carriers, absorbing certain substances from the blood, elaborating them into melanin, and passing them on to the epithelial cells. Even up to the present moment this view has its upholders, and is supported by the sarcomatous, *i. e.*, connective-tissue type of melanotic tumors. Unna, in his extensive studies upon the skin, first brought forward the view that these cells are of epithelial origin, derived from the Malpighian layer, and that, so, tumors derived from them are more allied to the epitheliomas or cancers than to the sarcomas proper. It has been pointed out, although never, it seems to us, with absolute conviction, that frequently in nevi and in early cutaneous melanotic growths

collections of cells of epithelioid, chromatophoric type are present in the epidermis, and constitute downgrowths, passing down into the masses of tumor cells, in which they are with difficulty distinguishable from the tumor elements. Were these cells to become the parent cells of the tumor, the pigmentation would be no new assumption. We have met with one case in which it was difficult to conclude that the epithelium had not taken on a melanotic metamorphosis, but could not determine whether this was directly associated with the underlying growth (Fig. 275).

This view is supported—not, we think, very strongly—by certain observations upon the different effects of transplanting white skin into a black patch in the guinea-pig and *vice versa* (Deflandre, Leo Loeb, Carnot), and general pathologists of the widest experience—such as Marchand and Lubarsch—have signified their adherence thereto—*i. e.*, they regard the chromatophores as of epithelial origin, and melanomas, therefore, as epiblastic in nature.

But against this view are the following considerations:

1. Pigmented tumors of pure epitheliomatous type are unknown, and, what is more, even in melanomas of the most characteristic alveolar carcinomatous type, employing Mallory's stain we never encounter an alveolus which throughout is devoid of interstitial substance.

2. If the comparison be made—as it has been—between the melanomas and the rodent ulcer, it is worthy of note that this latter, of all epitheliomas, forms the fewest metastases; of all tumors, the melanoma forms the most.

3. The embryological evidence that the chromatophores owe their origin to the epithelium is lacking in precision, or, more accurately, while several observers have described the modification of epithelial cells into epithelial chromatophores, the evidence is weak that the subepithelial chromatophores are of this origin.[1] What is noticeable in early nevi, in xeroderma pigmentosum and several other slighter states of cutaneous pigmentation is that the pigment cells in the cutis have a relationship not to the overlying epidermis, but to the vessels. As pointed out by both Ribbert and Borst, the normal habitat of the cuticular chromatophore—of the ordinary chromatophore, that is—is in the lymph spaces immediately around the vessels. Among the latest workers, Staffel,[2] studying these perivascular collections, finds every transition from collections of lymphocytes through others composed of lymphocytes, plasma cells, and the allied mast cells showing transition into pigment-bearing cells, either branching and with processes, or of

[1] Thus Meirowsky, Monatsh. f. prakt. Dermatol., 42, 43, and 44, has followed the development of pigment in the cells, more particularly of the rete Malpighii, after subjecting small areas of skin for a short time to the Finsen light. He has seen the pigment collected more particularly on the side near the source of light, and later has observed those pigmented cells send out processes between the other epithelial cells and into the cutis—assume, that is, the characteristic chromatophore type.

[2] Verhandl. deutsch. Pathol. Gesell., 11: 1908: 136.

the spindle-celled type. Studying the development of the two orders of cells he notes that the pigment granules are coarser in the cuticular than in the epidermal chromatophores. We are inclined to favor this view of the duality of origin of the cuticular and epidermal chromatophores. We know from the observations of Schridde and others that the plasma cells, like their congeners, the lymphocytes, have the habit of wandering; that they may assume a spindle shape in the tissues; that they may also, according to Maximow, give origin to cells with processes of the clasmatocyte order. *Cells of this nature undergoing an orderly proliferation in the lymph spaces would give origin to growths of the alveolar type; growing more actively, would infiltrate and exhibit a more purely sarcomatous structure.*

In their habit of growth it will be seen that these tumors approximate to our class of transitional lepidomas; nevertheless, neither in the earliest stages, nor in their mode of spread do they wholly fall into it. There is perhaps a closer affinence to the large-celled lymphosarcoma of the intestine, in which more than once we have found it difficult to determine whether we dealt with a sarcoma or a loosely growing and abundantly infiltrating carcinoma. In other words, the slowly growing lymphosarcoma has a tendency to respect lymph spaces.

Before closing, an attempt must be made to answer a question which will naturally have arisen, namely, How are we to explain the malignancy of cells apparently so highly specialized? To this the answer must be another question, namely, Is the deposit of melanin granules an indication of specialized function, or, on the contrary, is it one of imperfect metabolism? Nor is this question easy to answer; it demands a knowledge of the nature and origin of melanin, which more appropriately is taken up when we discuss pigments in general (p. 892). We shall not, therefore, discuss here the rival views regarding the functions of the chromatophores—whether they supply melanin to the epidermis (Kölliker, Delépine,[1] M. B. Schmidt[2]), or, on the contrary (as urged by Jarisch, Port, and others), procure their melanin from the epidermal cells. Nor shall we discuss the relationship of melanin to hemoglobin, as emphasized by Ehrmann.[3] The modern view leaves these in abeyance, and regards the melanin as a derivative from the nucleolar matter of the nuclei of the melanin-bearing cells (Rössle,[4] Meirowsky,[5] Staffel[6]), associated with distinct signs of nuclear exhaustion, not to say degeneration. This, however, does not in our opinion explain everything. These identical nuclear changes have been described in connection with so many cell deposits that we can only conclude that each individual deposit is not a direct development from the plasmasomes or chromidia, but is due to the interaction between the discharged nuclear matter and certain cytoplasmic or paraplasmic substances. Yet other

[1] Delépine, Trans. Path. Soc. Lond., 1893.
[2] Schmidt, Virch. Arch., 115.
[3] Arch. f. Dermat. u. Syph., 64.
[4] Zeitschr. f. Krebsforschung, 2: 1904: 291.
[5] Monats. f. prakt. Dermat., 44: 1907: 166.
[6] Verhand. deutsch. pathol. Gesellsch., 11: 1907.

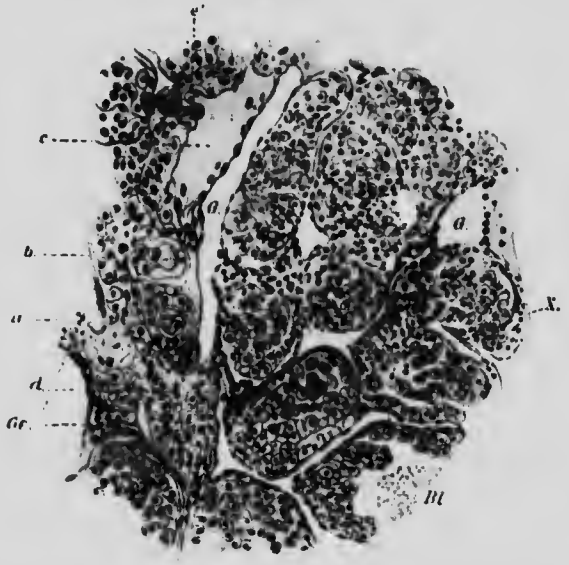
recent indications are that melanin is of the nature of an oxidized product of the aromatic radicals gained from disintegration of the protein molecule; that its presence in the cell represents either an excessive production and activity of an oxidase or a deficiency of the enzyme or other body, which carries the process further and converts the melanin into its colorless chromogen (melanogen). It may well be that the extraordinary deposit of melanin in melanotic tumors, far from being a progressive acquirement, indicates a deficiency in the disintegrative mechanisms of the cell, whereby the normal final stage of colorless chromogen formation, or of protein disintegration, is not reached.

OTHER TUMORS OF DOUBTFUL RELATIONSHIP.

There remain, it must be emphasized, other tumors whose relationship are not wholly determined; of them may be noted the:

Cholesteatoma.—This form is found more particularly in association with the membranes of the brain, and is characterized by the presence

FIG. 276



Tumor of the carotid gland: *G*, vessels; *Bl*, hemorrhage into a column of cells; at *d* the cells of the growth are taking on a more connective-tissue type; at *c*, hyaline degeneration

of little pearly nodules. These are formed of layers of cells of epithelioid or endothelioid type, and in the centre of the masses may be a cluster of cholesterin crystals. In appearance and structure they most closely resemble the endotheliomas, also encountered in these regions, and as such the majority of observers regard them. But

Ziegler[1] in some cases has encountered hairs and hair follicles, and regards them thus as of epithelial origin, secondarily, it may be, to fœtal inclusion of epidermal elements.

Tumors of the Carotid Gland.—Seated upon the carotid artery close to its bifurcation may be found, upon careful search, a minute cell cluster embedded in a capillary meshwork. It cannot be said that the exact relationship of this carotid body has been determined. The cells are chromaffine—*i. e.*, take up and are strongly stained by chrome salts, and as the cells of the adrenal medulla have the same properties, and

Fig. 277

Portion of the same tumor more highly magnified to show peritheliomatous arrangement of the tumor cells in relationship to the vascular endothelium. (Paltauf.)

they, as now accepted, are of nervous (sympathetic) origin, it is held by some that these are of like origin. But this cannot be said to have been definitely determined. The occasional tumors originating from the carotid bodies are of a type recalling the peritheliomas, and verge into the sarcomas proper.

Other tumors of irregular type and uncertain relationships have been recorded in connection with another small organ of undetermined relationships, namely, the coccygeal gland (Luschka's gland). These also, as indicated in Fig. 272, p. 759, tend toward the peritheliomatous type.

[1] Vide Bostroem, Centralbl. f. Pathologie, 8: 1897: 1.

CHAPTER XXIII.

THEORIES OF NEOPLASIA.

The examples afforded in the preceding chapters indicate:

1. That some of these growths owe their origin to cell rests. In addition to the whole groups of the teratomas and the teratoblastomas and allied forms, which we have considered separately, we have adduced as examples of this order the tumors originating from persistent rudiments of embryonic structures (gill clefts, branchial arch cartilages, etc.), from cells displaced during the course of development (aberrant hypernephromas, columnar-celled cancer originating in areas of squamous epithelium, etc.).

Cohnheim's Theory.—According to the oft-quoted theory of Cohnheim, it is these cells—cells which in the course of development have been displaced from their normal relationship, or have failed to undergo a normal atrophy—that are the essential nidus from which neoplasms originate. The theory, it must be noted, went very little farther; it did not lay down anything beyond the mere postulate of displacement favoring retention of embryonic properties and eventual aberrant growth. It did not explain why it is that not all of the abundant cell rests, which we may encounter in the human body take on aberrant growth, but only an occasional one, and that in exceptional circumstances; nor did it attempt to explain why after remaining latent for years, these begin active proliferation.

2. We are forced to admit that there are cases in which tumors, and more particularly those of a malignant type, originate from cells which must be regarded as having undergone *not congenital, but postnatal displacement;* cases, for example, of squamous epithelioma originating in the scar of an old ulcer, of columnar-celled cancer of the stomach or intestines similarly originating in the edges of an ulcer, and it may be of sarcoma originating at the site of a contusion. That this is so was emphasized by Roger Williams,[1] but the expansion of Cohnheim's theory to include postnatal displacement is more widely known in connection with Ribbert and his theory.

3. We accept, therefore, that autochthonous blastomas can originate from cells that have been displaced, and that very many examples—it may be the majority—of tumors come into this category. But does this include all cases? To this question we cannot but return a negative answer. *Cell displacement is not the essential.* There are undoubted cases

[1] Principles of Cancer and Tumor Formation, London, 1888; in many respects a remarkable work, based on broad biological considerations.

in which cells exhibit the cancerous change, and exhibit the cancerous type without any indication of preëxisting displacement. Our own attention was called to this fact some years ago in a study of an early multiple tumor of the adrenal cortex, in which occasional cells in the immediate neighborhood of the small mass of new-growth, while still retaining their relationship to the columns of the zona radiata, by their enlarged and deep-staining nuclei stood out as of the cancerous type. The number of these and their relationship, wholly unconnected with the main growth, appeared to preclude any possibility of their being outgrowths from the latter; they were part and parcel of the gland substance proper.[1] It is admittedly a matter of chance, and must be rare, to encounter tumors at this early stage, but I have recently come across another tumor of the adrenal showing the same peculiarity, and Jores and others have recorded similar observations. Foremost among these must be mentioned Hauser[2] and his observations upon the malignant metamorphosis of cells of the intestinal mucosa while still *in situ*, and Van Heukelom, L. P. Daniels, Tolot and Horst Oertel upon the direct cancerous transformation of the liver cells in case of multiple carcinomas of that organ. As Oertel states regarding his case: "It was plainly revealed that the origin of the cancer was a transformation of multiple growths, of multiple groups of liver cells, sometimes only involving few within one lobule. These microscopic areas, best observed in those parts of the liver which showed as yet no gross cancer formation, demonstrated a direct change of atrophic degenerated wasting liver cells into cancer cells while they were still in perfect continuity with each other and still entered into the formation of the lobule." Oertel describes three stages through which those cells pass: a first with extensive loss and granular degeneration of the protoplasm and disappearance of nuclear chromatin; a second of marked nuclear enlargement, the cell body still remaining granular; and a third, in which there is abundant smooth protoplasm around a very large well-formed nucleus, this last being identical with that of the cells of the fully formed cancerous areas. Not until cells of this order had proliferated was their connection with each other lost, and that independent growth observed characteristic of the ordinary carcinoma. This is a process which has for years been actively denied by many of the leading writers upon the subject. For my part I regard it as wholly demonstrated that it does occur; and it must be taken into account in the development of any adequate theory of neoplasia.

4. It is through examples of this order that we link the blastomas with the blastomatoid growths referred to in detail in the preceding chapters, growths originating as multiple diffuse localized hypertrophies of particular tissues, developing obviously not from a single cell, but by a generalized proliferation of the specific elements of a region. These blastomatoid tumors may show every gradation from simple idiopathic hypertrophy to pronounced malignancy.

[1] See Woolley, Trans. Assoc. Am. Phys., 17; 1902; 627.

[2] Das Cylinder epithelium des Magens und des Darms, Jena, 1890.

To recapitulate: from the point of view of the relationship of the cells giving origin to neoplasms, we recognize the following classes:

1. Teratomas from totipotential cells.
   - Twin teratomas, (fœtal inclusions).
   - Filial teratomas (ovarian and testicular, etc.).
2. Teratoblastomas from multipotential cells.
   - "Mixed" tumors.
3. Blastomas from unipotential cells.
   - Originating from congenitally displaced cells.
   - Originating from cells of postnatal displacement.
   - Originating from cells that assume neoplastic characters without displacement, and rapidly assume malignancy.
4. Blastomatoid growths.
   - Originating as a diffuse through local hypertrophy of the specific elements of a tissue, which may or may not pass from the hypertrophic to the malignant type.

The adequate theory of neoplasia must cover all these forms. But a distinction needs to be drawn between the teratomas pure and simple, and all the other orders; once again we find that classification is gradation, with transitional types linking the one class to the other. As was pointed out when discussing these, the *typical* teratomas exhibit in their cells the orderly progression from embryonic to differentiated tissue, and associated with this we observe that they have a restricted power of growth comparable with the like restricted power of growth of the normal individual. Their cells, it is true, do not form perfect, but incomplete organs, and with this certain of them may sooner or later take a blastomatous growth. When they do so this development of a "*tumor in tumore*" is an epiphenomenon. There is no primary anaplasia of the cells of origin of these typical teratomas, although when from them there develop secondary blastomatous growths there must be secondary anaplasia of certain of the component cells. And as regards the atypical teratomas (p. 602), it has to be noted that the growths develop, not from cells which have suffered a reversionary anaplasia, but from those which have never passed beyond the vegetative stage or attained the stage of full differentiation. In the teratoblastomas as a body we have indications of transition: some cells (in the mixed tumors of the kidney, for example) exhibit a capacity to develop into recognizable striated muscle fibers—into one of the highest and most specialized of the tissue cells—but along with these are cells which do not pass beyond the vegetative or "embryonic" type.

It is obvious that to cover all these forms, even of what we classify as blastomas, Cohnheim's well-known theory is inadequate. The same is true of the more elaborate theory of Ribbert.

Ribbert's Theory.—This theory is so frequently referred to at the present time that it is necessary to state its main contentions. According to it, cell displacement is the first essential, and these displaced cells take on active growth, not from any active exaltation of proliferative activity on the part of the cells themselves. With Weigert he holds that

the vegetative powers of the cells cannot be stimulated from without. If, therefore, a cell rest exhibits active growth, it is because of a diminished external resistance, because of a reduction of the antagonistic forces. He holds that the cell rest giving rise to a tumor cannot have its cells arranged in the normal order because in such case there would be the normal growth-restraining tension. That a retrograde change in the cells themselves is favorable to growth is admitted, but is regarded as secondary and not indispensable.

Now, isolation of cell groups, irregular disposal of cells, and lack of restraining tissue tension are to be encountered in the healing of wounds in connection notably with the epithelium which actively pushes over and into the underlying granulation tissue. Nevertheless, in such cases neoplastic development is the rare exception, not the rule. What is more, as we have pointed out elsewhere, Weigert's hypothesis is wholly untenable. In this very matter of tumor growth Ehrlich's observations upon transplanted adenocarcinoma of the mouse demonstrate the presence and increase of vegetative power on the part of the tumor cells, for with successive transplantation into fresh animals they may steadily manifest greater malignancy. And were further disproof needed, we have it in Bernard Fischer's interesting studies upon the chemotactic and proliferative stimulation of the squamous epithelium of the rabbit's ear by Scharlach R dissolved in oil.

Fischer,[1] from one side of the ear, injected into the other side through the cartilage, a solution of Scharlach R in olive oil, and found that this produced a great proliferation of the Malpighian layer of the skin of the other side, so that this formed finger-like cell processes passing into the subcutaneous tissue down to the droplets of oil, and even, in some cases, into the track of the needle through the cartilage. With this the accumulation of injected oil diminished, leaving the Scharlach R in a solid form in the tissues. With the absorption of the oil the proliferation ceased, and the epithelial processes underwent atrophy. There was no development of autonomous new-growth, but the convincing demonstration of a stirring up of the vegetative activities of the epithelial cells. These observations have been abundantly confirmed, among others by Klotz in our laboratory at the Royal Victoria Hospital.

Lastly, it must be noted that the theory takes no account of the assumption of malignant properties by cells *in situ*. Valuable as it has been in its time, the theory has shown itself inefficient.

Beard's Theory.—Another obviously inadequate theory is that of Beard, a theory which in certain circles in Great Britain and America has of late received great notice. With a wholly inadequate knowledge of the natural history of new-growths, that most versatile embryologist has laid down that all neoplasms originate from aberrant and misplaced germ and trophoblastic cells, and from the observation that the disappearance of the trophoblast (*i. e.*, yolk or nourishing cells of the ovum which do

[1] Verhandl. d. deutsch. pathol. Gesell., 10: 1907: 20, and Münchener med. Woch., 53: 1906: 2041.

not normally become a portion of the individual proper) coincides in point of time with the development and commencing activity of the pancreas, has concluded that this disappearance is due to the development of the fœtal pancreatic ferments. This, to say the least, is an insecure conception. He has suggested that pancreatic enzymes, if injected into the system, will likewise act upon (the trophoblastic) tumor cells, and at the present time there is an active propaganda in favor of "Beard's treatment" by injections of trypsin and amylopsin. We do not say that this is not a movement in the right direction; our view, expressed many years ago, is to the effect that it is along the lines of discovering bodies having a specific action upon the tumor cells that advance is to be expected. We would only point out that the premises are false; that many tumors originate from cells actually or functionally displaced, but that the evidence is wholly lacking that the majority of malignant blastomas arise from aberrant germ cells. If the chorio-epithelioma malignum arises from cells of trophoblastic nature, that is the only type of tumor of this nature. Dr. Beard is too apt to bear out the characterization that we once heard one delightful Irish lady give of another, "that when she gets a bee in her bonnet she rides it to death."

Parasitic Theories.—There are certain data which have accumulated during the last fifteen years regarding the incidence of atypical malignant blastomas, and more particularly of cancer proper, which we freely admit are, upon their face, difficult to reconcile with any theory save one requiring the increasing spread of some microbic causative agent. These are (1) the rapid increase in the mortality from cancer in most civilized countries; (2) the greater incidence of the disease, more particularly in certain low-lying localities, estuaries, and the borders of sluggish streams; (3) house incidence, certain houses affording a mortality from cancer over a series of years in striking excess over the average.

Upon the last we lay no weight; by the law of chance, just as one individual in a thousand may be of gigantic proportions, so one house in a thousand may show a great excess of cases of cancer—or of twin births—over the ordinary run of houses. But Behla's full study of the incidence of cancer in the different sections of a little German town is certainly most suggestive; the cases occurring in the low-lying houses near the sluggish stream were found far in excess of those in other situations.[1] In this he confirmed the earlier work of Haviland in England, and while as regards the general increase in cancer some weight must be laid upon the fact that improved hygiene and care of the infant favors the survival of the weakly, and even brings them to middle age, so that (*a*) the average length of life has been increased, or, in other words, more individuals are protected from death by other diseases that they may reach the cancer age (after thirty-five years) and succumb to malignant growths, and (*b*) more individuals with constitutional weakness survive than was the case in former years; nevertheless, the increase would seem to be proceeding at a more rapid rate than can reasonably be explained along these lines.

[1] Poppelmann has recently confirmed these results in the case of another small town. Zeitschr. f. Krebsforschung, 4:1906:29

In San Francisco the relative number of deaths from cancer increased seven times in thirty-two years, from 16.5 per 100,000, in 1866, to 103.6, in 1898. In Boston the rate trebled between 1863 and 1887. In New York State, according to Roswell Park, there were 2363 deaths from cancer in 1887; eleven years later there were 4456. According to Tatham,[1] in the period 1861 to 1870 the annual rate of cancer mortality per million living in England and Wales was, in males, 242; in 1891 to 1900 this had increased to 597, an increase of 150 per cent. For females the increase was 74 per cent., from 519 to 903.

Wützlorff's[2] statistics for Germany are equally remarkable. Taking deaths in hospitals, in 1879, 6330 were attributed to cancer; in 1898, the number had risen to 24,000. Even when the correction is made for increase in the number of hospital patients, the increase in the cancer death rate is 266 per cent. In the ordinary returns for deaths: in 1892, 2.6 per cent. of all deaths were returned as from new-growths; in 1898 (in but six years) the number had reached 3.5, an increase of 18.5 per cent.; it is attacking also at an earlier age than before, and attacks more men.

Nor is it that nowadays more cases are correctly diagnosticated than formerly; the postmortem statistics of certain old-established hospitals reveal an increasing ratio of cases found to be cancerous at autopsy, and this in different parts of the world. One of the most careful recent papers on this subject is by Barlow and Taylor upon the statistics of the St. George's and Middlesex Hospitals.[3]

But as already noted, if malignant growth be due to microparasites, there is no general consensus as to the nature of the causative organism; on the contrary, among those in favor of the parasitic theory, there has been a most extraordinary diversity of findings and of opinions. Bacilli (Schuller), micrococci (Doyen), blastomycetes (Russel, Sanfelice, Leopold), amœbæ and rhizopod forms (Sjöbring, Schmidt), sporozoa (Sjöbring, Malassez—1889, "coccidia"—Metchnikoff, Soudakewitsch, Ruffer, Plimmer, Korotneff—a gregarine, Rhopocephalus) have all had their advocates, and, what is more, not infrequently the same observer has not hesitated to describe now a causative agent of one order, later one of a wholly different order (Sjöbring, Gaylord). The latest form found associated with malignant growths, is almost naturally the spirochete. Observed first by Borrel and some European workers, Gaylord has made the fullest study of the same, and has found a remarkable form of spirochete associated with a large proportion of cases of inoculated and natural adenocarcinoma of the mouse. There is no doubt that this form is present at least in some of these, it may be in all, and that it is of the nature of a spirochete. What is more, Forbes Robertson[4] has encountered identical forms in a small number of cases of human carcinoma. Warned by previous experience, Gaylord exhibits a wise caution in drawing any deductions.

[1] Lancet, London, 1902, i, 745.
[2] Brit. Med. Jour., 1902: i: 805.
[3] Med. Exam. and Prac., New York, 1905: 719.
[4] Lancet, London, 1907: ii.

The parasites described by previous observers have all, in the main, been intracellular bodies, and the conception has been that, leading a symbiotic existence within the cells, these microbes have stimulated them to excessive growth. The interesting point, which we have personally seen to be the case in Gaylord's preparations, is that his spirochete exists in the surrounding tissues, or, if present within the cells at the advancing edge of a growth, it shows clear evidence of undergoing phagocytosis and destruction. If it bears any relationship to the growth, that relationship is of the nature of exerting a chemotactic or trophotrophic influence, whereby products in the outlying tissue stimulate the lepidic cells to proliferate and grow toward the region of greater concentration of the foodstuff or stimulant, as in Bernard Fischer's experiment (p. 771).

Very much more work, and widespread confirmation of results is necessary before we can be prepared to lay down that any form of microparasite is the specific causative agent of any form of malignant growth. Our present stand must be one not of absolute denial, but of agnosticism. *But even granting that it is ultimately found that certain microbes set up certain orders of growth, it must be recognized that the microbic theory obviously cannot be applied to neoplasms in general.* It can only have a limited application, and cannot be the foundation of the general theory of neoplasia. And this because it is equally obvious that there are certain orders of tumors which are to be ascribed to a totally different mode of causation—to the inherent, if aberrant, vegetative power of the constituent cells, and to that alone. We need no parasite to explain the aberrant growth of the syncytium which produces the chorio-epithelioma. There we deal with cells possessing naturally invasive and erosive powers, cells of another individual.[1] The same is true of all the teratomas and teratoblastomas and tumors originating during fœtal existence. Nor can those congenital cases of what we have termed blastomatoid developments be explained thus. In other words, the adequate theory of neoplasia must be one which will explain not cancer alone, but all types of tumor formation. *No parasitic theory suffices to do this.*

It is evident from the above that we are driven back to a *change in the biological properties of the cells giving origin to tumors*, and to look for some explanation of what it is that initiates the change. Here we have to choose between a long series of hypotheses.

Anaplasia.—It is to von Hansemann that we owe the first thorough study of the histological characters of cells of malignant growths. Cornil, in 1886, and Klebs had previously called attention to the existence in these tumors of irregular and atypical mitoses. Von Hansemann regarded these as evidence of cell change, of the production of generations of cells which through altered distribution of nuclear matter do not so much undergo degeneration proper, but become incapable of attaining perfect structure and function. This modification he has termed *anaplasia*, cell races being formed possessing abnormal properties, one of which is that of increased vegetative activity.

[1] Vide Adami, Syncytioma Malignum, Clinical Journal, Lond., June 18, 1902.

But (1) among neoplasms this unequal distribution of chromatin is characteristic only of malignant tumors; (2) it has been observed in other conditions besides malignancy (in forms of inflammation in the lower animals, which by experience we know do not lead to neoplasia); and (3) no explanation is afforded of the cause of the irregular mitoses.

Farmer, Moore and Walker,[1] Bashford, and others have more recently enunciated somewhat parallel views, describing ring form of chromosomes, such as are seen in the process of nuclear reduction of the oocyte and the spermatocyte, but upon further study have withdrawn their contentions.

Others, again, of whom, if we mistake not, Creighton some twenty years ago was the first, have described an adulterous connection, with nuclear fusion between the cells in malignant growths, and to this "rejuvenation" of the cells have ascribed their increased vegetative activity. The latest of these is Moore.[2] Certain of the stages of amitotic nuclear division are curiously like the figures afforded by this last observer. We see no adequate support for this theory, which again has no bearing upon the large mass of non-malignant tumors.

Bashford's Theory.—Another English worker, Bashford, from a study of the age incidence of malignancy in man and various species of animals, concludes that the lighting up of aberrant proliferative activity is a function of cell senescence: that as different orders of cells have different life periods, so may they give origin to tumors at different periods during the life of the individual. This hypothesis again covers only a small part of the ground (*e. g.*, does not include the teratoblastomas) and is inadequate.

From these we pass to theories of a wider scope.

Hauser's Theory.—One which, in point of time, we should have mentioned among the first is that of Hauser. Just as among the members of a species of animal or plant there may be variation, so here he postulated that among the descendants of a single cell, the ovum, cells might make their appearance exhibiting active vegetation coupled with modified properties, the descendants of which constitute a neoplasm. He regards this variation as favored by change in nutrition with excess of the same. As pointed out elsewhere (p. 546), it does not appear to be surely established that mere excess nutrition is in general a cause of hypertrophy and proliferation.

The Habit of Growth.—We ourselves[3] have laid stress upon the consideration that the cell that is differentiated for the performance of function, in the performance of that function uses up energy and cannot simultaneously store up energy to any extent for purposes of proliferation: it is the cell that either has not yet undergone differentiation or the one that has passed from a fully formed to a less differentiated state that is capable of active proliferation, not merely, as Bashford would hold, cells of the exhausted and senescent type, but premature or immature cells

[1] Proc. Royal Soc. London, 72: 1903. Ibid., 79: 1907.

[3] Adami, Brit. Med. Journ., 1901: i: 621.

also; that the mere existence of cells of this order in the body does not in itself initiate blastomatosis, nor even a stimulus of the ordinary type acting on such cells; that just as cells modified by inflammation or irritation undergo metaplasia, and from these modified cells we find originated tumors departing from the type (for example, in the inflamed gall bladder, the everted uterus, and other mucous membranes in which a flattened epithelium has replaced one of more columnar type, we meet with carcinomas approximating toward the epitheliomatous type), so in like manner cells which for a sufficient length of time have been so placed or so acted upon that they have been unable to perform function, while they have continued to gain nourishment, assuming the less differentiated, actively vegetative stage, gain the *habit of growth*, or, in other words, lose the habit of function; and it is the assumption of the habit of growth that is the point of origin of the neoplasm. This hypothesis, it is true, covers both cells, which as in the teratomas and teratoblastomas have been so situated that they have never been able to assume full function, and the blastomas developing whether from cell rests or from cells *in situ*. It demands that the grade of lack of assumption of complete adult type of the tumor cells is the expression of lack of development, or extent of reversion, of the parent cells of the tumor at the time when the habit of growth manifested itself.

Beneke[1] has given utterance to somewhat similar views. He regards blastomatosis as due to increase in growth energy on the part of the cells with contemporary lowering of the functional activity.

Other observers, however, have sought for a more tangible explanation of the process of *Entdifferenzierung*, anaplasia or kataplasia, that is so obvious a characteristic of tumor cells in general.

Marchand[2] emphasizes the fact that the difference between the normal embryonic cell and the so-called embryonic cell of tumor lies in this, that the former has the potentiality with continued growth to undergo eventual differentiation, the latter has not merely passed into a latent state as regards functional and structural differentiation, but has actually and permanently *lost the potentiality to undergo such differentiation*. He urges that there must first be a degenerative change in the cell leading to faulty metabolism, and that the products of the perverted cell have a toxic action upon the other cells in their neighborhood, weakening them and in this way leading to unrestrained growth. This appears to apply specially to the malignant blastomas, and is not so easily applied to benign growths or to teratomas and teratoblastomas. Undoubtedly the trend of recent work is to show that malignant tumors excrete or afford substances, some of them of the nature of enzymes, which are of toxic nature, and it is a reasonable view that these tell especially upon the immediately surrounding tissues, but the theory leaves it open to determine what is the cause of the primary degeneration.

Oertel's Theory.—On the basis of his studies already noted Horst Oertel seeks to give an explanation why the tumor cells have so completely

[1] Berl. klin. Woch., 1905, Nr. 22. [2] Deutsch. med. Woch., 1902: Nrs. 39 and 40

lost the power of undergoing subsequent full differentiation; why, to employ my terminology, they have gained the habit of growth, and lost that of function. The researches of the embryologist have shown that nuclear chromatin is not homogeneous; the existence and passage on from cell to cell of various orders of chromatin loops with curious persistency would seem to indicate that the different orders of loops convey different properties, whil. among the protozoa we find repeated examples of the existence of double nuclei, the one evidently associated with propagation, the other associated with the general or functional activities of the cell. Oertel thus suggests that in man and the metazoa in general the single nucleus contains chromatin of two orders, the one governing the functional, the other the proliferative or vegetative activities. What constitutes the primary cancer (or, we would add, other tumor) cell is a cell which has undergone loss of certain chromatin constituents of the former order; where these are lost the cell cannot reproduce them. The cell which has lost the chromatin controlling certain differentiating attributes can only give rise to daughter cells minus these, but endowed still with vegetative attributes. In this way races of cells are developed in which vegetative attributes are predominant but functional attributes to a greater or less extent have become lost. It is a matter for future research whether these two orders of chromatin actually exist in the mammalian cell, but the conception is admirable and has some justification, while it affords an anatomical basis for an observed fact, namely, that the cells of tumors in general approximate to the vegetative rather than the highly differentiated type.

Conclusions.—We have, it would seem, arrived thus far, that we recognize definitely among the blastomas some change in the biological properties of particular cells as an essential for neoplasia proper. We recognize, that is, an inherent and permanent alteration in the properties of the cells that constitute, or are to constitute, the neoplasm. It is not something from without that determines the continued growth, not an external stimulus, nor again a diminished external resistance. An external stimulus, it may be, starts the cells on that path which leads eventually to their assuming neoplastic properties; diminished external resistance may well favor active neoplastic growth; nay, more, it may well be that cells of a malignant type afford secretions inhibiting the growth, by depressing the vitality, of surrounding tissue cells. But all these are subsidiary. What is of primary importance is that the cells giving origin to an autochthonous new-growth are so modified that the energy acquired by the assimilation of food is not in the main discharged in the performance of function, as in the healthy cell in normal relationship, but is characteristically retained and accumulated for purposes of cell growth and cell multiplication.

What is the nature of this change we do not know with certainty; it is here that we have to turn to hypothesis. To lay down along the line of Hauser's theory that certain cells of a tissue in the course of their multiplication give rise to mutations, while satisfying the conditions that it is only one or a very few cells in a given tissue that give origin to a new-

growth, just as in a given species it is only one or a very few individuals that undergo mutation and become sports, does not carry us very far; on the contrary it is apt, unless employed with proper appreciation, to check further advance; whereby we mean that too often the term sport or mutation is regarded as synonymous with chance variation. So employed it would in this instance indicate that neoplasia is without definite cause and that it is hopeless to seek farther. Biologists, however, are coming to see that mutations in animals and plants are not chance occurrences. It is being recognized that alterations in environment favor their more frequent appearance. Regarded thus it is reasonable to regard the cancer cell as a mutation of the normal cell, for such a view is quite in harmony with the clinical observation that certain conditions —life period, trauma, chronic inflammation, etc.—favor the appearance of the blastomatous change. Like considerations apply also to the conception of anaplasia and to Beneke's view of modification in the cell properties, and to Oertel's most recent theory. There is, indeed, a close relationship between von Hansemann's theory of irregular distribution of chromosomes and Oertel's of using up or destruction of specific constituents of the nuclear chromatin of the adult cell. All recognize a change in cell properties, but none lay down what is the underlying influence or stimulus which brings this change about. Here it seems to us that our theory goes somewhat farther in postulating more fully than the others the nature of this change, namely, that there is no one stimulus, microbic or physical, that is responsible for the change in cell properties. As shown by a study of the life histories of different types of tumors, now it would seem to be merely long continuance in a state in which, through cell displacement, vegetative activity is possible but functional activity is inhibited, now a grade of chronic inflammation with accompanying arrest of function without arrest of nutrition, at one time of mechanical, at another of microbic origin; now, it may be a senescent exhaustion of the functional capacities of the cell that favors the assumption by that cell of vegetative to the exclusion of functional activities, an assumption accompanied by alteration in the histological characters of the cell. The more we study the life histories of the different orders of tumors the more we investigate the circumstances associated with the development of different examples of one particular order of tumor (such as the carcinomas), the more it is impressed upon us that there is no one specific causative agent, that a multiplicity of agents induce a particular grade of cell reaction; all these causes may lead to a modification in the cell properties, a modification that is not transient but permanent and conveyed to subsequent cell generations.

Finally, it must be asked what bearing has such a conclusion upon the quest for means of arrest and cure of malignant and other growths?

It is obvious, in the first place, that we hold that little is to be gained from the search for any parasitic cause. Even if found, we believe that once the cancer has taken on active growth, the mere destruction of the parasite would not modify the properties already impressed upon the cell.

If this be so, our attention should be directed in the immediate future not to the search for the cause of malignant and other growths, but to a careful investigation of the properties of tumor, as distinct from normal, cells, and more particularly to the inquiry into the factors which influence the growing powers of those cells.

Two possibilities suggest themselves, one along the lines of active bacterial immunity, the other along the lines of passive immunity.

1. As shown by Gaylord and Clowes,[1] and later by Ehrlich, by Bashford, and others, in a definite proportion of cases of successful inoculation of certain mouse tumors there is to be observed a later shrinkage and disappearance of the growths, and if now it is attempted to reinoculate these mice with the same or allied tumor material, the results are negative As also it has been found by Stieker[2] that where one of these experimentally induced tumors is growing actively in one region, a reinoculation in another place is apt to be without results. Stieker noted that while two implantations of mouse cancer made simultaneously into a mouse would both grow, after successful implantation in *one* region, inoculation in another was negative.

The phenomenon appears to be identical with what we encounter in syphilis, for example, and has been shown by Koch and others to occur in tuberculosis. And as in the latter case we are convinced that it is due to the development of antibodies by the organism, so in these cases we must conclude that the growth of the tumor cells at a focus leads to a like production of antibodies, and that here, as well as there, it is only when the growth of the parent tumor is so active, and the discharge of its products so great, that, as suggested by Ribbert, the antibodies are neutralized, the tissues becoming exhausted and the production of antibodies inadequate, that secondary inoculation or spontaneous metastasis formation becomes possible. If by inoculation of tuberculin into one in not too advanced a stage of tuberculosis it is possible to so exalt the general resistance of the organism, and so to increase the production of antibodies that the focal development of the tubercle bacilli is arrested and their death eventually brought about, so it would seem possible that extracts from the removed primary growth of a tumor might be employed to exalt the specific antineoplastic substances of the body at large, and so to prevent recurrence and bring about the atrophy and disappearance of metastases.

This has been proposed by Ribbert,[3] and has, if we are not misinformed, for more than a year been actually and independently tested by certain well-known investigators in New York.

Immunity so produced is within the bounds of possibility, but on the other hand, the general experience is that antibodies to the ferments and other substances developed by the functioning body cells are produced to a very slight extent. The observations of Flexner would seem to

[1] Jour. Amer. Med. Assoc., 47:1905:206.
[2] Münch. med. Woch., 1904:39.
[3] Deutsch. med. Woch. 32:1906:1693.

indicate that not all inoculable tumors induce sufficient general reaction to lead to the inhibition of secondary growth. Further, it is difficult to see how the wise dosage is to be determined, as it would have to be, for each individual and each individual case. By analogy it might easily be possible, as with tuberculin, to give doses of the extract which would have the contrary effect.

2. The second mode of destruction of new-growths that has to be tested is along the lines of passive immunity. It would seem quite within the bounds of possibility that substances may be discovered, whether drugs or animal products, or agents like the Röntgen rays and radium, to which the vegetative cells of the different orders of neoplasms will be more sensitive than are the fully differentiated cells of the organism. The indications are that we are approaching the successful application of bodies of this order. However inaccurate the reasoning that led Beard to suggest the use of pancreatic ferments, there is evidence that in certain cases these ferments act upon the cells of malignant growths, leading to their destruction and absorption, whereas they do not influence similarly the healthy cells. Von Leyden has extracted from the normal liver of animals a preparation of ferments which, applied to malignant tumors, is stated to cause their destruction with extraordinary rapidity, and Bier states that he obtains extremely favorable results of like order by hypodermic injections of pigs' serum. The outlook for the development of a rational antineoplastic therapy and for ultimate triumph over one of man's most terrible scourges is far from hopeless.[1]

[1] Articles bearing upon this subject are: Blumenthal, Ergebnisse d. exp. Path. u. Therapie, 1: 1907: pt. 165. (It may be noted that the observer was working on the effects of trypsin upon cancer before Beard's mode of treatment was indicated.) Beard, Lancet, 1902: i: 17; 1904: ii: 1200; 1905: i: 281; and New York Med. Rec., 1907: 24. Martin, New York Med. Rec., 69: 1906: 893. Neuberg and Ascher, Arb. a. d. Pathol. Instit., Berlin, 1906. Bergell, Ztschr. f. Krebsforschung, 5: 1906: 204. Pinkuss and Pinkus, Med. Klinik, 1907: Nrs. 28 und 29. Von Leyden, Deutsch. med. Woch., 1907: 913. Bier, Deutsch. med Woch., July 18, 1907.

CHAPTER XXIV.

CYSTS.

By the term "cyst" we understand a sharply limited and abnormal accumulation of fluid in any area unprovided with a channel of outflow. The mere localized infiltration of a tissue with fluid, such as occurs in acute inflammation, in local œdema or elephantiasis, does not constitute a cyst; there must be well-defined boundary wall or sac. An abscess, likewise, does not come under this term; its boundary is not defined with sufficient precision. The existence of a channel of outflow removes a well-defined collection of fluid from the category of cysts; an aneurysm, for example, communicating as it does with the arterial lumen, is not a cyst. We speak of all such localized dilatations of channels containing fluid as examples of *ectasia:* in addition to sacculated aneurysms, the varices or phlebectasis (localized dilatations of veins) come under this heading, as do lymph varices and the sacculations or diverticula that may occur along the course of the digestive tube.

That the accumulation is spherical or oval is also involved in the conception, as, again, that the fluid fills the sac; thus, we never speak of the accumulation of fluids occupying the larger serous cavities as cysts, even though etiologically these be identical in origin with accumulations in smaller serous cavities which we include among the cysts. It is a matter of illogical convention that a hydropericardium is not regarded as a cyst, whereas a hydrocele of the tunica vaginalis is so regarded.

Understood thus, the true cysts form a very heterogeneous collection, so various in origin and character that save as to study in etiology little benefit is gained from bringing them together under a common head. It is usual to conceive them in association with tumors, and they may as well be grouped together here as anywhere, although it must be understood that, save for the fact that they constitute local swellings, as a body they have nothing in common with the neoplasms. At most, this is to be recognized, that as a cyst grows in volume there occurs *pari passu* a growth in the tissue constituting its wall, but that growth does not constitute the cyst; it is not primary, but is governed by the pressure of the fluid accumulation. The formation of multiple cysts is a feature in one group of neoplasms, but these cystadenomas form a relatively small proportion of the cysts that occur in the organism. The term "cystoma" is only justifiable to the same extent as is "tuberculoma."

Classification.—Broadly we may classify the cysts into four groups of wholly distinct origin: (1) Those due to abnormal dilatation of pre-existing cavities of the organism, a result of secretion into those cavities at a greater rate than absorption proceeds from the same. (2) Il or-

rhagic cysts, due to the escape of blood out of the vessels into the tissue and subsequent encapsulation of the same. (3) Necrotic cysts, due to local death of tissue and liquefaction with encapsulation. (4) Parasitic cysts, due to the development (in itself normal) of metazoan parasites within the organism, such parasites possessing a cystic or saccular stage of development.

I. SECRETORY CYSTS.

Of these, the first constitutes the most important and largest group. We may subdivide this according to two methods, either according to the nature of the lining cells, which afford the secretion, or according as to whether the cysts be of congenital origin, due to developmental defects, or postnatal, due to acquired conditions. According to the first of these classifications we can further form classes in which the secreting cells lining the cysts are originally formed of:

1. Cubical or columnar "glandular" epithelium.
2. Endothelial.
3. Ependymal.
4. Squamous epithelial.
5. Composite.

Inasmuch as the congenital cysts with a few exceptions come into the first class, this would seem the more convenient classification to adopt, and this more particularly because there is a certain number of cases in which a given form of cyst of sundry organs may be either antenatal or postnatal in origin.

Regarding all of these, it is to be noted that when cellular activity leads to secretion of fluid into a cavity unprovided with a duct or passage of outlet, or when the passage is obstructed, that fluid is secreted against a certain pressure. The pressure in general is low, only a little above that of the mean blood pressure in the capillaries, but as the secretion is continuous and the absorption through the surrounding vessels and lymphatics is less rapid then the discharge into the cavity, there results a gradual distension of the cavity. It is under these conditions of moderate as distinct from excessive strain that, as pointed out elsewhere (pp. 93 and 541), cell multiplication is favored, and, as a matter of fact, we find that a cyst developed from a narrow tube or duct, as it grows in diameter, continues for long to be lined by epithelium or cells of normal type; there is actual growth and increase of the lining membrane, as of the underlying fibrous stroma, and this adapts the chamber to the increased contents. In this way a cyst may attain very great size and continue to be lined by a typical epithelium of one or other order. Eventually the lining cells exhibit a tendency toward atrophy and flattening, whether through overstimulation and subsequent exhaustion of the growth energy of the cells, through increased internal pressure, through malnutrition of the lining cells as a consequence of the progressive dilatation of the cyst, whereby the nutritive capillaries of the outer wall become flattened and the circulation is continued with increasing diffi-

culty, or, lastly, through the deleterious effects of the cyst contents. The watery contents of such a cyst are constantly undergoing absorption; the result is that the less diffusible products of secretion come to be more and more concentrated, until in the kidney and other organs we may encounter cysts filled not with water, but with inspissated, thick, even jelly-like or firm colloid contents. Which of these features plays the predominant part we do not know, but in old cysts it may be impossible to recognize any specific lining epithelium.

We shall in our review of the different forms of cysts call attention to the various factors leading to the formation of these cysts: obstruction of ducts, whether congenital or postnatal, persistence of portions of glandular and tubular organs which should have undergone complete retrogression during fœtal life, inflammation, distension of ductless vesicles present in the adult organism, etc.

"Glandular" Cysts.—I. **Of Antenatal Origin.—Congenital Cysts Due to Persistence of Parts of Embryonic and Fœtal Ducts.**—A very large group of cysts comes under this category. In the complicated metamorphoses of the embryo and fœtus it may happen that, with the closure of certain passages and atrophy of the same, portions of these do not undergo complete absorption. Such portions tend to form isolated tubular structures embedded in other tissues, and either immediately or it may be only after many years their cells may take on active secretory functions, cyst formation being the result.

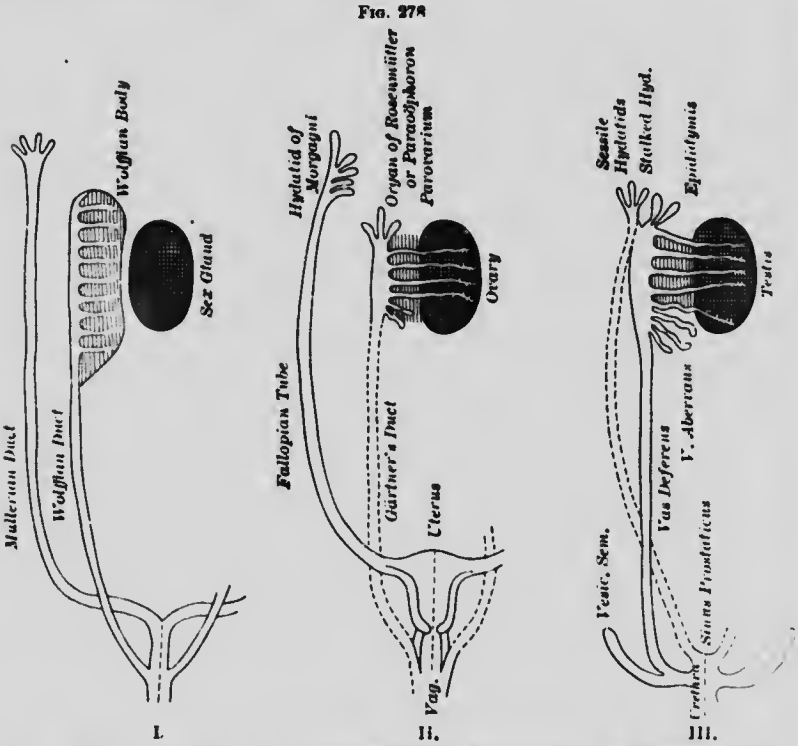
Of such may be mentioned: (*a*) *Thyrolingual cysts* in the median line of the neck, through distension of isolated remains of the primitive thyrolingual duct leading downward from the foramen cecum of the tongue. It is the distal branches of this which form the thyroid gland. (*b*) *Branchial cysts*, found in the remains of the second and lower branchial clefts; these occur upon the side of the neck from behind the angle of the jaw (second branchial cleft) to just above the sternoclavicular articulation.[1] Cysts of this order may either contain mucous fluid or sebaceous material, according as to whether they originate from the inner end of the branchial cleft (lined with mucous membrane) or from the outer (lined with squamous epithelium). (*c*) *Vitello-intestinal*, projecting internally or externally in the neighborhood of the navel. These are lined with mucous membrane and arise from a remnant of the vitello-intestinal or omphalomesenteric duct, the old communicating channel between the small intestine and the yolk sac. Similar cysts have been described in the neighborhood of the small intestines, communicating with this by a fibrous cord. (*d*) *Urachal cysts*, situated in the lower abdominal region, due to persistence of portions of the urachus.

(*e*) **Cysts of the Primordial Genito-urinary Passages in the Female.**—The Wolffian body and the Wolffian and Müllerian ducts undergo a

[1] See Bland Sutton, "Tumors, Innocent and Malignant," for a careful study of these cysts and the associated fistulæ (London, Cassell & Co., 1894, p. 324). In this work Bland Sutton gives a mass of data regarding the different forms of cysts which it is difficult to meet with elsewhere. His classification, however, strikes me as capable of improvement.

most complicated series of metamorphoses in the female, and as a result cysts are liable to form in unabsorbed remnants of the same, *i. e.*, in the residue of the Wolffian body, situated in the substance of the ovary, the head of the Wolffian duct and its side tubes (the organ of Rosenmüller), the continuation of the Wolffian duct through the broad ligament and alongside, or in the outer wall of the vagina where it opens near to the urethral orifice. This duct, when present, as not infrequently happens in the sow and cow, is known as Gärtner's duct. In connection with all of these remnants cysts may arise.

FIG. 278



Relationship of the sexual ducts and their rudiments in the two sexes: *I.* the indifferent primary type; *II.* the differentiation in the female; *III.* the differentiation in the male.

Cysts of the Wolffian body are apt to be multilocular (although they may be unilocular), to grow downward in the broad ligament, to have papillomatous vegetations, and to develop after maturity is reached.

Cysts of the free outer tubes of the *organ of Rosenmüller* (or paroöphoron), which do not communicate with the Wolffian body and ovary (and are known as Kobelt's tubes), are small, rarely larger than a pea.

Those from the vertical *connecting tubes of the paroophoron* are apt to become of great size; more often they are solitary. The smaller cysts are transparent and thin walled, with lining of ciliated columnar epithe-

linm; with increase in size the walls become thicker and opaque, the epithelium flattened, if not stratified; in the largest the epithelium has disappeared, and the contents are turbid, containing cholesterin and other products of cell degeneration. These cysts are apt to show themselves between puberty and the thirtieth year.

Cysts of Gärtner's duct are to be recognized as occurring in two positions: (1) in the broad ligament to the inner side of the ovary, giving rise to certain isolated cysts of the broad ligament, in general of no great size; and (2) in the vaginal wall, there also of no great size (compared with the huge cysts of the paroophoron), and either solitary or, rarely, in series.

There has been and continues to be discussion regarding certain small cysts that may occur in the uterine muscle, lined with columnar epithelium and often associated with new-growths of the muscle in the form of "adenomyoma." Many German authorities regard these cystic tubules as remains of Gärtner's duct; other investigators, more correctly, ascribe the tubules to deep ingrowth and sequestration of the uterine mucosa. We have considered these when dealing with the uterine "adenomyomas" (p. 690).

Hydatid of Morgagni.—The term hydatid of Morgagni is by many used laxly to indicate small cysts in the outer part of the broad ligament. This is a mistake; there is but one hydatid of Morgagni, the term, used correctly, being employed for the cystic dilatation of the longest of the fimbriæ of the Fallopian tube. The accompanying figure indicates the relationship of the various ovarian and tubal cysts.

(*f*) **Cysts of the Primordial Genito-urinary Ducts in the Male.**—In the male the mesonephros, or Wolffian body, is represented by the paradidymis, the Wolffian tubules by the vasa. Of the latter, we recognize three group , the main group constitutes the epididymis; the most distal, corresponding to Kobelt's tubes in the female, give rise to the *stalked hydatid* or *hydatids* at the upper pole of the testis or globus major of the epididymis.

These are sometimes mistakenly termed hydatids of Morgagni; it will be seen that they are not the homologues of the cysts of this name in the female.

The proximal remnants in connection with the lower end of the testis form a series of blind tubular remnants, forming the *paradidymis*. Along with these and resembling in its relationships the Kobelt's tubes (*i. e.*, being blind distally, but communicating proximally with the efferent tubes) is the vas aberrans. All these vestiges may be, rarely, the seat of cyst formations; to the blind tubules of the paradidymis are ascribed certain multiple cystic growths of the testis. Just as in connection with the Wolffian tubules in the female there may arise parovarian cysts, so apparently from the vasa efferentia, the homologous organs, there may arise solitary cysts, constituting what English authors describe as *encysted hydrocele* of the testis. Such "encysted hydrocele" has a totally different origin from the hydrocele of the tunica vaginalis, to be presently noted.

Of the Müllerian duct in the male only two remnants have so far been

determined, namely, the two ends, and of these, one only gives rise to cysts. This is the distal or anterior end in association with the globus major of the epididymis, which may be present as a small cyst, the *sessile hydatid*. The lower end fusing with that of the other side forms the *sinus prostaticus*, lying between the openings of the seminal ducts, the homologue of the female uterus and vagina.

(*g*) **Congenital Cysts Due to Imperfect or Arrested Development of Glandular Organs.**—The kidney and the liver supply the best examples of this order. Occasionally birth is rendered difficult by the huge size of the fœtal kidneys, or, following birth, death ensues quickly from obstruction to the action of the diaphragm by the greatly enlarged kidneys. At other times the condition is less extreme and is partial, and the individual

FIG. 279

Congenital cysts of the kidney from a newborn child dying shortly after birth. Both organs, greatly enlarged, consisted of an agglomeration of elongated cysts as shown here. (From the collection of the Royal Victoria Hospital. Zeiss objective D D without ocular.

may reach maturity. In such cases the kidneys may be found to be converted into a mass of cysts and dilated channels, varying in size from those just visible to the naked eye to others the size of a marble, or in the adult the size of a plum or larger. In these cases the renal tubules or the larger proportion of them are found not to communicate with the pelvis. A layer of dense fibrous tissue occupies the region of the calices. Above this the tubules are dilated and cystic.

There has been a long-continued debate as to the cause of such congenital cystic kidneys. Virchow regarded them as due to fœtal inflammation affecting the medulla and leading to constriction and atrophy of the terminal portions of the collecting tubules. Others have regarded the condition as adenomatous. The consensus of opinion at

the present moment is that we deal with a condition of arrested development. As to the exact nature of that arrest observers continue to be widely at variance, although the more recent exact studies of Schreiner and Huber, made with the aid of reconstructions of serial sections of the fœtal kidney, by Born's wax-plate method, would seem definitely to have settled the matter.

The original view of Remak and Kölliker, accepted by a long list of later observers, was that the whole of the renal tubules arise as evaginations and branches from the Wolffian duct. According to this view congenital cysts of the kidney can only be brought about by obstruction to the tubules after their formation. Virchow, as already noted, taking this view ascribed the obstruction to inflammation of the medulla.

So long ago as 1865 Kupfer recognized a separate origin for Bowman's capsules and the convoluted (secretory) tubules, and his researches have been confirmed by a succession of embryologists of repute (Balfour, Adam Sedgwick, Wiedersheim, etc.). The above-noted researches of Schreiner[1] and Huber[2] prove:

1. That the first indication of the fœtal kidney is an evagination from the Wolffian duct near the cloaca. This elongates, and becomes bulbous at its end. The stalk is the future ureter, the ampulla expands longitudinally and is the anlage of the future pelvis and collecting tubules.

2. Running alongside the Wolffian duct is a cell mass of mesenchymatous origin, the nephrogenic tissue. At the anterior end this gives independent origin to the Wolffian tubes. Behind, the renal ampulla penetrates into the mass.

3. The elongated ampulla (pelvis) gives rise to pairs of evaginations or branches, which proceed to dichotomise, developing the future collecting tubules.

4. The swollen or ampullary end of each branch becomes surrounded by a segregated mass of the nephrogenic tissue, and *in the inner zone of this tissue* there now form cell collections developing into vesicles—*renal vesicles*.

5. These vesicles elongate and fuse with the collecting tubules, so that their lumen opens into that of the ampullary ends of the collecting tubules. Elongating still further and becoming S-shaped, the distal end by invagination gives rise to the Bowman's capsule with its contained glomerulus; the other portions of the S give origin to the first convoluted tubule, the loop of Henle and the second convoluted tubule; in fact, to all the secretory portions of the renal tubule.

While thus an inflammation of the medulla in the later months of fœtal life might bring about obstruction, the simpler explanation of the congenital cystic kidney is that of a want of relationship or fusion between the renal vesicles and the outgrowths from the Wolffian duct. If the nephrogenic tissue proceeded to form renal vesicles without the renal ampulla proceeding to dichotomise and form the collecting tubes

[1] Zeitschr. f. Wiss. Zool., 71: 1902.

[2] Amer. Jour. of Anat., 4: 1905, Supplement 1.

we should expect the case of universal cystic degeneration of the kidney. Now we encounter kidneys of this order—kidneys with no pelvis, and, again, kidneys with a pelvis, but no signs of a medulla or of collecting tubules. We could expect also cases exhibiting in general a well-formed medulla and collecting tubules, but with these scattered cysts, due to local independent development of the mesenchymal renal vesicles without fusion with the collecting tubules, and, again, as a matter of fact we encounter these cases.

In the kidney in the newborn it is not uncommon to encounter what are evidently isolated imperfectly developed Malpighian bodies situated immediately beneath the cortex. These must be regarded as renal vesicles of latest development which have not as yet gained connection with a collecting tubule; in congenital syphilis causing, as it does, arrested development, these are apt to be relatively abundant. I cannot, however, accept the view propounded by Ribbert[1] that the cysts in the congenital cystic kidney are developed purely from the glomerular bodies. The renal vesicles are not merely the glomerular anlagen, but give rise to the whole secretory tubules, and the cysts in certain cases are clearly of tubular type both as regards their form and their epithelial lining.

Aschoff would proceed farther and give the like origin to all the isolated "retention cysts" encountered in later life. Here we cannot entirely follow him. It is true that such cysts form most often immediately beneath the capsule, in the region, that is, where we find latent and rudimentary renal vesicles. We do not deny that some, perhaps a considerable proportion of isolated cysts, are of this nature, but the renal tubules are certainly capable of dilatation as a result of obstruction. We may, indeed, have acute cystic dilatation of tubules in acute parenchymatous nephritis as a result of blockage of the narrow descending loop of Henle by the shed cells of the first convoluted tubules. It is rational to believe that interstitial fibrosis, by contraction and obliteration of lumen of tubules, may lead to similar obstructive cyst formation. It is striking how frequently these scattered cysts are associated with chronic interstitial nephritis.

In the liver we more rarely encounter similar congenital cysts. In those cases we have studied there has always been a marked degree of fibrosis around the bile ducts in the immediate neighborhood of such cysts. A diffuse enlargement of the bile ducts, and even of the bile capillaries throughout the organ, may be associated with congenital stenosis or obstruction of the common bile duct. We regard them all, then, as hepatic bile cysts of obstructive origin.

Congenital Cystic Diathesis.—Still more rarely we encounter cases of what has been termed the *cystic diathesis* with multiple cyst formation in both the kidney and liver, or as in a case studied by us in kidney, liver, and pancreas.

In our case the kidneys were of the typical congenital cystic type, as seen in the adult, *i. e.*, there was a pelvis and in certain areas well-

[1] Verhand. d. deutsch. path. Gesellsch., 2:1900.

formed collecting tubules, although large portions of both kidneys were converted into dense congeneries of cysts with no sign of collecting tubules or pyramids. The bile cysts were relatively few and small, and there was marked fibrosis around the bile ducts in their neighborhood; they were obstructive cysts. The distal half of the pancreas was alone affected, but this to an extreme degree all the tissue being replaced by large cysts. The rest of the organ was normal and the cystic transformation began immediately beyond a distinct groove on the surface of the organ formed by the tense band of the mesenteric vessels. These clearly had pressed upon the organ and compressed, and to some extent hindered its duct. We had clearly to deal with obstructive retention cysts.

Here clearly the occurrence of multiple cystic disturbances was a coincidence, or, at most, the diathesis was of the nature that obstructions, which in the normal individual would be overcome, in this individual were followed by dilatation and giving way and atrophy of the surrounding tissues, so that cyst formation resulted more easily than in normal individuals. A study of the recorded cases leads me to regard them as of the same nature.

II. Glandular Cysts of Postnatal Origin.—1. **Originating in Tubular Glands through Obstruction of their Ducts.**—Retention cysts of this order are widely distributed. The ducts may become plugged and obstructed by mucus, calculi, etc.; may be stenosed through the pressure of surrounding fibrous tissue, the result of a chronic productive inflammation, or compressed by the pressure of new-growths from without, etc. Cysts of this order lined by characteristic columnar or cubical glandular epithelium may develop in any tubular gland. The examples are very numerous: "Ranula" of the floor of the mouth through obstruction of the duct of the sublingual glands, or of the glandula incisiva situated farther forward in the floor of the mouth; salivary cysts through blocking of a salivary duct; mucous cysts, small and multiple, of the intestinal mucosa through blocking of the crypts; pancreatic cysts (*Ranula pancreatica*) of like origin, cysts of the mucous glands of the epiglottis, trachea, Cowper's glands, glands of Bartholin; bile cysts of the liver; the small, solitary, or sparse retention cysts of the kidney (see above), of the glands of the uterine cervix (*Ovula Nabothi*), of the lacrimal gland (*Dacryops*), of the ducts of the mammary gland (*Galactocele*), etc.; wens, atheromatous or sebaceous cysts (arising from the sebaceous glands in the hair follicles). In this group must also be included conditions of hollow organs lined by a glandular epithelium, as, for example *hydrops cystidis fellea* or cystic dilatation of the gall-bladder due to obstruction of the cystic duct, and appendicular cyst due to stenosis of the appendix vermiformis with dilatation above the region of obliteration. Some of the most remarkable examples of cyst formation are encountered in connection with the Fallopian tubes, when, through inflammation, they become closed at either end (*hydrosalpinx*). When through laceration in parturition and subsequent cicatrization the cervix uteri becomes occluded, there develops the condition of distension of the uterus with retained discharges known as *hydrometra*. These latter cases may, with

propriety, be relegated to the group of composite cysts to be presently noted.

2. **Originating in Ductless Glands.**—The thyroid and the pituitary body are both formed, as regards their main constituent, of closed vesicles. These under normal conditions become, many of them, excessively distended with secretion, and thus may present cysts visible to the naked eye. In the thyroid, which is more frequently affected, such enlargement constitutes one form of cystic goitre. To other forms of thyroid cysts we shall refer later.

Among the cysts of the ductless glands must be included *cysts of the corpora lutea* and *Graaffian follicular cysts* of the ovary. Both are somewhat aberrant in their mode of development. A further note regarding the former is given on p. 795. The Graaffian follicles are of mesothelial origin, originating from gland-like crypts of the germinal epithelium. The normal follicle has a fluid centre surrounded by several cell layers. The function of these specific cells would appear to be that of nourishing the developing oocyte situated within the discus proligerus. At times they actively secrete fluid, and small follicular cysts have been found still containing an ovum. More commonly the ovum has undergone disintegration, and cysts, the size of a pea, or larger, persist in the ovary; these are frequently multiple.

FIG. 280

Section from a case of multilocular ovarian cyst, showing early papillomatous ingrowths into certain of the cysts. (Ribbert.)

III. **Glandular Cysts of Neoplastic Origin: Cystadenomata.**—All adenomas of tubular glands or reproducing vesicular cell groups may, through continued production of (abnormal) secretion, give rise to multiple cystic growths. There are adenomas of certain organs which have a special tendency toward this cystic modification. First and foremost must be mentioned those of the ovary, or, as some would hold, of the Wolffian body. This *cystadenoma papilliferum* of the ovary, or multilocular ovarian cyst, may attain a great size and be composed of innumerable loculi or individual cysts, some as large as a child's head, others scarcely visible—all of them lined by a columnar epithelium. As indicated by the first title given, one group of these cysts from the ovarian region has, in addition, a pronounced tendency toward the development of intracystic papillomatous growths.

The breast is another region in which adenomata are prone to become cystic, although here it has to be pointed out that many of the conditions termed cystadenoma are not true neoplasms, but are primarily, at least, retention cysts of the milk ducts caused by chronic inflammation, or

are involution cysts, from stenosis of the ducts and subsequent cyst formation accompanying retrogressive changes and atrophy of the gland substance. It is from the walls of such cysts that there is a tendency for papillomatous and even carcinomatous intracystic masses to develop.

Cysts of other nature may develop in tumors—lymph cysts (p. 792) and necrotic cysts (p. 795). Relatively small cysts of glandular type may occur in one form of tumor not of the adenomatous or lepidic type, namely, in gliomas.

These are lined with cubical cells of the ependymal type, and are regarded as of embryonic origin, due to inclusions of processes from the developing neural canal. According to Saxer, the larger cysts in gliomas are of the nature of necrotic cysts. These become lined by what, at first sight, is a definite epithelium; more careful examination shows that this is not a true lining membrane, that it passes imperceptibly into the underlying glioma tissue; what happens is that from the accident of position the superficial cells bordering on the cyst take on a more cubical type.

IV. **Endothelial Cysts.**—The cases of endothelial or serous cysts of congenital origin are relatively few in number: they may fittingly be considered along with those of postnatal acquirement. The characteristic examples are serous cysts—sacs distended with serous fluid or lymph. Such sacs are lined with endothelium, either of some cut-off portion of a serous cavity, more particularly of the peritoneum, or of the lymphatic system. Examples of the former are scrotal hydrocele, and cysts of the canal of Nuck; of the latter, bursal cysts, "ganglia" (cysts formed by the cutting off of hernial protrusions of the synovial lining of tendon sheaths), many mesenteric and subpleural cysts, lymph cysts in association with macroglossia, and other conditions of congenitally obstructed lymph channels.

Of these serous cysts of congenital origin, some of the most remarkable are those known as *hygromata*. These lymph cysts of congenital origin may occur in various situations, but the largest and most remarkable examples occur in the neck—*hygroma colli*.

Here huge and progressive collections of lymph cysts may develop, either a few large, or a sponge-like congery of small cysts, and these ramify, not merely in the fasciæ between the neck muscles, but in the muscles themselves, the parotid and salivary and other tissues of this region, extending both upward and downward (into the thoracic cavity).

It is doubtful whether these should be regarded as simple serous cysts; some are of this nature, but many exhibit a very cellular stroma, and, as pointed out by Boyce,[1] there is evidence not merely of connective tissue, but of endothelial proliferation: ramifying columns of endothelial cell masses are to be made out, which, judging from transitional stages observed, ultimately become cystic. In other words we deal with definite lymphangio-endotheliomas (Borrmann[2]).

[1] Pathological Histology, p. 192.

[2] Borrmann has recently described, Ziegler's Beitrage, 40; 1906; 372, an hemangiomatous tumor of like benign type and undeveloped.

Other lymph cysts deserving of note are those which occur in the choroid of the eye, the chylangiomas of the intestinal wall (dilated lymphatics filled with inspissated milky chyle), and the serous cysts which may complicate tumors, notably uterine fibroids.

It is obvious that, since the tunica vaginalis is normally present as a closed sac, without accumulation of fluid, the accumulation of fluid in the same to form a hydrocele can only be brought about by modified activities of the lining membrane; there must, that is, be either increased secretion into the sac, or obstruction to the normal diffusion of fluid out of the sac, or both. It is probable that we have to deal with both. We cannot explain the first stage in the formation of a hydrocele (before distension of the sac shows itself) without assuming increased secretion, and this secretion must be governed by the state of the endothelial lining; in the developed hydrocele there is definite thickening of the tunica forming the sac, and this must hinder diffusion outward.

The same considerations govern bursal and lymph cysts in general; we have to recognize both obstruction to outflow and discharge, and active secretion. To form a cyst the pressure within the sac must be greater than that of the lymph in the immediately surrounding tissues, and this demands the latter condition. Such bursal cysts may be of intra-uterine or postnatal acquirement. The conditions leading to their development are increased pressure on a part, of an intermittent type, with movement of the loose connective tissue over some more rigid prominence, with rupture or separation of the strands of the connective tissue, resulting in a low form of inflammation, with the accumulation of serous fluid. The cavity thus formed, at first irregular, through proliferation of the endothelium of the lymph spaces involved becomes lined with endothelium, becomes also smooth-walled and cystic.

V. **Ependymal Cysts, Neural Cysts.**—The ependyma lining the hemispheres and the spinal canal is embryologically as an epiblastic tissue more nearly related to the "glandular" lining membranes, although functionally it is more of the nature of an endothelium, such as that lining the serous cavities; the cysts developed in connection with it may thus be treated as a special class.

Through stenosis, whether from imperfect development or intra-uterine inflammation, there may be brought about localized closure of some portion of the spinal canal, or, again, of the canals of communication between that canal and the external lymphatics. Either condition results in accumulation of the cerebrospinal fluid and cystic dilatation of the cerebral ventricles or of the spinal canal. In this way result the conditions of hydrocephalus internus, hydrocele of the fourth ventricle, cysts of the spinal canal (syringomyelocele) (see p. 246).

These conditions must be distinguished from the various forms of meningocele, serous or endothelial cystic states, partial or complete, involving the meninges. The ordinary hydrocephalus involves the lateral and third ventricles, the obstruction occurring in the iter. Hydrocele of the fourth ventricle, a condition first described by Virchow,[1] is a much rarer

[1] Die Krankhaften Geschwulste, 1: 183.

condition, brought about by obstruction of the lateral recesses of the fourth ventricle. These passages contain the choroid plexus of the fourth ventricle, and form the means of communication between that cavity and the subarachnoid space at the base of the flocculus; obliteration of one of these recesses, or of both, lead to unilateral or bilateral bulging and cyst formation at the base of the brain, with pressure upon and paralysis of the facial, auditory, and, it might be, of the glossopharyngeal and vagus nerves, all of whose root filaments lie in the neighborhood of the cyst. The condition, as in a case of my colleague, Dr. Bell, may be associated with a moderate grade of hydrocephaly.

VI. **Epithelial Cysts.**—These form a large group. The congenital "sequestration dermoids," and acquired implantation cysts of the skin, are more properly considered among the composite cysts, inasmuch as the fluid filling the cyst is in general the product of sweat and sebaceous glands, and not derived directly from the squamous epithelium; and there they will be discussed. Here it may be noted that the simplest form of implantation cyst, such as may be found beneath the skin of the fingers or palm in sewing-women and those performing rough manual labor, may, under the microscope, exhibit a simple squamous epithelium without glands, and nevertheless possess pultaceous or atheromatous fluid contents. Such cannot be regarded as true secretion; the fluid is the product of the disintegration and autolysis of the more centrally situated cells. We refer to cysts of this order in this place to call attention to the fact that their walls are in the main composed of squamous epithelium. Occasionally, as in the orbital tissue, simple cysts are found lined by stratified epithelium without glands which, nevertheless, have clear fluid contents.

VII. **Composite Cysts.**—Under this category are to be included those cysts whose walls are formed of more than one form of epithelium, and in which the secretion of the cystic fluid is from glands discharging into the main cavity. The sequestration cysts above mentioned are of this character, and closely allied are the teratomatous cysts, such as the ovarian dermoids; hydronephrosis of the kidney and its pelvis is a typical example.

Sequestration cysts are due to the inclusion and detachment of portions of the true skin in the region of the fissural lines of the body below the line of fusion of the two sides of the dorsal groove, of the thoracic abdominal cleft, the facial clefts, etc. In all these regions cysts may be encountered lined with squamous epithelium, and either containing glairy fluid (from sudoriferous glands) or pultaceous fatty fluid (from sebaceous glands); or, in addition to these, hairs both loose and attached.

Such cysts may not be merely superficial, but may be situated relatively deep in the tissues. It must be remembered, as pointed out by Bland Sutton, that the bony vault of the cranium is of relatively late development; originally the skin over the head was in contact with the dura mater; thus, through abnormal infolding and sequestration a skin cyst may eventually form attached to the dura mater and beneath the

cranial vault. The same is true of the anterior cleft of the body and the sternum; sequestratio dermoids may develop in the mediastinum beneath the sternum.

Postnatal *implantation cysts* may be of similar structure; through trauma, a portion, large or small, of the surface epithelium may become lodged in the underlying tissues; may become grafted there and proceed to grow. The active growth of a squamous epithelium, it will be recalled, occurs in the lower Malpighian layer; the inevitable tendency, therefore, is for the growing edge of this outer surface to curve inward until a globular mass is formed.

If the original graft have accous or sudoriferous glands associated with it, the secretion from distends the cavity and a cyst results.

We have dealt with te ous cysts in discussing the teratomata (p. 603).

The subject of *hydro sis* will be dealt with in more detail in the second volume. Here would only call to mind that hydronephrosis

FIG. 281

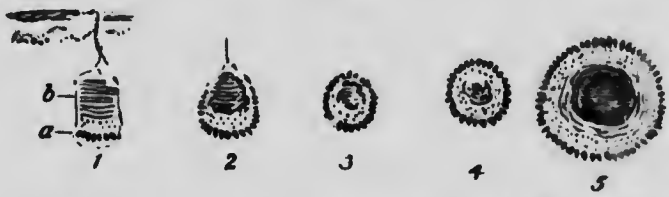


Diagram to illustrate mode of formation of an implantation cyst of skin: 1, shows a fragment of skin depressed into the underlying tissues: the actively growing cells of that fragment are upon its under aspect, at *a* (the palisade layer of the rete Malpighi): the stratified flattened cells of the epidermis (at *b*) have lost the power of growth; 2 and 3 show the continued growth of the cells of the rete Malpighi, which from the want of growth of the cells at *b* must come to surround those cells, and form as at 4 a solid, and later as at 5, a hollow sphere.

is brought about by obstruction, congenital, or more often acquired, of the urinary passages, at any point between the prepuce (phimosis) and the pelvic origin of the ureter. Such obstruction leads to distension of the passage above the point of closure, and that distension tells especially upon the pelvis of the kidney. There are cases of hydronephrosis in which the pelvis alone is affected, the kidney substance not recognizably involved. Most often intrapelvic pressure leads to atrophy of the pyramids, and this atrophy is progressive until the kidney may be represented by a large sac, a foot or more long, and of proportional girth, the kidney substance proper being represented by a thin layer of tissue a millimeter, or little more, in diameter.

In this connection may be noted the cysts of the jaw, both simple and multilocular, due to aberrant development of the teeth sacs and enamel germ remains. These may contain clear or atheromatous fluid, may be lined with squamous or merely a single layered cubical epithelium, and may or may not contain, projecting into them, one or more teeth; when teeth are present we have the true *dentigerous cyst*

II. HEMORRHAGIC CYSTS.

Extensive hemorrhages into the substance of sundry organs may result, not in the ultimate absorption of the exuded fluid, but in cyst formation. The hemorrhage leads to the destruction of the tissue of the infiltrated area; eventually a capsule is formed around the exuded blood, but while this is proceeding, through the combined agencies of leukocytes and autolysis the bodies of the corpuscles and the cell debris undergo removal, as does also the diffused and altered hemoglobin; so that, after a few weeks, the cyst is found to contain a thin blood-stained fluid, and, eventually, all the pigment being removed, the contents come to be a clear serous fluid. The last indication of the hemorrhagic origin of such a cyst is the presence of modified blood pigment in and around the fibrous capsule. The organs in which such hemorrhagic cysts are specially liable to be found are the brain (substance of the hemispheres, base, internal capsule and pons), the goitrous thyroid, scalp of the newborn, and children (*Cephalhematoma*), pinnæ of ears (in football players and lunatics—*Othematoma*).

Bradley,[1] following Rokitansky, has pointed out that the large cysts with serous contents found in the thyroid, from their structure, and the various stages found, can only be regarded as the results of hemorrhage into a nodular goitre.

The cephalhematomata are interesting in that there is a tendency toward the development of a ring or margin of true bone at their base, proceeding from the pericranium where it is raised from the bone, the hemorrhage, in these cases at least, being situated beneath the pericranium. A crateriform, osseous growth upon the skull is the result. Bland Sutton figures an extreme example of this condition found in a monkey.

The corpus luteum of pregnancy occupies an intermediate position; in its earliest stage it is definitely a blood cyst, but soon, without further hemorrhage, the volume of its contents increases, the contents with this becoming paler. The recent researches of Prenant, Born, Jolly and Marshall[2] denote that the corpus luteum affords an internal secretion, and indicate that the lutein cells, far from being degenerative, play a very active part in connection with the secretion of diffusible substances which influence the mucous membrane of the uterus and the economy in general. (See p. 329.)

III. NECROTIC CYSTS.

These, in mode of origin, are closely allied to the hemorrhagic cysts. When there has been an extensive necrosis of tissue of a non-infective

[1] Journal of Experimental Medicine, 1: 1896: 401.
[2] Philosophical Trans., Royal Soc., B. 198: 1906.

type, as in large infarcts, complete absorption of the dead matter and replacement by cicatricial tissue does not occur, but in its place the central area of such a mass undergoes autolytic liquefaction, the soluble products diffuse out and lymph diffuses in; around the space a cicatricial capsule becomes formed, and thus a cyst results. A not uncommon seat of such necrotic cysts is the centre of large cancerous nodules. Through the centrifugal growth of the tumors the central cells become cut off from due nourishment, and it is held that those cells of glandular type afford relatively abundant autolytic enzymes; the nature of the growth hinders due cicatrization and replacement of the dead matter by granulation tissue. Thus, where under these conditions the growth does not fall in and become umbilicated, central cyst formation results.

IV. PARASITIC CYSTS.

Throughout the animal kingdom various metazoan parasites of the order of vermes, and of these preëminently the *Tæniadæ*, pass one cycle of their existence in an encysted stage within the tissues of their host, and the cysts formed by them may assume relatively large dimensions. In man the one parasite that forms cysts of large size is the Tænia echinococcus. Smaller cysts, just visible to the naked eye, are formed by the Trichina spiralis. These most commonly are situated within muscles, and are of an elongated oval shape, having the larvæ trichinæ coiled within them. The echinococcus cysts, on the other hand, may be as large as an orange, and yet larger, and may be variously distributed, being commonly known as—

Hydatid Cysts.—The liver is the commonest seat, although they may occur in very many organs and tissues—in the brain, spinal canal, eye, kidney, heart wall or cavity, lungs, mammary gland, bone, omentum, peritoneum, etc. They may be either single or multiple. Microscopically they are characterized by possessing an external capsule of laminated hyaline tissue, within which is a cellular and granular layer, from which at first there projects a single club-like head, with water-vascular system, and a circle of characteristic hooklets. As the cyst grows secondary heads with hooklets and surrounding cysts bud off from the wall internally, and these cysts are apt to become free in the hydatid fluid. In this way the single original hydatid may become filled with very numerous daughter cysts. Examination of the fluid tapped or expressed from such a tumor reveals the presence of hooklets in the sediment. Occasionally, certain of the cysts are sterile, *i. e.*, contain no heads and no hooklets.

More rarely in the liver, and the same is usually in bone, the daughter cysts, instead of being developed from the inner wall of the parent cyst, project outward, in which case there is developed a multilocular cystic formation, which, in the old days, was mistaken for a cystadenoma. The character of the hyaline wall, apart from the hooklets in the contents, suffices to determine the true nature of this more diffuse cystic

state. It should be added that, outside the cyst wall of the hydatid proper, there is developed an adventitial fibrous wall, at times of considerable thickness, through the irritation and productive inflammation set up in the tissues of the host.

FIG. 282

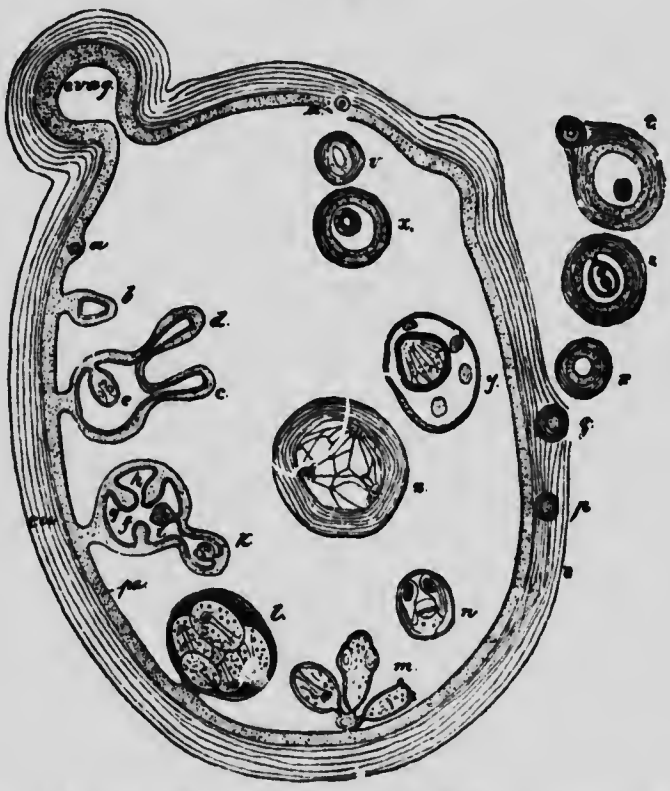


Diagram of an Echinococcus hydatid: *cu*, thick external cuticle; *pa*, parenchymal (germinal) layer; *c*, *d*, *e*, development of the heads according to Leuckart; *f*, *g*, *h*, *i*, *k*, development of the heads according to Monez; *l*, fully developed brood capsule with heads; *m*, the brood capsule has ruptured, and the heads hang in the lumen of the hydatid; *n*, liberated head floating in the hydatid; *o*, *p*, *q*, *r*, *s*, mode of formation of secondary exogenous daughter-cyst; *t*, daughter-cyst, with one endogenous and one exogenous granddaughter-cyst; *u*, *v*, *x*, formation of exogenous cyst (after Kuhn and Davaine); *y*, *z*, formation of endogenous daughter-cysts (after Naunyn and Leuckart); *y*, at the expense of a head; *z*, from a brood capsule; *cug*, constricted portion of the mother-cyst. (R. Blanchard, slightly modified.)

CHAPTER XXV.

THE REGRESSIVE TISSUE CHANGES.

NORMAL HISTOLYSIS AND CYTOLYSIS.

Just as, for a proper study of the progressive-tissue changes, it was found advisable to consider first the phenomena of normal growth, so, as an introduction to the consideration of the regressive-tissue changes, it is well to take first into account the natural decay of tissue elements. Although we give scant attention to the fact, it is almost needless to say that, from the embryonic period of life onward, individual cells and indeed individual tissues undergo a process of natural displacement and decay. Tissues and organs in the embryo, representatives of ancestral structures, make their appearance and then disappear; the thymus, functional in early life, attains its maximum development during the first two years of extra-uterine existence, then slowly shrinks and undergoes absorption; the lymph glands are largest during the early years, after which they exhibit a progressive diminution in size; as the milk teeth grow and emerge, they cause the atrophy of the tissue immediately surrounding them; after a few years their roots, in turn, undergo absorption before the growing permanent set of teeth; after each pregnancy the uterine tissue undergoes involution; that is, to say, its cells which had undergone hypertrophy or had become hypertrophied, now, to a large extent, atrophy; the ovaries again atrophy at the menopause, and, in general, with advancing years, one and all of the tissues of the body give evidence of shrinkage and loss of substance; that is, loss of component cells. And while any one tissue—with the possible exception of the nervous system—may, for long years, appear to be unchanged, we know that this is far from being the case. Red corpuscles and leukocytes have a life period of, at most, a few weeks, they disintegrate or are eaten up by other cells and younger corpuscles take their place. The same is true of the cells forming the epidermis and hair, although there the life period is longer. The same again would appear to be true of gland cells, and, even so stable and solid a structure as bone, when carefully studied, is seen to be undergoing constant change, the cells of the older trabeculæ dying, the bone substance becoming dissolved, and new cells and new bone substance being laid down in their place.

We know relatively little concerning these processes of normal cytolysis and histolysis, although our knowledge has, of late, undergone a material increase. But, leaving out of account for the moment the condition of simple atrophy, so called—conditions, that is, in which

we can recognize more or less clearly some departure from the normal in the direction of either reduced nutrition or modified function as the cause of the regressive change, and, considering only what could be regarded as strictly normal cell and tissue destruction, even here we become impressed with the fact that not one but several processes are at work. These processes group themselves into two orders, namely: (1) changes occurring in the cells themselves, and (2) processes acting from without upon the moribund cells whereby they are destroyed and removed. Taking first the changes occurring in the tissues and the cells themselves, we have to admit that under certain conditions, nothing very obvious is to be made out in the cells that are about to die or be destroyed. We cannot with certainty state that a given leukocyte, seen in the tissue or in the blood stream, was at the height of its activity when fixed and stained or was about to disintegrate. We are only too apt to forget that our histological studies are made upon dead material and that we must be most cautious in our interpretation of what we observe in the cells which have been fixed—and killed—by ourselves as compared with cells which have died without our intervention. So, also, while it is true that examining a given smear of the blood we may observe certain red corpuscles which are paler and more œdematous looking, we perhaps rightly judge that these cells are approaching the limit of their existence, yet, when we examine the cells of the spleen pulp, which, acting as phagocytes, have removed what are presumably damaged or moribund erythrocytes from the circulation, we cannot state confidently that the cells so removed present any marked difference when first ingested from those that are left behind.

Often, however, we can make out that the cells composing a given tissue are becoming older. In senile atrophy, for example, which, as already pointed out, is truly a physiological process, we can see that the individual cell elements undergo a definite amount of shrinkage. They become smaller, and the finer details of cell structure tend to disappear. The transverse striation of muscle fibers, for example, is not so sharply marked. This is the true normal, simple atrophy.

Nevertheless, although the process be a normal one, we are forced to recognize that, as a cell fails and shrinks, so does it become less and less able to carry out its metabolic processes. Substances absorbed by it may thus not be properly broken down and converted and then products of cellular activity will not be properly excreted, while, again, the products of the gradual breaking down of the cell substance, if they are not of a soluble nature, are apt to become heaped up within the cell. Thus, we should expect to find and as a matter of fact, we do find—that, under what are wholly normal conditions, cells undergoing atrophy and about to be disintegrated may exhibit much more than mere simple shrinkage. And, thus, under normal conditions, we may find the prototypes of disturbances which are apt to affect the cells in pathological states. Many of the so-called degenerative processes are liable to show themselves in this physiological or normal histolysis. The most familiar example of this is to be seen in senile atrophy of the heart-muscle fibers.

There is, perhaps, no more common histological finding in the tissues of old people than the so-called brown atrophy of the heart-muscle fibers. In this condition, hand in hand with the shrinkage in size of the fiber, there is to be recognized in the cell at either pole of its nucleus, a deposit of fine reddish-brown granules. This deposit we suppose is the product of breaking down of the myohemoglobin which normally is diffused through the muscle fiber. (See p. 884 for discussion of this subject.) As the cell substance breaks down, this is supposed to undergo conversion in such a way that an insoluble residue is left behind.

Perhaps the best illustration of such changes is afforded in connection with the involution of the uterus after parturition. During pregnancy the muscle fibers here have undergone an extreme hypertrophy. Now, during the week following delivery, the shrinkage is equally remarkable. From being on an average (according to Sänger[1]) 208.7 μ long, they become reduced to an average length of 24 μ. The shrinkage is, by no means, everything. Accompanying it, the fibers have a more *cloudy* appearance and some, but not all, show along their length fine, refractile globules which, treated with osmic acid, turn black. There is thus a condition of what is termed *fatty degeneration*, which in some fibers may be extreme. The nuclei also of these fibers become diminished in size. Nor are the muscle fibers the only portions of the tissue to show change. In between the more internal bands of fibers the connective-tissue cells become the seat of a deposit of fat, in fact, become converted temporarily into fat cells, losing this fat again by the fortieth day. The vessels also become markedly altered; many of the smaller ones become completely obliterated and disappear, the larger vessels show a characteristic overgrowth of the intima leading to considerable diminution of the lumen, while their adventitia becomes thickened and translucent. This is described by some as a hyaline degeneration, but Mayer,[2] perhaps more correctly, ascribes the appearance to a great laying down of elastic connective-tissue fibers. Here, therefore, we encounter cloudy and fatty degeneration, fatty infiltration and fibrosis all occurring under normal conditions.

New conceptions with regard to forces at work leading to the physiological atrophy of cells as again to pathological atrophy, have been afforded by the studies originated by Bordet upon the cytolysis of cells derived from a different species of animal (p. 489). We can go still farther. We have observations showing that when individuals of one species only are employed, we can, by successive inoculations, cause the blood serum of one animal to destroy certain cells of another animal of the same species. If this be so, may it not be that, throughout life, a due development of the various tissues and their keeping within bounds, so that one tissue does not invade the other beyond a certain point, may be due to the development of *heterolysins* (p. 339), which developed by cells of one order destroy those of another order? So that, for example, the healthy cell prevents the excessive growth of cells of

[1] Festschr. f. E. Wagner. Leipzig, 1888. [2] Arch. de Physiol. 1887.

another nature in its immediate neighborhood by the discharge or excretion of these heterolysins. If this be so it is conceivable that when an individual cell through functional activity or through other causes becomes worn out, it is no longer able to sufficiently protect itself by its heterolytic substances, and, as a result, it is killed and undergoes dissolution under the action of heterolysins secreted by other orders of cells. The French school, and more particularly Metchnikoff, have propounded these views. However attractive they may be, it has to be confessed that much more work has yet to be done before they can be regarded as established.

Leaving out of account, for the time being, inherited or acquired cell weakness and the conditions which lead to abiotrophy (p. 809), we are forced to recognize that the two prime factors which tell upon the health of the individual cells are (as we have already pointed out in the chapters upon Overgrowth and Progressive Tissue Changes), nutrition and the performance of function. If either of these be seriously disturbed, we are liable to have cell failure and the development of atrophic states.

Theoretically, we can imagine a series of disturbances which will lead to simple atrophy of the cells. The nutrition of a part not being primarily affected, if there be loss or arrest of function, the cells will undergo atrophy from disuse. Or, again, if the work of the cell be excessive, exhaustion of that cell will set in, the cell substance will be broken down more rapidly than it is formed, and the cell as a whole will shrink. Again, if primarily there be no disturbance of function but inadequate nutrition, then the cell substance cannot be built up at the same rate as it is being broken down and shrinkage inevitably results. Or, lastly, it is possible that, if there be excessive nutrition, the work of the cell may be hampered by overabundant material, so that, again, there is a relative disuse of the cell and, with that, a tendency, if not primarily to atrophy, eventually to do so. But in general it is clear that when one of this group of disturbances shows itself, then, as a secondary result, the other comes into action and favors the production of cell shrinkage and general atrophy. For example, when, through section of its nerve, a given muscle is rendered incapable of function, or, again, when without section of the nerve, the muscle is given enforced rest as, for example, when a healthy limb is cased in plaster bandages, then, accompanying this arrest of function, the vessels contract and there is diminished nutrition and thus, in its turn, must favor the rapid development of the atrophic state. While, where the nutrition is diminished, the functional using up of the cell substance (we use this term in its broadest sense) and the inadequate supply of material to replenish the loss, render the cell less and less capable of function, so bringing it to rest.

Now, as a matter of fact, it would seem that all these causes present themselves in practice as leading to atrophic conditions of the tissues. We thus recognize: (1) Disuse atrophy. (2) Atrophy due to excessive function. (3) Atrophy due to lack of nourishment. (4) Atrophy due to excess of nourishment.

1. **Disuse Atrophy.** Cases in which atrophy follows primary arrest of function frequently manifest themselves. We have already mentioned one, namely, enforced rest of muscular tissues. In such enforced rest, in a very few days, there is a noticeable shrinkage in the size of a muscle and the girth, for example, of a limb. The shrinkage, in fact, is remarkable. There is not, in the earlier stage, any diminution in the number of muscle fibers; the individual fibers diminish in size; they show the phenomena, that is, of simple atrophy. The same is the case when a nerve going to a muscle becomes divided or destroyed. As a general rule, it may be laid down, not only for muscular tissues, but also for glandular organs, and even for structures as solid as bone, that lack of exercise is shortly followed by atrophy.

Some of the most interesting examples of atrophy from disuse have been observed in connection with the nervous system. It was usually thought that when a nerve was divided there resulted purely what is known as Wallerian degeneration, that only that portion of the nerve away from its trophic centre became degenerated. But, for some years past, with the development of more careful observation and of more delicate technique, this has been proved to be not the case. So that now it may be laid down very definitely that, when by destruction of the main axon a neuron can no longer perform its function of conveying impulses of a definite order, that loss of function is followed by a very definite, if in some cases a slowly developed, atrophy. So long ago as 1874 von Gudden[1] pointed out that section of the optic nerve led to shrinkage and atrophy of the external geniculate body. The importance of this observation for long failed to be realized. Only in 1894 did Nissl, by his special method of staining, show that very definite alterations could be recognized in nerve cells soon after solution of continuity of their axons. Within twenty-four hours of excising part of the facial nerve in the rabbit, he obtained recognizable changes in the Nissl bodies of the cells of the seventh nucleus with rarefaction of these bodies, and a faintly granular change. In from a week to a fortnight the change was very much more advanced. Frey, in 1887, next pointed out the cellulipetal degeneration of the proximal end of a divided nerve. This is characterized by diminution of the caliber of the nerve fibers and shrinkage in size of the nerve cells. He showed further that if the rabbit's eye be extirpated, there is a considerable diminution in the size of the lateral geniculate body through disappearance, not of its nerve cells, but of the gelatinous substance between those cells which represents the terminal ramifications of the optic fibers. If, on the other hand, the visual area of the cerebral cortex be destroyed, the lateral geniculate body degenerates, not by disappearance of the gelatinous matter, but by atrophy of the nerve cells. He concluded, therefore, that two groups of neurons make up the optic path, one passing from the retina *toward* the optic centre at the base, the other from the optic centre at the base to the cortex. The true disuse atrophy is that seen in the

[1] Gesamm. u. hinterlass. Abhandl., Wiesbaden.

second series of experiments. The more recent papers of R. A. Fleming[1] and of Warrington[2] still further prove this atrophy of disuse. In section of efferent nerves the axis cylinders become thinner, but do not disappear, there being great reduction in the myelin. The ganglion cells of posterior roots show degeneration much earlier than do the multipolar cells of the anterior horn. By the seventh day it may be noted that the nuclei have diminished in size, often becoming excentric, that the Nissl's bodies have become grouped more centrally and have diminished in number, occasionally they become broken up into a dust-like cloud, while, as a result of the shrinkage of the whole cell, there is an enlargement of the pericellular lymph spaces. Only after four weeks are similar changes to be observed in the cells of the anterior horn. Fleming con-

FIG. 283

Disuse atrophy, section from bulb at level of the middle of the hypoglossus nucleus from a case of unilateral cortical atrophy (infantile polyencephalitis), to demonstrate disuse atrophy of associated neurones. *L*, left side of cord; *R*, right side; *p*, right pyramid (normal); *p'*, left pyramid (degenerated); *st*, stratum interolivare, greatly diminished on left side; *fai*, internal arciform fibers greatly diminished on right side; *pcp*, area of posterior column which in right side shows fibers mainly resorbed; *XII* reduction and diminution in size of cells of hypoglossus nucleus. (Mingazzini.)

cludes, it seems to me very reasonably, that as in health the cells of the posterior horn receive their stimuli from without, they should suffer more and suffer at an earlier date than do the motor cells whose axis-cylinder processes are directed toward the region of injury. The anterior motor cells can well be stimulated and so metabolism be initiated by the stimuli proceeding down the cord; whereas, in the posterior horn, through paralysis of the muscles, the cells are completely or almost completely cut off from their usual stimuli and so are brought to a condition of much more complete disuse.

[1] Lancet, London, 1896; ii; 508.
[2] Journ. of Physiol., 1898.

In short, as Monakow[1] pointed out now some years ago, neurons cannot be regarded as independent and automatic units. Their maintenance in a state of health and vigor demands that they receive stimuli from without, and unless they receive these stimuli they are incapable of action. In the absence of such they undergo a disuse atrophy.

2. **Atrophy from Overwork.**—A similar atrophy may result from excessive function. Here, again, the best examples occur in connection with the neuromuscular system, special groups of muscles and their nerve centres which are overworked in the performance of certain movements are apt to exhibit, following upon hypertrophy which has resulted from increased work, the onset more or less rapid, of atrophy. Neurons, or it may be the muscle fibers, become exhausted and worn out, and, as a consequence, we have paralysis with atrophy of the involved muscles (p. 360). We have examples of this in the various professional paralyses; atrophy of the muscles of the upper arm in blacksmiths, etc.; of the muscles of the forearm controlling the finer finger movements in piano players, etc.

3. **Atrophy from Malnutrition.**—Of simple atrophy secondary to diminished nutrition, also abundant examples can be afforded. Here we leave out of account, for the moment, those cases in which nutrition is wholly cut off resulting in the rapid death of the part supplied by a given artery. The cases we have to deal with are those in which with general diminished nutrition, without the quality of the blood being altered, there is diminished quantity passing to a part. Thus, where tumors of various natures press upon a large arterial trunk, we have shrinkage and atrophy of the part supplied by it, or where there is pressure not so much upon the arteries as upon the small capillary vessels, the same is the case; notably, continued pressure upon any viscus leads to the simple atrophy of the parts pressed upon. Even so dense a tissue as bone may thus be gradually destroyed by a more or less elastic fluid mass pressing upon it. In this way we find that, at the edge of a growing tumor, the cells of the surrounding tissue become shrunken and diminished in size, their nourishment has been interfered with and they atrophy. We frequently come across cases in which more particularly thoracic aneurysms lead to atrophy and absorption, either of the sternum or the subcutaneous tissue (the aneurysm coming to point, sometimes even to rupture, through the skin of the chest); or, on the other hand, of the vertebral column, the bodies of the vertebræ becoming eroded.

Lack of nourishment of the body as a whole—as in prolonged fasting and longer—leads also, it need scarce be said, to a very definite atrophy of the tissues. This atrophy is delayed not a little if while food is withheld water is available for drinking, though the appearances in the tissues are much the same whether water be given or withdrawn. Beyond simple shrinkage of the elements of the tissues there are no marked changes until the animal has lost 10 per cent. of its weight, then

[1] Arch. f. Psychiatrie, 27: pt. 1.

cloudy and granular alterations are to be seen in the cells of the larger glands—liver and kidney—and in the muscle fibers. In the liver cells, according to Statkewitsch, the glycogen disappears at a comparatively early stage, and there is a cloudy swelling, giving place later to a more coarsely granular swelling; later, again, in the outer cells of the lobules, there is extensive fatty infiltration; large fat globules distending the cells. In the mucous cells of the salivary glands there are the appearances of fatty degeneration. Nerve cells come to exhibit vacuolation.

4. **Atrophy from Overnutrition.**—With reference to atrophy from excessive nutrition, the case is not quite so clear. Notwithstanding, the sterility of the overfed and obese is an indication of what may be termed atrophic changes, occurring in the germinal cells, while the cardiac weakness of the very obese and of those suffering from fatty infiltration of the heart and the general lack of active performance of function on the part of the sundry glands, is not wholly explained by the fatty infiltration and by the disturbance of function brought about, by the heaping up of fat either in between or actually within the individual specific cells of those tissues.

SENILE ATROPHY.

Very intimately allied to this normal histolysis is the condition of senile atrophy, which also is, strictly speaking, a physiological process—a process of natural wearing out of the elements of various tissues, although in it, we see—perhaps not very clearly—that something else comes into play, namely, in some individuals, it makes its appearance at an earlier period and is much more marked than it is in others. So that we have to admit a certain constitutional state either favoring or delaying the process, as, again, we have to see that the incidence of the atrophic process is apt to vary in individual tissues. For example, while, as a general rule, the brain is one of the organs which is latest to show the signs of atrophy, we come across cases in which shrinkage of the brain and the coincident mental enfeeblement are perhaps the most marked feature.

While there are these exceptions, there is a certain order in the appearance of senile atrophy of the various tissues. The first to atrophy are organs which become functionless during the course of natural life. These we have already discussed. Closely allied to them may be placed the lymphadenoid tissues. Judging from their relative development during childhood and youth, these are most active at that period. They all—lymph glands, Malpighian bodies of the spleen, and, we may add, the red bone-marrow—undergo great diminution with advancing years. Next are to be placed tissues not in themselves active, but containing reserve material, *e. g.*, fatty tissue. Nervous tissue is, as a rule, the last to show marked atrophy, while a large group composed of the connective tissues, muscles and glands, occupy an intermediate position. Of these last three groups, referring rapidly to the changes

there made out, beginning with the fat cells, it may be noted that here two orders of events show themselves: either the gradual shrinkage and disappearance of the fatty contents, the cells reverting to a connective-tissue type, or as the fat in the individual cells disappears its place is taken by a serous fluid and the tissue assumes a semitransparent appearance. (See p. 837.) Whether the latter, so-called *serous atrophy*, should be regarded as a pure senile change is doubted by some. It is in those exhibiting other senile changes that we most frequently encounter it, noticeably in connection with the epicardial fat, but, when present, it is usually associated with some marantic condition; yet it is so common in the purely senile atrophy of the marrow of bones that it is, I think rightly, mentioned here. In both conditions there is a distinct tendency toward proliferation of the nucleus of the fat cell as Flemming was the first to point out.

Passing now to the active cellular tissues, muscles, fibers, and glands, here the first result of this physiological senile atrophy is diminution the size of the individual elements of the tissue. This is very characteristic in connection with muscle and is to be noted also in glandular organs like the kidney. Only when, at a later stage, there is an actual diminution *in number* of the component cells of the tissue by complete shrinkage and death do we have the condition of *hypoplasia*. But with this we are apt to encounter other changes, namely, the presence of deposits within the cells. These deposits are well marked in those cells which normally contain pigment. The muscle cells, for example, owe their color to myohemoglobin and, as they shrink, we observe in them a deposit of insoluble reddish-brown pigment granules which appear to be derivatives from the myohemoglobin of the lost cell substance. This is particularly well marked in the muscle fibers of the heart. In fact, we know no more common change in the bodies of those past middle age than the exhibition of this so-called brown atrophy of the heart-muscle fibers. Here the pigment lies heaped up in the undifferentiated cytoplasm at either pole of the nucleus. In senile atrophy of the liver, similarly, a considerable deposit of brownish pigment is met with throughout the cytoplasm of the shrunken hepatic cells.

We have already called attention to Metchnikoff's views upon senile atrophy and upon the existence of a certain constant antagonism between the different orders of cells composing the tissue.

In bones the most marked feature is a process of rarefaction whereby the individual bones become markedly lighter, and, as a result of the loss of solid osseous substance, the liability to fracture is distinctly increased. There is no great reduction in the size of the individual bones; in other words, the loss of substance is largely central, the outer periosteal layers showing little absorption; it is the internal trabeculæ and lamellæ that are, in the main, absorbed. The medullary cavity becomes greatly increased in size, the Haversian canals enlarged, the individual trabeculæ become eroded and thinned and reduced in number by the complete absorption of some, and, with this, the medulla shows pronounced change. The red cellular medulla disappears and its place

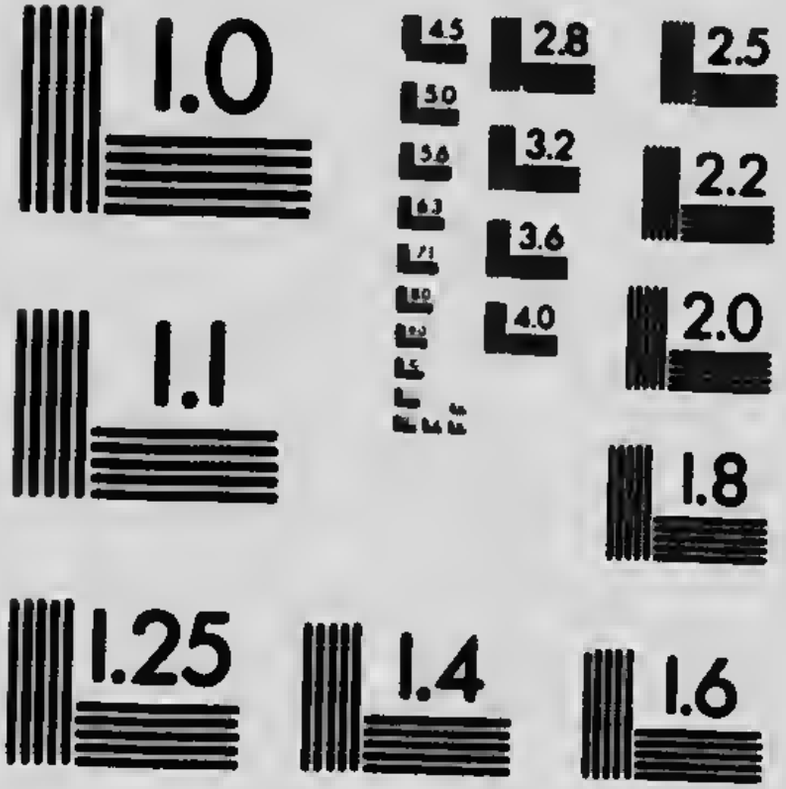
is taken by fat cells, which, in the later stages, show the serous atrophy just described. Here, again, we have an example of the replacement of a lymphoid tissue by fat cells.

The senile skin, with its characteristic wrinkling, presents a series of changes affecting, not so much the epidermis as the dermis and subcutaneous tissue; loss of subcutaneous fat, diminution of vascularity by thickening of the arterial coats and obliteration of some of the smaller vessels accompanied by lessened lymph in the interstices of the tissues, all of these together with the shrinkage of the underlying and muscular tissues, favor the wrinkling. But, in addition, as has been recently pointed out, there is a distinct alteration in the elastic fibrils of the dermis.

These alterations in the elastic-tissue fibrils (accompanied by loss of elasticity and of resilience) are important factors in the senile changes occurring in the two very important tissues, the arteries and the lungs. As the elastic sheaths of the large arteries lose their resilience—and this most frequently occurs first at the region of greatest strain, although in some cases the loss may be general—the arterial tube, dilating under the blood pressure, is unable to return to its normal caliber; it remains permanently expanded. One of two orders of events may now take place, either (1) the expansion is permanent and where it is generalized we find diffuse dilatation of the artery which may be so extreme as to develop a *fusiform aneurysm*, or, where it is localized, there is formed a *saccular aneurysm*. In either case microscopic examination shows that all the coats of the artery in the affected region are thinned and atrophied, this atrophy going on to complete disappearance of the inner coats in some cases of the latter condition. The increased caliber of the artery leads to slowing of the flow of the blood and all the consequences of the same in the region and the tissues supplied by that artery. Such dilatation and aneurysm formation is, however, rarely the result of pure senile atrophy. As a matter of fact, in such physiological atrophy we see a correlation between the loss of elasticity of the arterial wall and the force of the heart beat. Associated senile changes in the heart lead to lessened blood pressure. It is when the loss of elasticity of the arterial wall is premature from excessive effort, syphilis, gout, and the like, and the blood pressure above the normal, that these changes are most often encountered. Or (2) we find evidences of compensatory changes. As the arterial wall gives way, there is a connective-tissue overgrowth in the intima, as the result of which the lumen is restored to the normal. There is developed, in short, a condition of *arteriosclerosis*, a condition so common in those advancing in years as to be physiological. But the compensation is not complete; the new tissue growth, while it eventually comes to contain elastic fibrils, does not replace the lost elasticity. On the contrary the artery is now rendered more rigid and this increased rigidity of the tube leads to the pulse waves being conveyed with greater force into the smaller arteries and arterioles, which, in their turn, have to undergo compensatory changes to the detriment of the tissues supplied by them.

MICROCOPY RESOLUTION TEST CHAR.

(ANSI and ISO TEST CHART No. 2)



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A like senile loss of elasticity and degeneration of elastic tissue in the lungs underlies the *emphysema* so common in old people. Here, again, the loss of resilience may be premature as the result of increased strain thrown upon this tissue as by forced expiration, etc., and in short by anything leading to overdistension of the air sacs. But, as a normal condition, the elastic fibrils of the walls of the air sacs lose their resilience with advancing years.

As a result, if by any cause the air sacs become overdistended, they have not the inherent power of contracting to the normal size, but tend to remain distended, and, when so distended, instead of the encircling capillaries being circular on section, they become flattened out, that is to say, oppose a greatly increased resistance to the onflow of blood. With this the alveolar walls atrophy, become thinned, and, in parts, wholly absorbed, so that neighboring alveoli run together to form large, thin-walled, and largely useless air sacs. This emphysematous atrophy, together with increased laying down of connective tissue, around the arteries and the bronchi, are the most characteristic changes occurring in the senile lung.

Throughout the organs of the body, with the exception of the central nervous system, there is this same tendency in senile atrophy for the specific constituents to be accompanied by an increased fibrosis. This is, in part, *relative;* as the cells of the higher order diminish in size and in number, and the cells of the lower order—those of connective tissue—remain unaffected, the necessary result is that, in the shrunken organ, the fibrous tissue appears more prominent, and its proportion increases. But it is, in part, also, an actual increase—a *replacement fibrosis;* as the one element of a tissue diminishes the other proliferates and takes its place. The senile liver and spleen exhibit well these compensatory changes, the increased size of the trabeculæ of the spleen being very marked. Over and above both this relative and replacement fibrosis, there is a third form as already indicated, namely, the *perivascular* and, more particularly, the *peri-arterial.* How far this is primary, leading to the atrophy of the specific constituents of the tissue by reduced nutrition, and due to the alteration in the conditions of the circulation already noted, how far secondary to the atrophic changes already occurring in the organ, cannot be said with precision, but its intimate relationship to the vessels would seem to indicate that it is very largely primary. In any case, peri-arterial fibrosis is an important feature in senile changes.

We have, in the preceding paragraph, excepted the central nervous system from these fibrotic changes. A certain but relative slight amount of fibrosis is apt to occur in this and then in connection with the vessels. Anything like the productive fibrosis in the brain substance proper is, under all circumstances, curiously rare; the glial cells have little tendency toward such. Remembering the liability shown by newly formed connective tissue to contract and compress included structures, it is fortunate for proper cerebration that this is so. When the brain in its rigid case atrophies, not solid tissue but fluid replaces the shrunken

substance; increased cerebral fluid is poured out between the membranes and a condition is developed of *hydrops ex vacuo*.

ABIOTROPHY.

Somewhat closely allied to senile atrophy is a condition which has recently been brought into prominence and has, by Gowers, been termed *abiotrophy*. This is the condition of premature death of the tissues or portions of tissues, not as the result of any immediate irritant. Possibly this should be regarded merely as a conception and explanation of premature cell decay. Nevertheless, if but a conception, it is a valuable one, inasmuch as it appears to explain in a manner more satisfactory than any other the development of certain otherwise obscure conditions. There is a series of morbid disturbances of the nervous system in which certain cells and systems of cells and the associated tracts present degeneration, and, eventually, complete disorganization, the rest of the nervous system, apparently, showing no change. The development of these conditions is progressive. Many cases are hereditary. Nor can we find any one factor or set of factors to explain them unless we suppose that these cells have a shorter life than have the other neurons, that they exhibit a premature senility leading to precocious death. Such would seem to be a most satisfactory explanation of conditions like Thomsen's disease and other familial paraplegias. In these diseases, for a time, the mental and nervous conditions develop in a normal manner. In a few years one particular set of muscles undergoes atrophy with corresponding paralysis, and the motor centres governing these muscles show localized atrophy of their cells. Somewhat similar, it would seem, to these hereditary conditions, are the nervous disorders which may follow long years after an attack of syphilis, notably the condition of tabes or locomotor ataxia. One method of regarding these conditions is to imagine that syphilis is a disease that is never wholly cured, that, once in the system, the germs continue to grow and to produce their toxins, and that these toxins have, as it were, a cumulative affect until, at last, owing to their continued irritation, they bring about the death of certain groups of nerve cells which are more susceptible to their influence than are others. The difficulty in accepting this view is that, in such cases, we have no other sign of the continued existence of the germs of syphilis. We do not find, for example, indications of active gummata or other syphilomata. The individual is incapable of infecting others with his disease, and, judging, by macroscopic and microscopic appearances, the disease is, and has been for years, wholly arrested. It is more satisfactory to suppose that, during its active stage, there had been a certain amount of irritation and intoxication of these particular groups of cells. Or, again, it may be that there has been a general intoxication of all the nerve elements to such an extent that, although the intoxication has been recovered from temporarily, the cells have, notwithstanding, been weakened so that now,

under the normal strain, these cells, being called upon to perform no more than the normal amount of work, become easily exhausted and undergo premature dissolution. This second possibility is mentioned inasmuch as, while it is cells in connection with the lower portion of the cord controlling the lower limbs that, in general, first give out, there are cases on record of those who, leading a sedentary life, do not employ the lower limbs in walking to the normal extent, but use the arms and upper extremities actively (*e. g.*, coachmen), and, in these, the paralytic condition is apt to manifest itself first in the upper extremities. It is the nerve centres controlling the groups most commonly in use that first undergo atrophy.

A most suggestive example of what may be termed general abiotrophy, throwing light upon these more specialized abiotrophies has recently been adduced in Bardeen's studies upon the effects of *x*-rays upon frogs' spermatozoa. By subjecting the sperm to the rays for a few minutes it is found that they are still capable of fertilizing the ova; the individual life begins, but the larvæ, growing, all die prematurely, none survive beyond the second week. There is, that is, cell exhaustion after a certain early period.

REVERSIONARY METAMORPHOSIS; KATAPLASIA.

In studying the various conditions of atrophy, we cannot fail to be impressed by the fact that, in addition to mere shrinkage of the individual specific cells of a tissue, another order of changes is frequently met with which I have elsewhere spoken of as reversionary degeneration,[1] but for which, perhaps, a better term is that of kataplasia, introduced by Beneke. We find frequently, that is, that in the process of atrophy accompanying the gradual disappearance of their specific features, certain highly organized cells present appearances which simulate very closely and very curiously those presented by the developing cell. We may without hesitation say that there is a harking back or reversion to an earlier and more embryonic condition. The most striking example of this is to be seen, as Fujinami and others have pointed out, in striated muscle fibers. Such striated muscle fibers, if their development be studied, originate from cells rich in cytoplasm, known as sarcoblasts. In these, at first, no signs of striation are visible, but gradually, along one side of the cell, the striæ are seen to make their appearance, and thus, at one stage, we find cells frequently multinuclear, with undifferentiated protoplasm in the immediate neighborhood of the nuclei, and differentiated protoplasm with striation showing itself in the cell substance away from this. As the fibers become more developed, the number of nuclei diminishes; the amount of undifferentiated protoplasm becomes less and less until at last in the complete

[1] Jacobi Festschrift, 1900: 422.

fiber we have relatively rare nuclei situated in the outer aspect of the fully formed fiber.

If we examine the muscle fibers at the edge of the invading new-growth, in fibers which are undergoing compression and diminution in nutrition, we find that the very reverse processes are occurring. The first disorganization of the fibrillar structure takes place around the nuclei more particularly, so that the nuclei become surrounded by a definite area of undifferentiated cytoplasm. They multiply and, as this process continues, we find, in place of fully formed striated fibrils, large multinucleated protoplasmic masses, while, as a last stage, we have evidences that these masses may divide up, the cytoplasm accumulating around individual nuclei, so that separate cells pass off from the multinucleated masses closely resembling the individual sarcoblasts of the embryonic period. The stages here closely reproduce in reverse order those seen in the process of development. And this is far from being the only example of this process. The bile ducts and the liver cells have a common origin. The liver, for example, if we follow its development, first shows itself as a series of separate cell columns, and only as the organ becomes larger and more important does this tubular arrangement of the hepatic cells become unrecognizable, the vascular relationship of the individual liver cells becoming more prominent than the relationship toward each other, although, throughout, the bile capillaries represent the lumina of the primitive hepatic tubules. As already stated, in the development of the human liver there is a stage in which there is an absence of differentiation between the epithelium lining the bile ducts and the hepatic cells proper. When, now, as happens frequently in cirrhosis, there is progressive atrophy of the hepatic parenchyma, it is frequently possible to notice that the transition from hepatic cells to bile ducts becomes gradual. At the periphery of the lobules clusters of liver cells are to be seen separated off from each other by intervening fibrous tissue, and these cells are of an intermediate type. They are small; the nuclei also are smaller than those of the ordinary liver cells, but larger than those of the bile-duct epithelium; the amount of cytoplasm is greatly diminished; there is a want of a perfect, well-defined lumen. This well-defined lumen, we may add, is also wanting in the developing bile duct. We have, in short, a reversion to the period in which bile-duct epithelium and liver cells were undifferentiated. It is these imperfectly formed strings of cells which compose the so-called proliferated bile ducts observed in many cases of cirrhosis of the liver. Let us repeat, these are not true bile ducts, for the arrangement of the cells is not perfect.

A certain amount of confusion has originated with regard to these from a want of recognition that two separate orders of events may show themselves in the cirrhotic liver; namely, that liver may, in the main, show evidences of progressive atrophy, or, on the other hand, may exhibit compensatory hypertrophy. Undoubtedly, in the latter case, we have the reverse process occurring, namely, where the liver cells have been quite destroyed there may be a development of new liver

cells from the still persistent bile ducts. Acknowledging this, the process of formation of apparent bile ducts while there is progressive atrophy is also to be recognized.[1]

Herein, it must be admitted, is the difficulty in arriving at a conclusion regarding individual cases; it is not always easy to determine whether we deal with cells in the process of reparative development or with these kataplastic changes. In the first case here cited there can be no question; the processes seen at the periphery of a growing tumor, although similar to those described as occurring in repair (p. 570), are degenerative, not regenerative.

And other instances may be afforded, notably the cubical appearance taken on by the lining cells of the pulmonary alveoli in cases of chronic compression of the lung, or of interstitial fibrosis, reverting thus to the type of epithelium seen in the lung before birth; in cases of subacute inflammation of the kidneys, not only the epithelium of the tubules, but also that of the glomeruli may assume the embryonic cuboidal type.

Not only in inflammatory disturbances, but also in senile conditions this tendency to reversion may be detected, a matter, as already stated, of some importance in connection with the theory of neoplasia. Such kataplasia comes very close to the anaplasia which von Hansemann demands as the starting point for new-growths, and may well be a factor that has to be taken into account.

[1] The most recent study and discussion of the debated subject of regeneration *versus* degeneration of the liver cells in different conditions is by Professor Muir, Journ. of Pathol., 12: 1908: 287, where is afforded a good bibliography.

CHAPTER XXVI.

THE REGRESSIVE TISSUE CHANGES—(Continued).

THE DEGENERATIONS AND INFILTRATIONS.

While we are forced, for various reasons, to recognize the condition which we term simple atrophy, we have already said enough to show that, even in the simplest cases, we in general have to deal with more than a progressive reduction in the volume of the cell constituents. This very heaping up of what we may term by-products must, in itself, tell upon the cell and its activities. So that, be . from a histological and physiological standpoint, the cell undergoing simple atrophy eventually becomes degenerated. The attempt has been made in the past to distinguish between the two orders of events, either of which might lead to, or might accompany, regressive disturbances in the cell. On the one hand, it was thought that there could be recognized processes of pure regressive metamorphosis, the abnormal products that appear within the cell being due to the breaking down of the cytoplasm; on the other hand, that there was a process of laying up of preformed material gained from the lymph or blood. Conditions exhibiting the former process have been spoken of as degenerations proper; those showing the latter, as infiltrations. Undoubtedly we do encounter examples of what are true infiltrations. The leukocytes in the coalminer's lung, containing inc- partic'es of coal, certainly contain substances which have been obtained from outside, and which have not been acted upon by the living protoplasm of the cell. But the more we study the various regressive metamorphoses, the more is it brought home to us that uncomplicated infiltration is compa.atively rare. We are apt, for example, to speak of fatty and glycogenous infiltration—in the liver cell, for example—but if we study the physiology of these processes, we are rapidly forced to the conclusion that we have to deal with something much more complicated than mere absorption of fat or of glycogen from the blood or lymph. The cells, it is true, become infiltrated with or contain the substances in question, but the process is not that of direct absorption of the fat or glycogen in a preformed condition from body fluids. Everything points to a series of synthetic processes, the activities on the part of the cytoplasm leading to these deposits. We do not, for example, under normal conditions, detect fat as such, in the blood. On the contrary, we have evidence that, to a very large exten, it is saponified before it is absorbed by the intestinal mucosa. We may, as Heidenhain pointed out, find a few leukocytes containing fatty globules in the terminal portions of the villi aft- a meal containing

fat, but, as we pass down the villus, it seems very clear that before the villus is left, these cells dissolve up and break down, and in their place no fat is seen; it has been converted into some soluble compound. The liver cell, however, absorbs that soluble compound from the blood, and reconverts this by the activity of its ferments into fat. The same would seem to be true in connection with glycogen. On the other hand, as we shall proceed to point out more fully, in discussing the subject of fatty degeneration, when in the diseased cell there appear minute globules of fat, and the cell shows evidences of breaking down, the old idea that in these special cases we had the actual process of breaking down of the proteid framework of the cell substance, with liberation of the fatty molecules, has also to be given up, at least to a considerable extent. Recent observations point to the fact that degeneration of this nature is not the prevailing type. The evidence would seem to prove that the minute globules of fat have, in the main, been absorbed from without. We can rarely, therefore, make a clear distinction between the degenerations and the infiltrations, although for convenience we retain these terms for particular conditions. Here I shall treat these conditions together, and, in order to pass them in review in due order, I shall consider the various constituents or derivatives of the cell and cytoplasm as follows:

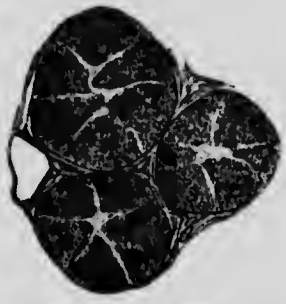
1. Albuminous degeneration.
2. Carbohydrate degenerations.
3. Fatty changes.
4. Disturbances in the amount of water within the cell substance, œdema of the cells, etc.
5. Albuminoid, or conjugated protein degenerations, *i. e.*, appearance of bodies which are compounds of protein with other substances.
6. Degenerations accompanied by the heaping up of other products of cell metabolism. Calcification. Calculus formation. Pigmental deposits.
7. Infiltration due to the taking up by the cells of materials foreign to the body—exogenous infiltrations.

CLOUDY SWELLING.

Under various conditions—in fact, this is the most common morbid change we encounter in certain tissues at autopsy—muscular tissues and certain glandular organs exhibit a condition which is now most frequently known as cloudy swelling, or albuminous degeneration. Upon making a section of the affected organs, they have a duller appearance. Instead of the healthy look of the heart muscle, for example, it appears as though, to use an oft-quoted description, the heart had been momentarily dipped in boiling water. With this there is a certain amount of swelling, best seen in the kidney, where the cortex, which is particularly affected, is on section found raised slightly above the level of the medulla, the diameter of the cortex

being at the same time somewhat increased. And, now, upon examining sections of the tissue, whether freshly cut, or after treatment with the ordinary hardening reagents, the individual cells are no longer so transparent as normal. They have a cloudy, ground-glass appearance, while, in well-developed cases, the nuclei look as though obscured by the deposit of a finely granular material in the surrounding cytoplasm, and stain more feebly than normal. These are the main features of cloudy swelling. The main chemical reactions are that, by the agency of weak acid, or weak alkali, this cloudiness can be cleared up; something is dissolved out of the cells which now becomes transparent. That something would seem to be, from its reaction, a body of a proteid or albuminous nature, unacted upon by alcohol or chloroform, but stained brown by iodine, and giving the xanthoproteic reaction.

Fig. 284



Cloudy swelling of cells of convoluted tubules of kidney. × 400. (Ribbert.)

Conditions Leading to Cloudy Swelling.—As already stated the conditions under which we find these particular changes are very many. Most commonly they are met with in cases of acute infection and high fever. They may show themselves, however, under the action of certain poisons, as, for example, in the early stages of phosphorus poisoning; following upon extensive burns, and here as early as six hours after the infliction of the burn; in cases of subjection of the individual to a high external temperature; in cases where there is no sign of febrile disturbances, or, even, as already indicated, a few pages back, in conditions of prolonged hunger, in which the irritant setting up

Fig. 285

The Altmann granules in normal cells of the convoluted tubules of the kidney. (Lubarsch.)

Fig. 286

Enlargement and irregularity of the Altmann granules in renal epithelium, with cloudy swelling (experimental inflammation of the kidney). (Lubarsch.)

the disturbance, if any, must be a direct product of metabolism, or when, on the other hand, we have to deal with the first stage in the disorganization of the cytoplasm.

Examination of the cells of the convoluted tubules of the normal kidney that has been suitably hardened after death, reveals the fact that their cytoplasm is not homogeneous, but exhibits closely set rows of minute globules or granules running across them from the basement

membrane to the lumen. These minute globules are so closely packed that they almost simulate rodlets; in Henle's tubules, indeed, employing Müller-formalin, they may be quite indistinguishable from closely packed rodlets traversing the cell, although by other modes of hardening their composite nature is revealed. These stain intensely with iron hematoxylin, and are dissolved out by weak acid. In cloudy swelling they are replaced by an irregular distribution of what are apparently similar globules, but on the whole larger, varying considerably in size. These globules are evidently of the same order as those seen in the healthy cell, but now they are swollen and disordered. With this, nuclear changes show themselves. Contrary to the usual teaching, the nuclei of the cells are not always obscured. One has but to study a series of kidneys exhibiting the naked-eye appearance of cloudy swelling to be convinced that this is not so; there may be well-marked swelling, with opaque, finely granular appearance of the cytoplasm, and with the nuclei more deeply stained and larger than usual. There appear to be three stages: the first, of increase in the chromatin of the nuclei; the second, of accumulation of the chromatin in clumps at the periphery of the nucleus, the achromatic substance being accumulated in the centre (chromatolysis), the final stage is such extensive loss of chromatin that the nucleus is almost unrecognizable, if it does not undergo karyorrhexis. The indications are those of stimulation, giving place to exhaustion of the nuclear material, with loss of chromatin.

The exact relationship of these changes to those occurring in the cytoplasm have not been determined. Lukjanow[1] is of the opinion that the development of the albuminous granules is associated with the actual giving off of "plasmosomes," or minute globular extrusions from the periphery of the nucleus, and that these undergo alteration and conversion into the cell granules; but this view still lacks confirmation, save to this extent, that fatty degeneration and cloudy swelling are very intimately connected, that in all cases of definite cloudy swelling minute fatty globules are present also in the cytoplasm (Bennario[2]); and several observers have noted the plasmasome formation in well-marked conditions of fatty degeneration.

The preliminary increase in size and staining power of the nucleus, together with the increase in the bulk of the cytoplasm, would suggest that in cloudy swelling we deal with increased absorption on the part of the cell, and that the albuminous globules are the indication of matter assimilated and not utilized. Virchow, indeed, regarded the cloudy cell as supporting his view that inflammation was, at base, a stimulus to increased nutrition. On this view cloudy swelling is an indication of increased absorption of foodstuffs with imperfect conversion and utilization of the same. It is possible that both opinions are correct up to a certain point. Cloudy swelling manifests itself in the active tissues of the body, the muscles and the main excretory glands; in the

[1] Grundzüge einer allg. Pathologie der Zelle, Leipzig, Veit, 1891.

[2] Die Lehre von der trüben Schwellung, Würzburg, 1891.

latter case, in evident connection with the removal from the blood of toxic matters. It may, indeed, be produced by overwork. Thus, Schilling[1] has demonstrated that in the rabbit, if one renal vein be ligatured, and its kidney, therefore, rendered functionless, in forty-eight hours there is developed well-marked cloudy swelling in the convoluted tubules of the second order in the other kidney. Evidently, in this case, the cells are stimulated to increased work and increased absorption by the excess of normal urinary constituents, and the cloudy swelling is a precursor of subsequent hypertrophy. The nuclear changes can only be regarded as exemplification of the fact that the nucleus takes an active, if not a controlling, part in cell function; and, further, of the principles already laid down, that increased activity within certain limits leads to increased growth, beyond those limits to increased disintegration of living matter—in this case of the nuclear chromatin.

That the cytoplasm in the ordinary cases of cloudy swelling undergoes actual growth, is at least debatable. The cells obviously increase in size, but this increase is in part due to the increase in paraplasmic deposits (the "cloudy" granules or globules), in part due to a hydropic condition, and increase in watery constituents. Cloudy swelling may, indeed, pass on imperceptibly to a vacuolar or vesicular degeneration of the cell, as may be demonstrated in intoxication with progressive amounts of cantharidin.

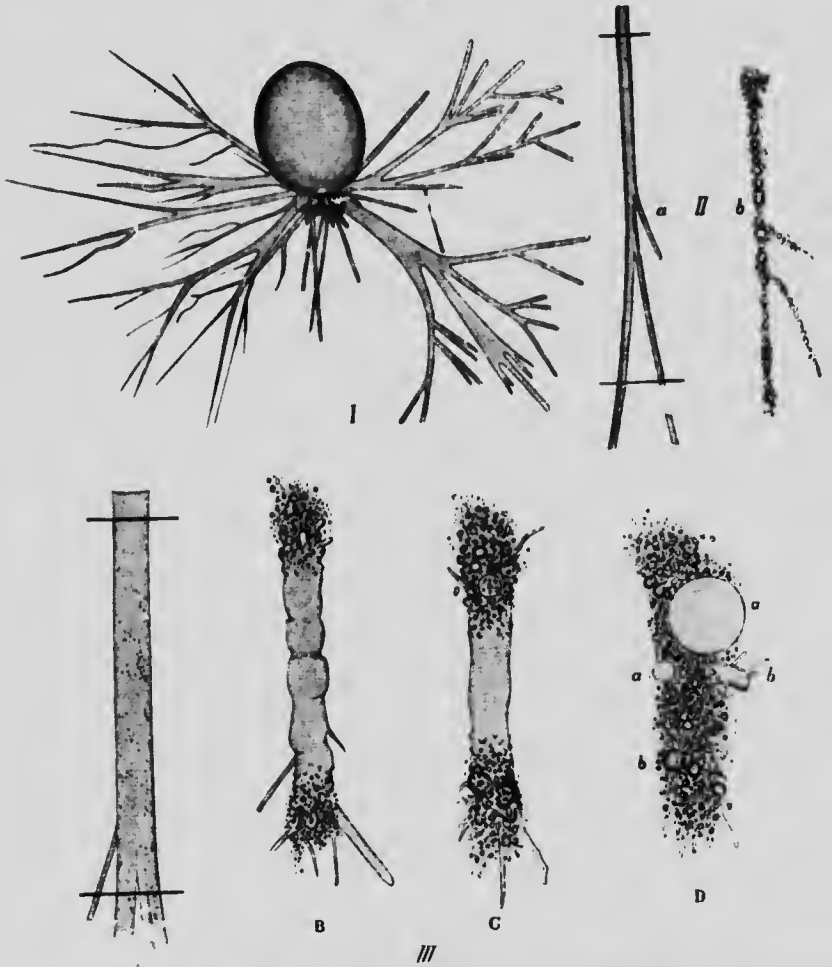
The albuminous globules, we would repeat, appear to be of the same order as the smaller paraplasmic globules seen in the normal cell. Regarding the processes of assimilation and disassimilation of living matter as largely reversible, such paraplasmic matter may be indifferently either matter absorbed and in part built up, or be matter dissociated from the cell substance proper, and in part disintegrated.

This condition of cloudy swelling must not be confused with another condition, that of *granular degeneration* to which Durante[2] more especially has called attention, or "tropfische Entmischung," as it has been termed by Albrecht.[3] The latter is a disintegrative condition of the cytoplasm itself, an indication of cell death. If, as pointed out by Landsteiner,[4] the kidney cells be taken and placed in water, they become filled with small, cloudy, packed vacuoles. The condition appears to be allied to the *granular degeneration* noted by Verworn[5] in injured infusorians. In many of these, if the unicellular organism be cut in two, from the surface of the wound inward, the previously homogeneous cytoplasm now, when exposed to the water, becomes progressively converted into an agglomeration of minute droplets. Durante and others have noted this granular disintegration in muscle cells in severe febrile conditions; it may follow upon cloudy swelling, but where, as in the latter condition, weak acetic acid, dissolving out

[1] Virchow's Arch., 135: 470.
[2] Bull. de la Soc. Anatomique, Février, 1900.
[3] Lubarsch's Ergeb., 2: 1895: 151. [4] Ziegler's Beitr., 33; 1903: 237.
[5] General Physiology. Translated by Lee, p. 236.

the droplets, brings back the striated condition of the fibers, in the former the striæ are wholly lost; we deal with a liquefactive necrosis. Similarly, Landsteiner notes that in the kidney cells above described, staining with iron hematoxylin demonstrates the presence of the finer

FIG. 287



Hyalopus (Gromia) dujardinii, granular disintegration: *I*, whole individual; numerous pseudopodia are extended from the egg-shaped membranous shell; at the left they are being drawn in; *II* and *III*, pseudopodia cut off; granular disintegration is developing; the globules and droplets of protoplasm are held together simply by a loose viscous ground substance; between them lie scattered large hyaline protoplasmic droplets and viscous globules. (Verworn.)

albuminous granules between the larger droplets of disintegrated cytoplasm. It is not improbable that imbibition of increased fluid is, as Albrecht suggests, a factor in the production of the larger albuminous droplets of cloudy swelling, as compared with the extremely fine albumin-

ous granules of the normal; but these remain clearly distinct from the vacuoles of granular disintegration.

To epitomize, cloudy swelling is the expression of overstimulation of the cell by absorbed substances leading to disordered metabolism and the heaping up of paraplasmic matter of albuminous nature. It is not in itself a necessary cause of cell death. Judging by the constant presence of the condition in deaths from febrile disorders, it is a constant accompaniment of bacterial intoxication, and as such must often be followed by return to the normal state.

Like the granular disintegration just noted, "*waxy degeneration*" of the muscle is an expression, not of reaction on the part of the living cell, but of cell death. The condition is, therefore, more appropriately considered along with the necroses (see p. 900), and this notwithstanding the fact that the albuminous constituents of the cytoplasm are in the main involved.

Fibrinous degeneration, in the strict sense, *i. e.*, the formation and deposit of fibrin in the living cell, is, if it ever occurs, very rare. Mallory[1] gives pictures of intracellular fibrin in vacuoles within the liver cells, but these cells, as he points out, are undergoing necrosis, and in general the fibrinous or fibrinoid coagulation within cells is an evidence of cell death, and so must be considered along with the necroses.

[1] Journal of Medical Research, 1: 1901: 261.

CHAPTER XXVII.

FATTY ACCUMULATIONS.

INTRACELLULAR FAT ACCUMULATIONS.

In strict succession it would be proper to discuss next the albuminoid degenerations, *i. e.*, those associated with the development of what the British and American committees upon protein nomenclature would term scleroproteins and conjugated proteins.[1] These infiltrations and degenerations are of a complex nature; or, more accurately, our knowledge as to their causation and nature is very imperfect. It will be better, therefore, to take up first the conditions associated with heaping up of the other primary foodstuffs within the cell—fats, carbohydrates—and, we may add, water.

Taking first the fatty accumulations, two conditions are to be recognized, which, for want of a better terminology, it is usual to describe, following Virchow's original distinction, as fatty infiltration and fatty degeneration. Well-marked conditions of the two are strongly contrasted; there are, however, intermediate states which it is difficult to distinguish surely; the cause of this difficulty will be evident when we come to consider the nature of the processes.

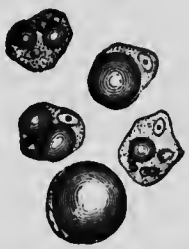
FATTY INFILTRATION.

Neutral fat is a constituent of most of the tissues of the body, but this in a state in which it is not recognizable within the cells, either by simple microscopic or by microchemical means. The kidney tissue, for example, may, by all the usual microscopic methods, by osmic acid, or by Sudan III, show not a trace of fat; nevertheless by appropriate chemical means, as much as 23 per cent. of the total solids, may be demonstrated to consist of fats. In one tissue, however—fatty tissue—the amount present is extreme, so that the cells are distended with fat in the form of large globules; so distended that the nucleus is pushed to one side, and the cell assumes a signet-ring appearance. There are certain regions of the body in which this fatty tissue is normally present, notably in the subcutaneous connective tissue, in the omentum and appendices epiploicæ, around the kidneys (suet), in the cardiac grooves, etc. We must regard the cells accumulating the fat in these regions as normal. It is when connective-tissue cells else-

[1] See Appendix A, p. 917.

where, more particularly in the interstices of tissues, become the seat of identical accumulation of, and distension with, fat, and assume the identical appearance, that we speak of the fatty infiltration of a tissue. Such may occur between the cardiac muscle fibers, between the fibers of skeletal muscles (as in pseudohypertrophic paralysis, p. 540, Fig. 171), or, again, in the pancreas. There is yet another order of cells that becomes physiologically (as during pregnancy) the seat of notable accumulations of fat, namely, the liver cell, and this also, through the accumulation, is apt to assume the signet-ring appearance. Where fat is heaped up in the liver in this manner we also speak of fatty infiltration. And the accumulation may be extraordinary: in the fatty liver of alcoholism, Perls determined that four-fifths of the total solids, and close upon 41 per cent. of the total cell substance (including water) might be fat. It must be clearly borne in mind that *in all other parts of the body* fatty infiltration involves the connective-tissue cells; *in the liver*, the connective-tissue cells are not affected, but the liver cells proper.

Fig. 288



Liver cells in various stages of fatty accumulation. × 300. (Rindfleisch.)

Such accumulation of visible, neutral fats in the *otherwise normal* cells of connective tissues and the liver occurs in a variety of conditions; these may be classified:

1. *Physiological.*—As already noted there is heaping up of fat in the liver (particularly in the more central cells of the lobules) during the latter months of pregnancy and during lactation, apparently as a preparation for the latter.

2. *Overnutrition.*—More fatty matters being taken in or elaborated than can be burnt up in the performance of function. The "aldermanic" type of individual and the overfed Strassburg goose, with its "foie gras," are the familiar examples of this form of fatty infiltration.

3. *Substitution (?).*—Fatty infiltration, and not, as vulgarly supposed, cirrhosis, is the commonest affection of the liver to be met with in those addicted to alcohol—and this notwithstanding the fact that the confirmed alcoholic is a small eater. Two explanations have been afforded for this fact: (1) that alcohol, acting on the nerve centres, or directly on the cells of the body, lowers functional activity and oxidation, and so the fat absorbed is not burnt up; (2) that alcohol is in itself a foodstuff capable of easy oxidation, and that it replaces more particularly the fats, so that these, not being oxidized, remain and accumulate in the liver cells. The more recent studies upon metabolism in animals treated with alcohol favor the latter view. Probably both factors must be regarded as operative.

4. *Diminished Oxidation:* (*a*) *Congenital.*—There are those so constituted that, despite small appetite and consumption of food, if anything, below normal, they appear inevitably to become fat; others,

on the contrary, who, with ravenous appetites, remain as lean as Pharaoh's kine.

Waldvogel[1] has thrown light upon these phenomena. Injecting a solution of β-oxybutyric acid into the chest wall of healthily lean persons, there was a slight rise of temperature, but no oxybutyric or acetic acid appeared in the urine, nor was there increased excretion of acetone; it was completely consumed. The same dose administered to obese individuals was followed by no rise of temperature, this suggesting that the oxidation is slower, while the excretion of acetone was increased the next day, and acetone could be recognized in the breath. He concluded, therefore, that the obese are unable to oxidize the fat acids reaching the intermediate metabolism with the same intensity as do healthy persons, and that the defective transformation of the fatty acids leads to accumulation of neutral fat in the cells. It is suggestive in this connection that the administration of thyroid extract, which materially accelerates the oxidative processes of the organism, materially reduces obesity.

(*b*) *Through Disease.*—It is noteworthy that in tuberculosis there is a tendency in some to become obese (this is noted more often in cattle); in others, and this is more frequent, despite general emaciation, the liver is found at autopsy in a state of well-marked fatty infiltration. The most satisfactory explanation is that of diminished oxidation—lowered vitality with lowered functional activity of the tissues, and, as a consequence, lessened burning up of the fats taken as food. Along with this we have to recognize a certain amount of transposition of fat from the normal stores in the subcutaneous and other tissues to the liver.

FATTY DEGENERATION.

In this condition we deal with what is *primarily a cell degeneration*—the deposit of fat accompanying and being the result of depressed and damaged cell activities. The cell nuclei exhibit marked indications of chromatolysis and degenerative changes; the cytoplasm becomes filled with minute, dust-like fatty globules, so that, stained with Sudan III, or Scharlach R, the whole cell body takes on diffusely the characteristic orange-reddish color, the high power demonstrating that this is due to abundant minute fatty dots.

The long-established test for the presence of fats, osmic acid, is now recognized to be imperfect. This blackens the globules of oleic acid and its compounds, but has no effect upon palmitin and stearin compounds. Among the oleic acid compounds it affects "myelin," not merely turning the myelin globules gray, as Kaiserling and Ogler point out, but eventually a deep black (apparently through the gradual dissociation of the oleic acid constituent). This is true, also, we find with lecithin (Riedel's lecithol). Sudan III, on the other hand, is taken

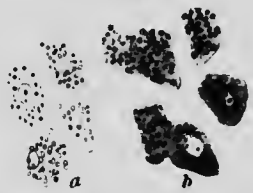
[1] Epstein Festschr., Deut. Arch. f. klin. Med., 89: 1906.

up by, and so stains all fats, and exhibits a differential stain for soaps (Fischler, confirmed by Klotz). Scharlach R has similar properties. Both are employed in weak (60 per cent.) alcoholic solutions, and the staining is due to the fact that fats dissolve these dyes more readily than does the alcoholic solvent.

The tissues especially liable to be affected are (1) those liable to exhibit cloudy swelling (gland cells, more particularly those of the liver and kidney, and muscle fibers, particularly those of the heart); (2) endothelial cells of bloodvessels; (3) certain cells undergoing normal retrogressive changes (cells of the sebaceous glands).

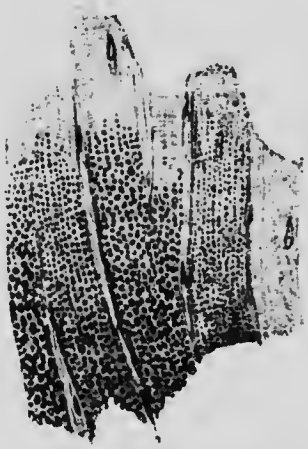
Intermediate Conditions.—The same accumulation of fat in the form of minute globules, *without* pronounced nuclear degeneration, occurs normally in two orders of cells, namely, in the cortical cells of

Fig. 289



Fatty degeneration of liver cells: *b*, fresh cells, cloudy and granular, nuclei not clear; *a*, the fine, fatty globules seen more clearly after treatment with acetic acid. (Ribbert.)

Fig 290



Fatty degeneration of heart-muscle fibers, showing different grades of involvement of the individual fibers; fresh specimen. (Ribbert.)

the adrenal, and in the hypertrophied plain muscle fibers of the uterus during the process of involution following upon parturition. Contrariwise, conditions may be noted in which, with well-marked evidence of nuclear degeneration, there accumulate in the cell large fatty globules along with small. This, in phosphorus poisoning affecting the liver. There are thus, histologically, intermediate states between well-marked fat infiltration and fatty degeneration.

Herxheimer's observations upon the thymus indicate yet another intermediate stage, which may, however, be closely allied to that seen in the uterine muscle fibers.[1]

According to Gegenbaur, the thymus continues to grow in size until the end of the second year. Herxheimer found that even before the end of the first year this organ contains fat in abundance. This is in the form of fine granules tending to coalesce, in part in the lymphocytes, which form the main constituents of this organ, and here more

[1] Verhandl. d. deutsch. pathol. Gesell., Jena, 1904: 258.

particularly at the periphery of the follicle; in part, in the connective-tissue cells of the stroma. Here it was in greatest abundance in the connective-tissue cells around the capillaries and smaller vessels. This clearly is not a degeneration proper; it attacks the cells at a period of active growth. Later the fine granules run together, and then are found the large fat cells characteristic of the thymus in its later retrogressive stage. It may here be noted that the levator palpebræ superioris, one of the most active muscles of the body, contains normally abundant fat, in the form of fine globules; here, again, we cannot deal with a degeneration. Lastly, Shattock and Dudgeon[1] have noted that in chlorotic and secondary toxemic conditions the polymorphonuclear leukocytes of the circulating blood exhibit fine fatty globules, staining with Scharlach R, without there being any sign of nuclear disturbance (although such may be present along with fatty change in pus cells). Cesaris-Demel has recorded similar observations.

Causation.—These intermediate cases we will discuss later; leaving them aside for the moment, and considering only the typical cases, as regards the condition leading up to the degeneration, two groups of cases may possibly be distinguished: (1) those in which the fatty degeneration follows upon cloudy swelling, and so may be regarded as the second stage in parenchymatous inflammation of organs, and (2) simple uncomplicated fatty degeneration—(*a*) physiological, and (*b*) pathological.

Fatty degeneration of the first order is apt to accompany all severe fevers—pyemia, septicemia, the acute exanthemata and typhoid; the cause is clearly identical, namely, bacterial intoxication. Subjection to high temperature equally produces cloudy swelling followed by fatty degeneration. As regards the second order, the physiological fatty degeneration seen in the cells of sebaceous glands, as, again, in the cells of the mammary glands during lactation, is a somewhat remarkable process. In the former case there is a constant multiplication of the gland cells proper; of the two cells, the products of an act of multiplication, the outer, which we may term the daughter cell, becomes filled with fatty globules of fair size (larger than those seen in parenchymatous inflammation), but much smaller than those of fatty infiltration, and uniformly scattered through the cytoplasm. With this the nucleus becomes paler and shows evidences of chromatolysis. Eventually the cells of this order become liberated and break down, and, as a result, a fatty emulsion fills the lumen of the gland.

In the mammary gland a parallel condition has been observed.

The nucleus of the gland cell multiplies by direct division until two or three nuclei are present in the cell. Next, the nucleus nearest to the lumen undergoes chromatolysis, and it can be observed that its chromatin passes into the surrounding protoplasm. With this there is not true cell division, but in the outer portions of the cell fine fat droplets collect, and this outer portion, containing the degenerated nucleus, is discharged

[1] Proc. Roy. Soc. B., 79: 1907: 427.

into the lumen, giving rise there to the fatty globules of the milk. Nissen[1] calls attention to this breaking down of the nucleus and disintegration of the phosphorus-containing nucleoproteid, and the characteristic presence in milk of a phosphorus-containing protein, namely, casein.

In man the chromatolysis of the nucleus in these glands is very obvious; according to Altmann[2] the process is somewhat different in the sebaceous glands of the inguinal folds of the rabbit (where they are very abundant). The process here is more of the nature of a secretion. The cells are filled with granules, which, in the centre around the nucleus, do not react with osmic acid, but show transition toward the periphery into the fatty granules, which, discharged, fuse into definite globules.

One of the most recent studies upon this subject is by Professor Arnold.[3] He admits that the first signs of fat in the cell show themselves in the immediate neighborhood of the nucleus, and regards this as an indication that the formation of milk fats is a synthetic process, in which the nucleus takes a part, also, that amitotic nuclear changes may occur during the process, but lays down very definitely that the process of fat accumulation and discharge may proceed without nuclear disintegration.

There are thus divergent views regarding the nature of milk secretion, but, evidently, the cells of the mammary gland do not absorb and excrete the droplets of fat as such; the process is much more complicated; the fat is absorbed in a soluble form, the process of converting it into neutral fat is accomplished by intracellular enzymes, and the production and activity of these enzymes is accompanied by using up and eventual disorganization of the nuclear and cytoplasmic material.

Simple pathological fatty degeneration occurs in two orders of cases: (1) In certain cases of acute non-bacterial intoxications—by arsenic, antimony, bismuth, carbon-monoxide poisoning, mineral acids, pyrogallic acid, chloroform, phloridzin, etc., and (2) in conditions of malnutrition, notably in certain anemias (pernicious anemia, advanced chlorosis, and cachexias, and the anemia following severe hemorrhages), as, again, in the later stages of starvation. With these, although, as above noted, the appearances are intermediate, must be included the pronounced fatty degeneration of phosphorus poisoning.

We do not pretend that all these intoxications produce fatty degeneration not preceded or complicated by cloudy swelling. This point has not been sufficiently studied. We are inclined to believe that study will demonstrate a preliminary or accompanying cloudy swelling in many of these cases, as occurs in starvation and in phosphorus poisoning; but this is not marked, and in certain conditions, as in chloroform poisoning, there is no evidence of cloudy change, although it is true that in the neighborhood of the nucleus non-fatty granules, the so-called plasmosomes, make an appearance.

[1] Arch. f. mikr. Anat., 26: 1886: 337.
[2] Die elementar Organismen, 1890.
[3] Ziegler's Beitr., 38: 1905: 421.

Etiology.—Fatty Infiltration.—What are the underlying causes of these two conditions of fatty infiltration and fatty degeneration? Regarding the former there can be no question as to the origin of the fat; it is storage fat, accumulated in the cells, either as the result of an intake of food material affording neutral fats over and above the capacity of the tissues to oxidize, or of oxidative capacities of the tissues below the normal, so that foodstuffs reach the stage of neutral fat, but do not forthwith pass beyond that.

But even in this case, we would repeat, the process is not that of simple taking up of already formed neutral fats from the blood and lymph. Neutral fats—glycerides of the fatty acids—do not exist as such in the fluids of the body under normal conditions; only in pathological conditions, as in diabetes and advanced alcoholism, do we encounter lipemia or an emulsion of fine fat droplets in the blood. In what form they exist there is a matter of debate, whether as simple soaps of the fatty acids, or as more complicated soluble compounds. The laying down of neutral fats in the cells necessitates, therefore, a dissociation and a subsequent combination of fatty acids and glycerin; and this, it has been demonstrated, is accomplished by the agency of intracellular enzymes—lipases. (See p. 78.) Nay, more, that the nucleus of the fat cell is concerned in the process, is indicated by the remarkable presence of a vacuole within it. We do not see vacuoles in any other normal cells of the human organism, and that the vacuole is related to the deposition of neutral fat is indicated by Shattock's[1] observation that it reacts with Sudan III, *i. e.*, is of a fatty nature.

Fatty Degeneration.—The long-accepted view was that fatty degeneration is, as the name implies, the result of a breaking down of the cell substance, with liberation of the nitrogen-containing element of its proteins, and retention of its carbon-containing moiety, and conversion of the same into fat.

Many arguments were adduced in favor of this view; the cells were seen clearly to be undergoing disorganization; in conditions favoring fatty degeneration, the N. output was found increased, the CO_2 output diminished;[2] there is actual increase in the fat in the fatty degenerated liver, even in starving animals;[3] and this fat has been regarded as formed at the expense of the carbohydrate constituents of the cell, for, in phosphorus poisoning, with increase in the fat, there is notable absence of glycogen (Stolnikow and others). There is evidence that fats are capable of development from proteins. F. Hofmann[4] demonstrated that the larvæ of the fly, *Musca vomitoria*, grown from eggs placed on ox blood containing a known quantity of fat, contained considerably more fat than was present in the control eggs and the ox blood combined. Similarly, Burdach[5] found that in the develop-

[1] Trans. Path. Soc. Lond., 54: 1903: 215.

[2] Fränkel and Geppert, Centralbl. f. med. Wissensch., 1883: 583; see also Bauer, Zeitschr. f. Biol., 7: 1871: 63.

[3] Stolnikow, DuBois-Raymond's Arch., 1887, Suppl. Bd. 1.

[4] Zeitschr. f. Biol., 8: 1872: 153

[5] Diss. Regensburg, 1853.

ment of the eggs of the snail *Limnaeus stagnalis*, the fat increases from threefold to fourfold. Pettenkofer and Voit,[1] feeding dogs on meat free from fat, determined on analysis that the C. was retained in the organism in the form of fat. Hoppe-Seyler determined that, upon keeping, the fat of milk increases, the casein diminishes. The formation of adipocere was explained by Virchow[2] along these lines, namely, of conversion of the proteins of the corpse into fats.

Much of this evidence has been discredited or put on one side as not bearing upon the case in point. It has been found, for example, by numerous observers, that, while the fat in the liver may be increased, the total fat of the body is not increased, but may be definitely diminished in cases of fatty degeneration.

This was well demonstrated by A. E. Taylor,[3] who, taking two series of frogs, one as control, the others, in which he had induced fatty degeneration, killing and desiccating them, and then extracting the total fats, found that there was an actual loss, and not a gain, of fats.

Kobert has noted that, while in the living animal phosphorus easily sets up fatty degeneration of the cardiac muscle, if the removed ("überlebendes") heart be taken and transfused with fluid containing relatively enormous doses of phosphorus, not the slightest trace of fatty degeneration is to be made out. More recent and exact studies have shown that Pettenkofer and Voit's observations are valueless, from the fact that meat, which, to the naked eye, is free from fat, contains, nevertheless, a very considerable proportion; their dogs were fed with fat. The most convincing series of experiments are those of Rosenfeld.[4] Rosenfeld demonstrated, in the first place, that if a starving animal be poisoned with phosphorus, the accumulation of fat in the (fatty degenerated) liver is accompanied by a corresponding diminution of the fat elsewhere in the organism, in the skeletal muscles, for example; and, secondly, that if a dog be poisoned with phosphorus or phloridzin, and coincidently fed with a foreign fat, such as tallow (mutton fat), in which the relative proportion of palmitic, stearic, and oleic acids are widely different from those present in dog fat, the composition of the fat obtained from its "fatty degenerated" liver approximates to that of the foreign fat. The same is true, according to Schwalbe, when it is fed with the patent fatty preparation known as iodipin, although Wells could not confirm.

It is obvious, from these experiments, that the bulk of the fat making its appearance in the liver cells in these experiments is absorbed, and is not the product of the breaking down of the cell cytoplasm, and that in fatty degeneration what we have to deal with in the main is a translation of fat in the organism from the fat cells and customary fat deposits of the organism to the liver, and, as Leick and Winckler have

[1] Liebig's Ann., 1862, Suppl. Bd. 2, 52, and 361.

[2] Würzburger Verhandl., 3: 1852.

[3] Journ. of Exp. Med., 4: 1899: 399.

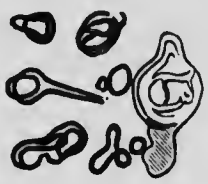
[4] Verhandl. d. deutsch. path. Gesellsch., Ergänzungsheft of the Centralbl. f. Path., 1904: 71.

shown, to the myocardium (for in the heart-muscle fibers there may be found the same accumulation of foreign fat), and Löhlein and Landsteiner and Mucha (contrary to Rosenfeld) show an increase in fat in the kidney also. The other organs of the body, with the exception of the pancreas, lose their fat. The experiments appear to be so convincing that there has been a movement to replace the terms "fatty infiltration" and "degeneration" by "physiological" and "pathological fat infiltration," respectively.

Myelinic Degeneration.—Already, however, there is a reactive movement; the matter is seen not to be so simple. We have to take into account the existence of what, to distinguish it from pathological fatty infiltration, I would term myelinic degeneration, or what Kaiserling and Ogler have termed *myelinic metamorphosis.*

Attention has been called to this more especially through the study of autolysis. If liver, kidney, or muscle tissue be removed from the organism, and placed for twenty-four hours in the incubator at 37° C.,

Fig. 291



Double contoured myelin bodies of irregular rounded shape with processes. (Perls.)

Fig. 292

Juice expressed from adrenal cortex, seen under crossed Nicol's prisms, showing isotropous, fatty globules and anistropous myelin globules (with black cross).

under strict aseptic precautions, it is found that the cells now contain abundant irregular doubly contoured globules or granules, which swell up with water, undergoing change of shape, which may be doubly refractive, and are soluble in ether and alcohol. They possess, in short, the properties of the substance or substances to which, more than fifty years ago, Virchow directed attention, and, from their resemblance to the brain-marrow and its properties, termed *myelin.* These, then, are myelin bodies.

As to the chemical nature of myelin, there has been abundant debate. Virchow was not sure that he dealt with a single substance; the elder Beneke regarded it as of the nature of cholesterin compounds; Liebreich held that the protagon which he had isolated from brain substance must be present to afford the myelin reactions. Quincke pointed out that these reactions are afforded by many substances, among them

the simple soaps. Recent observers have largely favored the hypothesis that they are of the nature of lecithin, compounds of the nitrogenous base cholin, with glycerophosphoric acid, and two atoms of fatty acid, one of which, according to Thudichum, must be oleic acid. There are those who, like F. Müller, still favor the protagon hypothesi and others, like Stoerk, who favor the cholesteryl compounds. The study made by Professor Aschoff and myself[1] of the physical properties of the myelins leads us to the conclusion that the only known substances which have the property of forming doubly refractive "fluid crystals" at room temperature (as have the myelins) are compounds of oleic acid. The indications are that several compounds are present in pathological conditions—and some physiological—which can form doubly refractive globules, and, with water, swell up into bizarre shapes —cholesteryl oleate, cholin oleate, and lecithin or its dissociation products; that, therefore, in brief, the myelin bodies of the organism are one and all lipoid bodies—allied to the soaps—in which the fatty acid essentially concerned is oleic acid.

As to the myelin developed in autolytic processes, indications all point to its being of the nature of a lecithin compound. Analysis shows that in the early stages of autolysis there is a pronounced increase in the lecithin from the liver and other organs. This may, in the liver, be as high as 15 per cent. of the solids of the liver at the end of twenty-four hours' autolysis, according to Waldvogel[2] and Dietrich. With prolonged autolysis, the lecithin undergoes marked diminution, with corresponding increase in the fatty acids, neutral fats, and cholesterin. Clearly there is dissociation of the lecithin with appearance of simpler fatty bodies and cholesterin.

Whence is derived the lecithin in these cells? A certain proportion is present in the normal cell. It is suggestive, in the first place, that a characteristic constituent of lecithin is glycerophosphoric acid; another, the nitrogenous base, cholin. Now, the one prominent protein or nitrogenous compound, or group of compounds, in the cell which contain glycerophosphoric acid is nuclein; or, more accurately, the nucleins—and these, it has been demonstrated, are associated with the nuclear chromatin or stainable material.

It is more than suggestive that, as pointed out by Albrecht and Dietrich, coincidently with the appearance of the myelin granules in the cell undergoing autolysis, there is solution and disappearance of the nuclear chromatin. In other words, a glycerophosphoric acid compound appears in the cytoplasm coincidently with the disappearance of such compound from the nucleus. It would seem, therefore, that lecithin-like bodies are primarily derived from the nucleus. Whether this occurs from simple splitting off has not yet been determined—whether, that is, the nuclear chromatin has combined in its

[1] Proc. Roy. Soc. Lond. B., 78: 1906: 359. See also Aschoff, Verhandl. deutsch. pathol. Gesellsch., 10: 1907: 166, and Adami, Harvey lectures, 2d series: 1908: 117.

[2] Münch. med. Woch., 53: 1906: 402.

molecule certain fatty acid groups, or whether, in dissociation, the nucleinic cholin and glycerophosphoric acid unite with fatty acids present in the cytoplasm, or dissociate the fatty acid from its previous state of combination in the cytoplasm. This, at least, is certain, that in the cell as a whole, as demonstrated by Hildesheim and Leathes,[1] after autolysis for three days, there may be from 10 to 40 per cent. more recoverable fat than from the fresh organ. Whether here we deal with a synthesis of fatty acid from glycogen (which undergoes diminution) or a dissociation of fatty acid from relatively firm combination with proteid matter, or both, is not determined. In favor of the latter view the observations of Gies and others indicate the existence of compounds between proteins and fatty acids, as, again, do the observations of A. E. Taylor,[2] that the "fixed" fat of parenchymatous organs—the fat, that is, unrecognizable by microchemical means—can be extracted by ether after the tissue has been digested with pepsin—a mode of liberation which suggests strongly that the protein moiety of the compound becomes dissociated.

Autolysis and cell degeneration are two very different conditions, the one occurring in the dead, the other in the still living cell. But both are disintegrative, and we have dwelt at such length upon these autolytic phenomena because, in our opinion, they are to some extent paralleled by observations upon the degenerating cell, and throw light upon the process of degeneration.

In the first place, as shown many years ago by Stolnikow,[3] and confirmed by Ziegler and Obolonski,[4] Albrecht and Schmorl, and others, in the acute fatty degeneration, such as is produced by phosphorus, study of the cells of the liver and kidney shows that, coincident with the appearance of fatty granules in the cell, there is a remarkable process of chromatolysis with discharge of "plasmosomes," or minute masses of chromatin from the surface of the nucleus into the surrounding cytoplasm. According to Stolnikow, more than half of the fat present in the phosphorus liver is in the form of lecithin.[5]

As to the cause of the disintegration of the nucleus and discharge of the chromosomes, a suggestion of Wells[6] deserves consideration, namely, that phosphorus and the other poisons already mentioned act by inhibiting or destroying the higher cell activities, and notably the production of oxidases, while not influencing the lipases or enzymes associated with the elaboration of fats from fatty acids, etc.

[1] Jour. of Physiol., 31: 1904; Proc., p. 1. [2] Jour. of Med. Research, 2: 1903: 59.

[3] DuBois-Raymond's Arch. f. Physiol., 87, Suppl. Bd. 1.

[4] Ziegler's Beitr., 2: 1887.

[5] This statement, however, must be accepted with caution; more recent observers (Kubow, Arch. f. exp. Pathol., 32: 1905: 173), showing that even in advanced fatty degeneration there is no increase in lecithin. We would suggest that if the lecithin, as it develops, becomes broken down with liberation of its fatty acid, as shown by Waldvogel, it is the first stages of experimental fatty degeneration that should be studied.

[6] Chemical Pathology, p. 341.

It is interesting to recall in this connection the cases of the co-existence of fat and myelin in the conditions of normal "fatty degeneration"—in the cortex of the adrenal (where the cells are filled with fine, fatty globules; and, as first shown by Kaiserling and Orgler,[1] doubly refracting myelin globules are also present), and in the thymus undergoing retrogressive change; as, also, the association already referred to between the fat and casein (a phosphorus-containing protein) derived from the cells of the mammary gland, and the increase in the fat of milk upon standing, and autolysis, which has been noted by several observers.

Lastly, in a very exact series of studies, Löhlein[2] has demonstrated that in the human kidney, as had previously been urged by von Hansemann, two distinct conditions are recognizable—a fatty "infiltration," in which fatty globules alone are to be detected (in the cells of the convoluted tubules and the ascending limb of Henle's tubes), and a "fatty degeneration" in which abundant doubly refractive globules, the smallest only recognizable with the immersion lens, are present, along with definitely fatty, simply refractive globules, both in the cells of the convoluted tubules and in the endothelial and other cells of the interstitial tissue. This condition was always associated with indications of cell and nuclear degeneration, and was found by him in conditions of acute and chronic inflammation (Bright's disease), and very well marked in the different stages of amyloid kidney.

Löhlein has introduced another method of recognizing the myelin: sections of tissues left sufficiently long in Müller-formalin, and cut frozen, when washed in physiological salt solution, exhibit minute, needle-like crystals, with stumpy ends and in clusters, in place of the myelin globules. Upon heating gently the crystals became reconverted into doubly refractive globules.

All these data point to the existence of a lecithin or myelinic degeneration leading to the appearance of fatty globules in the cells. Possibly this presence of fatty compounds is the explanation of the histological difference between the fine globules of the "degenerated" cell and the coarser globules of the "infiltrated."

On the other hand there is not a little to be said in favor of the presence of cholesteryl oleate and other cholesterin fatty compounds as the cause of the myelin droplets in at least certain cases of degeneration. These are favored by Stoerk[3] and Aschoff,[4] and according to Craven Moore[5] the action of formalin upon cholesteryl oleate affords the crystals noted by Löhlein. The two views are not absolutely contradictory: if lecithin be treated with sterile liver juice it affords cholesterin, fats, and fatty acid, from which cholesteryl compounds may well be developed.[6]

Wells,[7] in his recent and most valuable work on *Chemical Pathology*,

[1] Virchow's Arch., 167: 1902: 296.
[2] Virchow's Arch., 180: 1905: 1
[3] Sitz-Ber. d. Kais. Akad. d. Wiss. in Wien. Math.-Naturw. Kl., 115: 1906, Abth. 3: 1.
[4] Loc. cit.
[5] Med. Chronicle, Manchester, 47: 1907: 204.
[6] Waldvogel and Meyte, Mü[illegible] med. Woch., loc. cit.
[7] Chemical Pathology, 19[illegible] eq

would ascribe the fat in the kidney, spleen, nervous tissue, lung, in cases of fatty degeneration, to a rendering visible of the previously fixed fat already referred to. He emphasizes Rosenfeld's observation that the rendering visible of the fat in the kidney is often accompanied by an actual decrease in the amount of fat recoverable from this organ; a kidney containing 16 per cent. of fat (*i. e.*, below the normal quantity) may exhibit marked fatty degeneration, whereas another yielding 23 per cent. may show none. On the other hand he holds that fatty degeneration in the liver and heart muscles is not due to such liberation of combined fat, but to accumulation from the blood, the difference in appearance from that seen in normal infiltration being due to cytoplasmic disintegration.

We cannot believe that the process is quite so simple. As we have pointed out, we can have similar accumulation of fat in fine droplets in the adrenal—in which the cells are not undergoing disintegration—and in liver and kidney we encounter identical nuclear changes and discharge of plasmosomes. We are inclined to question, also, the probability of the fats as such, and not rather fatty acids, being in combination with cytoplasmic matter. We can only conclude that *there is a basal difference in the mode in which the fat is laid down in the cell in infiltration and degeneration, respectively.*

Lastly, we must note certain observations, so recent that their exact bearing upon the problem before us is difficult to estimate. Continuing certain observations of Leathes, Leathes and Hartley[1] show that, while the connective-tissue fats are almost entirely formed of the neutral fats of oleic, stearic, and palmitic acids, from the liver, kidney, and heart muscle of man and the higher animals, are to be obtained in fair amount by a process of saponification, members of the higher fatty acid series, fatty acids soluble in ether but insoluble in petroleum ether—acids of the linoleic and linolenic series, etc: ($C_nH_{2n} - 4O_2$, $C_nH_{2n} - 6O_2$, and possibly $C_nH_{2n} - 8O_2$). Dunham,[2] as regards the kidney, has recently demonstrated the presence of another of the higher fatty acids—carnaubic acid, $C_{24}H_{48}O_2$.

Conclusion.—To sum up and endeavor to harmonize these contradicting views, it would seem that:

1. There is a physiological process of absorption from the fluids of the body of the precursors of the neutral fats, which precursors, absorbed into the cell in a soluble state, are by the action of lipases converted into neutral fats. By reversible action of the same enzymes (p. 70) these neutral fats so formed may be redissolved and discharged from the cells. When not so discharged, the neutral fats may accumulate in large globules, and the accumulations may be so excessive as to assume pathological proportions, and be known as fatty infiltration.

2. In this process there is no indication of the intermediate formation of myelin-like bodies. That the nucleus takes part in or controls the

[1] Jour. of Physiol., 36: 1907: 17; see also Leathes, ibid., 31: 1904: 1.

[2] Proc. Soc. for Exp. Biol. and Med., 5: 1908: 58

process is suggested by the presence of fat-containing vacuoles in the nuclei of normal fat cells.

3. In many tissues fats, or fatty acids, are present in a form unrecognizable under the microscope or by microchemical tests; this would indicate that a certain proportion of fatty matter must be present in the cell in a combined state.

4. Observations upon autolysis and phosphorus poisoning indicate a process in which the appearance of fatty globules within the cell is preceded by the increased formation of lecithin and bodies of myelinic nature.

5. This myelinic degeneration is apparently a process distinct from ordinary fatty infiltration. In well-marked cases there is obvious disintegration of the nucleus, with discharge of the nuclear chromatin into the cytoplasm.

6. The fact that the nuclear chromatin contains nucleins as a main constituent, that both nucleins and lecithin contain characteristically glycerophosphoric acid, and afford cholin as a disintegration product, indicate that the lecithin, as regards these two constituents, is derived from nuclear matter.

7. The observations of Rosenfeld and others upon the translation of fats in phosphorus poisoning from the ordinary fat deposits of the body to the liver and heart muscle, are best harmonized with the above observations by regarding the glycerophosphoric acid and cholin of the lecithins as derived from nuclear material; the fatty acid constituents in these organs as, *in the main*, derived from fatty acid compounds brought to the cells from the other tissues in a soluble state, and there disintegrated; the fatty acid molecules combining with the glycerophosphoric acid and cholin to form lecithin.[1] By the disintegration of these lecithins, we must suppose, that the fatty acids, joining with glycerin, form the fine, fatty particles characteristic of fatty degeneration. In fact, even in those organs in which, during degeneration, the fat is increased, the formation of lecithin-like bodies may be brought about by combination with, and dissociation of, the fixed fats of the cytoplasm.

8. The disappearance of glycogen from the cells undergoing fatty degeneration suggests that it may be one of the sources of ultimate fat; as, indeed, it may be concerned in physiological fat formation.

[1] There are several lecithins; according to the fatty acids present, so may there be dioleolecithin, oleostearolecithin, etc.

CHAPTER XXVIII.

THE REGRESSIVE TISSUE CHANGES—(CONTINUED).

GLYCOGENOUS INFILTRATION.

THE evidence that we have concerning pathological alterations in the glycogen contents of the tissues is, at most, meagre.

We recognize that glycogen plays an important part in normal metabolism; that, through ferment action, the starches of the food are converted into sugar; that, despite a large meal of carbohydrates, starches, or sugars, there is no marked increase in the sugar of the circulating blood; that absorbed sugars are rapidly taken up from the circulation, more particularly by the liver cells and the muscles of the body; that in these organs they are stored as a less soluble modification, glycogen, or, as it has been termed, "animal starch;" that the liver may be regarded as the main storehouse and controller of the carbohydrate equilibrium of the system, the muscles as the main consumers of glycogen, muscular activity being dependent largely upon the dissociation of glycogen into carbonic acid, lactic acid, etc., carbohydrates affording by their dissociation the most easily and rapidly utilizable energy. In the liver we have evidence that points to the presence of reversible glycolytic enzymes which, under the one order of conditions, convert the soluble sugars into the less soluble glycogen; in the other, convert the glycogen into easily diffusible sugars, which pass into the blood, and so to the muscles and other tissues of the body (p. 70).

The physiology of glycogen is thus fairly well understood up to a certain point, and, histologically, if care is taken to deal with fresh material, or material which, when fresh, has been hardened in absolute alcohol, it is not difficult to differentiate and recognize the glycogen within the cells in the form of discrete vacuoles. As pointed out long ago by Claude Bernard, the discoverer of glycogen, if the tissues be kept, then through enzymic action the glycogen becomes converted into sugar, dextrine, and then it is unrecognizable microscopically.

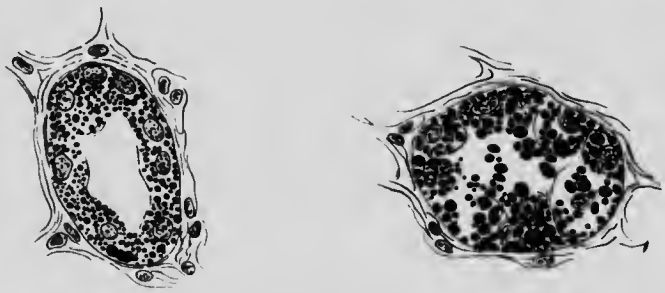
Glycogen is only relatively insoluble, forming a colloidal solution, and the fresh tissues must, therefore, not be brought into contact with water; they may be hardened in alcohol saturated with iodine and cut in iodine mucilage (Ehrlich) and mounted in iodine glycerin; or, after hardening in alcohol and passing through the ordinary procedure for cutting, may be treated with a mixture of tincture of iodine, 1 part to alcohol absolute 4 parts, and cleared with origanum oil. The glycogen by these methods is stained brownish red to claret color; unlike amyloid, it gives no reaction with sulphuric acid.

By using a special carmine stain with material prepared in celloidin, Best[1] has recently made a great advance in the ease with which glycogen can be detected in tissues.

It is in the liver that we most easily recognize glycogen histologically, and that we find the greatest variations. By chemical analysis it can be gained from both liver and muscles, as also from embryonic tissues. In these growing tissues it may be present in large amounts.

In moderate conditions of diabetes it has been found in considerable abundance in the liver cells, in severe cases it wholly disappears; but in these it has been noted in the heart muscle, and, characteristically, in the cells of the ascending loops of Henle in the kidney. What is its significance in this position has not been surely determined. In starvation and wasting diseases it disappears largely from the skeletal muscles and the liver; its absence from the former has been regarded as the explanation of the muscular weakness that accompanies these conditions; there is no store of readily convertible "fuel."

FIG. 293



Glycogen globules in cells of Henle's loops of kidney from case of diabetes mellitus; each dark intracellular globule represents a red-staining globule by Best's carmine method. (After Gierke.)

Just as glycogen is abundant in embryonic tissues, so has it been found abundant in new-growths of "embryonic" type; it may be detected in many neoplasms of a distinctly cellular and actively growing type, but more particularly in chorio-epitheliomas, myomas, endotheliomas, testicular and adrenal tumors.

Lubarsch[2] found osteomas, fibromas, hemangiomas, gliomas, and colloid cancers to contain no glycogen, and that it was rarely present in adenomas, lipomas, and lymphangiomas. The correspondence which Brault[3] thought to exist between the embryonic type of a tumor and its glycogen content is not, therefore, complete, though, on the other hand, Gierke's[4] contention that deficient oxidation is the cause of its appearance, cannot be supported.

[1] Ziegler's Beitr., 33: 1902; see also Gierke, ibid., 37: 1905: 564.
[2] Virchow's Arch., 183: 1906: 188.
[3] Jour. de Physiol. et de Path. gén., 6: 1904: 295 and 720.
[4] Ziegler's Beitr., loc. cit., gives full bibliography.

The presence of glycogen in large quantities in renal hypernephromas was regarded a few years ago, by Lubarsch, as one of the arguments in favor of the origin of these growths from adrenal tissue, for this also is apt to contain considerable glycogen; it was later determined that richness in glycogen characterizes very many cellular tumors.

Lastly, glycogen has been detected in pus cells, though here there has been some debate by Czerny and others regarding the existence of other iodine-staining globules possessing intermediate properties between glycogen and amyloid material. This view, however, has not received acceptance.

Save for a doubtful observation by Frerichs, no relationship had until recently been determined between glycogen and the cell nucleus; now Huebschmann[1] draws attention to the fact (and Rössle confirms) that in advanced cases of diabetes, while there may be no glycogen in the liver cells, certain nuclei are to be seen, sometimes in abundance, which are distended with one or several globules of glycogen. More rarely he encountered these glycogen-holding nuclei in other conditions (nutmeg liver, etc.). Glycogenous infiltration and fatty degeneration do not co-exist; although glycogen deposits, contrary to the usual teaching, have occasionally been observed in liver cells, the seat of coincident fatty infiltration.

HYDROPIC DEGENERATION.

It will be remembered that attention was called to the fact that in cloudy swelling there is a definite increase in the watery contents of the cell. What would seem to be a further stage in the same condition, and one associated with yet graver disturbances in the cell, is the appearance of definite vacuoles in the cytoplasm, containing a watery fluid, which vacuoles may attain so great a size that the cell undergoing disorganization bursts, and, with its neighbors, becomes represented by a vesicle visible to the naked eye.

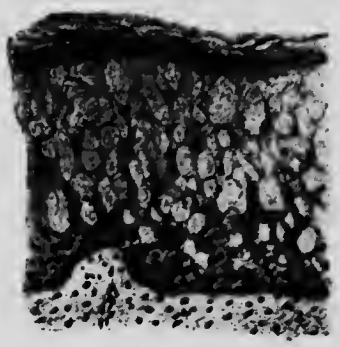
The most striking example of this hydropic degeneration is met with in the lower layers of the epidermis in cases of smallpox; the vesicular stage of the pock is essentially brought about by the acute hydropic swelling and disintegration of neighboring cells. Experimentally, a similar condition can be induced in the cells of the convoluted tubules of the kidney by the exhibition of cantharidin.

This rapid imbibition and accumulation of a fluid in a cell can, upon physical grounds, have only one explanation. The constitution of cytoplasmic matter, as also of the nucleus, is colloidal, and colloidal membranes (for such we can regard the surface layers of cells) have characteristic properties. They hinder the diffusion of crystalloid molecules to a considerable extent. Although animal cells possess no well-formed outer membrane (as do plant cells), we are led to believe that in

[1] Verhandl. d. deutsch. path. Gesellsch., 11; 1908; 35

animal cells a fine layer of similar nature acts physiologically as such a membrane. We therefore conclude that the essential cause of hydropic degeneration is some dissociation of the complex colloid material of the cytoplasm, whereby, either by cleavage or ionization, crystalloid bodies make their appearance in the cytoplasm As an illustration of conversions of this order, it may be noted that the peptones, leucin, tyrosin, etc., which are the products of the breaking down of (colloidal) proteins, are of distinctly crystalloid nature. So long as such products are present within the cell body in greater concentration than they exist in the surrounding medium, there will be a tendency to osmotic diffusion inward of watery fluid until such time as the osmotic pressure on the two sides of the membrane becomes equal. In other words, the cell swells up and becomes hydropic.

FIG. 294



Hydropic degeneration: epithelium from a smallpox papule. The epidermal cells greatly swollen, distended by large vacuoles. × 300. (Ribbert.)

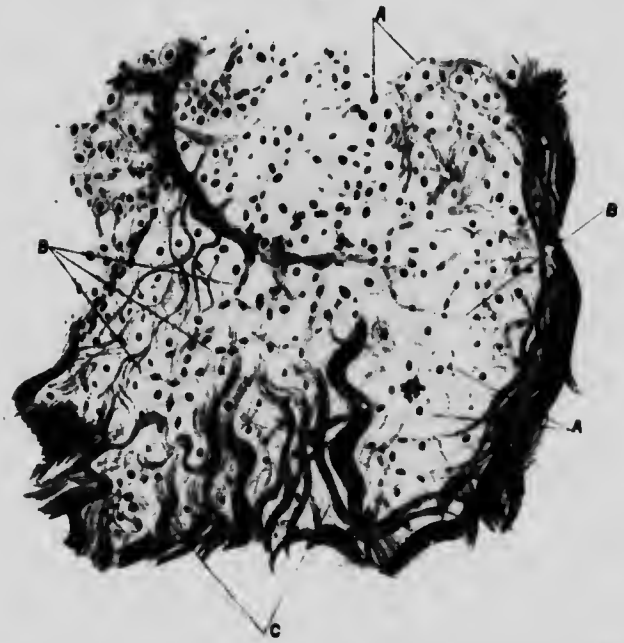
Vacuolar Degeneration.—A condition which may possibly be closely akin to the hydropic degeneration is vacuolar degeneration, in which isolated vacuoles of medium size make their appearance in sundry cells, and, it may be, actually within the nuclei. The condition has been noted more particularly in connection with the voluntary and cardiac muscle fibers, and the ganglion cells of the central nervous system. Thus, in typhoid fever, oval and spindle-like vacuoles have been observed within well-striated muscle fibers, and Nerlich and others have called attention to similar vacuoles in the ganglion cells of nerve centres in tetanus and acute infections. Hodge has shown that strong electrical stimulation brings about diminution in the size of ganglion cells, with the development of numerous vacuoles. It is suggested that in all these cases there is strong stimulation of the nerve cells, with increased dissociation of the cytoplasm, and that here, as in the case of cloudy swelling, the products of dissociation lead to osmotic absorption of increased fluid.

Serous Atrophy.—This is seen in wasting diseases affecting more particularly the epicardial and perirenal fat deposits; in place of the normal fatty tissue there appears a translucent gelatinous tissue. It is essentially, as pointed out by Flemming, a fat atrophy, with disappearance of the fat out of the cells, so that they no longer react with osmic acid and other stains for fat. The cells, however, do not wholly shrink, the place of the fat being taken by a serous fluid, which further infiltrates the extracellular tissue.

Herter[1] has reproduced the condition in the pig by prolonged fat starvation, and found that he could arrest its appearance by giving a marked excess of carbohydrates.

[1] Jour. of Exp. Med., 3: 1898: 293.

FIG. 295



Serous atrophy of fatty tissues of neck of pig after prolonged feeding with fat-free diet: *A*, fat cells which have undergone serous atrophy (contents not stained by osmic acid); *B*, capillaries; *C*, bundles of elastic fibers. (After Herter.)

Degenerations Associated with the Deposit of Compound Proteins.

There is a complicated series of degenerative conditions in which there is laid down in the tissues or spaces of the body material which, in the unstained condition, has a translucent or glassy appearance. When colorless and firm, we speak of the deposits as *hyaline;* when colorless and fluid, or semifluid, as *mucoid;* when semisolid, or solid, and of brownish, glue-like appearance, as *colloid*. There was a time when these appearances and terms were regarded as indicating the presence of specific substances, and, as a consequence, the terms hyaline, mucoid, and colloid degeneration are still employed, with, as a result, very considerable confusion. We now know that these different appearances may be brought about by a multiplicity of substances, but from the wide use of the terms it is still necessary to bring together the various conditions under the old names, distinguishing under each title the various orders of substances which may give rise to the different orders of deposit. One exception may be made, that, namely, of amyloid infiltration. This, in an unstained condition, is preëminently hyaline in appearance, but its reactions are so characteristic that for long it has been admitted as a separate entity.

MUCOID DEPOSITS.

Mucoid Degeneration and Mucinous Deposits.—Physiologically, mucin—or, more correctly, the mucins (for there is considerable variation in composition of mucinous material gained from different regions)—is laid down in the organism in two conditions: (1) as of definitely *intracellular* origin, and (2) as *intercellular* matter, without obvious secretion from cells. The type examples of the former are afforded by the mucous salivary glands, and the goblet cells of the intestinal mucosa, of the latter by the mucin of "Wharton's jelly" in the umbilical cord, and the mucinous intercellular matrix of embryonic tissues in general.

In either case we deal with material which has definite physical and chemical characteristics; it is viscid, swells up with water, is soluble in weak alkalies, is precipitated by acetic acid, not being dissolved in excess, as also by alcohol. It stains with basic dyes, more particularly with thionin.

Its composition, as above noted, varies,[1] but the true mucins have this in common, that they are composed of, and on decomposition yield, a protein and a carbohydrate, glucosamin, which reduces Fehling's solution; or, according to Levene,[2] chondroitin-sulphuric acid. They thus show some relationship to cartilage and the amyloid material, to be presently noted.

Closely allied in physical properties are the *pseudomucins*, bodies also yielding a reducing substance, and being of the nature of glycoproteins, the reducing substance, according to Leathes, being a reduced chondrosin (the carbohydrate constituent of chondroitin-sulphuric acid). Of these pseudomucins, more than one has been distinguished. They differ from the mucins proper in not being precipitated by acetic acid. We may dismiss them by saying that they are found in considerable quantities in ovarian cysts, which never contain true mucin, and that in this situation they are clearly products of excretion from the lining columnar cells.

Intracellular Mucinous Production.—The main condition in which we observe a condition of excessive production of mucin is in catarrhal conditions of mucous membranes. In these not only is there a marked increase in the number of goblet cells, and excessive discharge from these, so that the surface becomes covered by a layer of mucus, but the individual cells may degenerate, their whole substance, the nucleus included, appearing to become used up, so that we can truly speak of a mucoid or mucinogenous degeneration of the cells.

Mucus, as such, however, would not seem to be present in the cells, but a precursor, *mucinogen*, and this in the form of small globules. The histological studies upon the development of goblet cells indicate that a succession of events occurs of the same order as that described by Nissen

[1] See Cutter and Gies, Amer. Jour. of Physiol., 6: 1901: 155.

[2] Medical Record, 1900, i: 188.

for the mammary gland cells, namely, direct division of the nucleus, passage of one daughter nucleus into the outer part of the cell, when it undergoes chromatolysis and gives off plasmosomes, which, as they pass farther from the nucleus, swell up and take on the characters of mucinogen globules. When the goblet cell ruptures and discharges these globules, they swell up and fuse into a homogeneous mass of mucin. The other nucleus left behind becomes surrounded by an increasing mass of cytoplasm, and so the cell becomes restored.

An even more active, not to say excessive, development of mucous cells and production of mucin occurs in that form of carcinoma originating from mucous membranes, more particularly of the intestines, known, unfortunately, as "colloid" cancer. In this the production may be so extreme that, through pressure, if not through the actual mucoid degeneration of the cells already noted, the cells of the cancer alveoli undergo destruction, and the alveoli become represented by masses of dense, inspissated mucin. The semisolid translucent material found in these cancers is not true colloid; it gives all the reaction for mucin.

Interstitial Mucinous Infiltration.—This may be found pathologically in:

1. Senile atrophic tissues, as in the cartilage and bones (medulla) of old people.

2. In the connective tissues in experimentally induced myxœdema, and in the same areas in the early stages of the disease in man.

This mucoid nature of the swollen subcutaneous tissues gave the name to the disease, and the earlier observers regarded increased interstitial mucin as the characteristic change in cases of atrophic disease of the thyroid. Halliburton has shown that in cases of longer duration there is no increase in mucin beyond what is found in normal connective tissue These findings suggest that in the first stage of the disease the connective tissues revert to an embryonic type, and that, as the proliferated tissue cells mature, the mucin, as in the developing fœtus, undergoes diminution.

3. In actively developing tumors of the connective-tissue type, sarcomas, fibromas, etc., and in the interstitial tissue of carcinomas.

The frequency of mucoid changes in tumors is more apparent than real (see p. 662), and true myxomas are rare. Simple œdema of a tumor, by separating the connective-tissue elements, gives at first sight the appearance of interstitial mucoid without any mucin being present. Most so-called myxofibromas are œdematous fibromas.

4. In inflammatory new-growths, as in developing granulation tissue

In all these cases it will be observed that we have to deal with either active tissue growth, with immature tissue, or, on the other hand, with tissues undergoing reversion. The remarks made (p. 810) upon reversionary metamorphosis will have prepared the reader to comprehend why it is that these apparently opposed conditions present the same change.

Our knowledge of the intermediate metabolism in cells is so slight that we know nothing of the stages leading up to the formation of glycoproteins. The observations above recorded upon goblet cells indicate that the nucleus in the one series of cases controls their formation; there is no

evidence that it does this in connection with interstitial mucin, save that Hektoen records that, in advanced cases of senile atrophy of bone and cartilage, globules or masses of mucin (mucinogen) are to be recognized within the cells of the affected areas.

AMYLOID INFILTRATION.

We noted that mucin is to be regarded as a glycoprotein, a compound between protein and a nitrogenous carbohydrate. Another substance of the same order is amyloid—a hyaline deposit not found in normal tissues, though allied to the matricial matter of cartilage.[1] Into what knowledge we possess regarding its composition and mode of formation we will enter after having detailed the well-ascertained facts regarding its microchemical detection and distribution in the organism.

Amyloid material laid down in the tissues produces characteristic changes in the appearance of those tissues, and gives most characteristic reactions. The deposit may be either (*a*) *generalized*, affecting several organs, and this is the most common condition, or (*b*) *localized*, then affecting relatively small areas of tissue and inflammatory and other new-growths. The statements which follow refer in the main to the generalized form, the localized being discussed later.

Generalized Amyloid Infiltration (Amyloidosis).—This, when advanced, affects a large number of organs, but is most noticeable in the spleen, liver, and kidneys. The only tissues which, so far, have not been found affected are the epidermis and cutis, bone, lung tissue, and nervous tissue proper. If the spleen and liver be unaffected, there is little use in studying the other organs for this change.

Naked-eye Appearances.—The spleen is found distinctly enlarged, and with rounded edges, pale, and usually much firmer and denser than normal. Upon section it has a semitranslucent, waxy appearance (hence the terms waxy, bacony, and lardaceous degeneration), and either this appearance is evenly diffused (bacony spleen), or rounded bodies project from the cut surface, somewhat of the size and appearance of boiled grains of sago, embedded in the same (sago spleen). These little elevations are the affected Malpighian bodies. The liver shows a similar or more marked enlargement, is firm, with obtuse edges, and is pale and waxy upon section; the kidney also shows distinct enlargement and pallor; whether it is firm or flaccid depending upon the existence or non-existence of extensive parenchymatous disturbances.

Reaction of Amyloid Material.—In these and other organs the presence of amyloid change is most rapidly and most surely determined by the iodine reaction. On to the cut surface is poured official tincture of iodine diluted until it is the color of port wine, or Lugol's solution, or, best of all, according to Kyber,[2] iodine, gr. 10; pot. iod., 1 dram;

[1] Wells makes the useful suggestion that "chondroid" is a more appropriate and less confusing name.

[2] Virchow's Arch., 81: 1880: 278 and 420.

aq., 10 ounces. This should be left on until the surface assumes a pure yellow tint, when any amyloid material present will take on a red or brownish color. Care has to be taken to wash off previously any blood which may have exuded on to the surface. If, now, a 5 to 10 per cent. solution of sulphuric acid be poured on, the amyloid areas assume a dark-violet to black color, the non-amyloid parts remaining unaffected (Virchow). It should be noted that the sulphuric acid reaction is not absolutely constant. In general the iodine reaction is regarded as decisive.

The iodine reaction is also of use in sections, though here, by transmitted light, it is the affected parts that have a semitransparent, yellowish appearance, the rest of the section being granular and more brownish. Such sections are best mounted in glycerin, or Farrant's solution, to which some iodine has been added. With a little experience, the existence of anything beyond the slightest grades of amyloid infiltration can be detected in sections of tissue stained in the ordinary way with hematoxylin or hematoxylin and eosin. The position of the affected parts in the spleen, liver, or kidneys, and the peculiar translucency and lack of stain are most characteristic. The condition is, however, most clearly demonstrated by the differential stain afforded by watery solutions of many of the basic aniline dyes, notably gentian violet, methyl violet, and methyl green. A long series, including saffranin, might be given. To give good results, material, if not fresh, should have been kept in alcohol; or, if in Müller's fluid, this must be well washed out and the tissue kept for some time in alcohol before applying the test. To clear the groundwork, and to fix the stain more thoroughly in the amyloid areas, it is advisable to place the section for a short time in very dilute tannic, or even hydrochloric, acid, after washing out the excess of stain in water. Methyl violet sections, for example, so prepared, show the amyloid material standing out sharply as a rich rose pink against a paler, often somewhat slaty colored background.

When we come to study such preparations carefully, the seat of the amyloid change becomes evident. It is in connection more particularly with the capillaries; this is especially noticeable in the liver. Here it is the intermediate zone of the individual lobules that is at first affected. It is in connection with the capillaries of this region that the deposit occurs, and becomes so pronounced that, apparently through the pressure as well as through disturbance of nutrition, the cells lying between the thickened capillaries become atrophied.

Careful examination of suitable specimens shows that the endothelium of the capillaries is not the seat of the change—that the endothelium still remains, although its cells may undergo fatty degeneration. The amyloid material is laid down outside the endothelium, and laid down irregularly, so that one side of a capillary may have a much thicker deposit than the other. As a result of this infiltration two things happen, namely, that the capillary itself is compressed and its lumen diminished, and that the liver cells, both by pressure and by disturbance of nutrition, show evidences of fatty degeneration and atrophy, until in advanced cases, in this intermediate zone, scarcely any liver cells may be seen, and

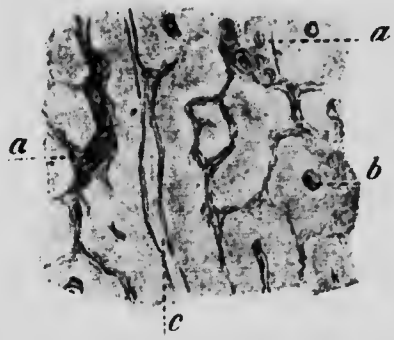
there appears to be little more than a belt of translucent amyloid material. As the process advances, the amyloid deposit trespasses more and more upon the periphery of the lobule, as also, to a slighter extent, toward the centre, until very little healthy liver tissue is left.

At the same time the process affects the branches of the hepatic artery. Here it is the middle coat that is primarily affected, and in that, apparently, not the circular muscle fibers, but the connective tissue. From here the change extends more particularly into the deeper layers of the intima. In very advanced cases the connective tissue of the walls of the veins may also show amyloid change. One note of caution is here to be given, namely, that employing the iodine reaction upon the liver, this also acts upon and causes brownish discoloration of the glycogen within the cells, so that at first sight it may be thought that there are intracellular deposits of the amyloid material. Treatment with the aniline stains, however, has no effect upon the glycogen, and demonstrates that here we are dealing with a different substance.

FIG. 296

Amyloid degeneration affecting the liver: slighter grade: the cells are still present with but moderate atrophy: the irregular deposit of amyloid around the capillaries is well marked. (After Ribbert.)

FIG. 297



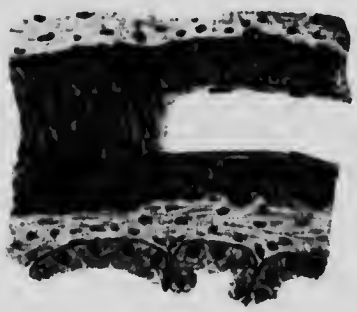
Amyloid degeneration of liver advanced: *a*, atrophied liver cells; *b*, transverse section of a capillary surrounded by a broad ring of amyloid material; *c*, a capillary cut longitudinally. (Ribbert.)

What is true of the liver is true of the other organs of the body. Amyloid substance is, in the main, laid down immediately outside the endothelium of the finer capillaries. It is liable to affect also the middle coats of the smaller arteries. Only in advanced cases is it seen affecting the walls of the veins. More frequently, as in the spleen, it may affect the connective tissue. So, too, in advanced amyloid change in the kidney, the basement membrane of the collecting tubules is seen clearly to become the seat of these deposits, though care has to be taken to distinguish between the appearances thus produced and the very similar appearances brought about in the longitudinally arranged capillaries of the medulla. We have never been able to satisfy ourselves regarding the intracellular development of amyloid material in the form of spherules, though some observers have described such deposit within

the cells. Nor can we accept Maximow's conclusion that the Altmann's granules in the liver cells play a part in the development of the amyloid material, for the amyloid deposits around the hepatic capillaries clearly continue to grow after the liver cells have undergone total atrophy.

Conditions under which Amyloidosis Shows Itself.—Amyloid deposits show themselves most characteristically in conditions characterized by prolonged suppuration and discharge from the system of proteins in one or other form. The most frequent precursor is tuberculosis of bones in the form of Pott's disease, with cold abscess formation, or of osteomyelitis of the extremities, though it frequently follows, also, intestinal and abdominal tuberculosis; in uncomplicated pulmonary tuberculosis it is relatively rare. Chronic ulcerative syphilis is at times responsible, subacute or chronic suppurative osteomyelitis with sinus formation. More rarely it has been found associated with leukemia and malarial cachexia; still more rarely, with chronic Bright's disease (albuminuria) and prolonged and excessive lactation.

FIG. 298



Amyloid degeneration of the media of a small artery of the kidney: the amyloid deposit is around the muscle fibers leading to their atrophy. (Ribbert.)

Localized Amyloid.—Apart from the generalized amyloidosis, there is encountered occasionally a restricted local amyloid deposit, with no signs of the change in the usual sites, the liver, spleen, etc. Such may be found in localized granulomatous masses, of tuberculous or syphilitic origin; it has been noted in granulation tissue of the conjunctiva, in connection with the cartilages of the larynx and upper part of the respiratory tract, and somewhat characteristically in tumors —fibromas and sarcomas—of the upper air passages. It is noticeable that in these conditions, as pointed out by Ribbert, the smaller vessels are relatively unaffected; the amyloid change affects the interstitial tissue, forming a network which, Eden suggests, follows the lymph channels. It has been noted also in the lymph glands nearest to areas of local suppurative inflammation.

The Nature of the Amyloid Matter.—The blue color gained by treating the amyloid material with iodine and sulphuric acid led Virchow to suspect some relationship between it and the vegetable products, starch and cellulose, hence the name by which it is now universally known—*amylum* starch. Needless to say, this was a mistaken deduction, and soon its protein nature was demonstrated (Friederich, Kekule). But for long the nature of this protein baffled analysis. It appeared to be related to hyaline material, and cases were reported in which there was apparently a combination of, or a transition between, hyaline and amyloid material—cases of only partial reaction with iodine and the aniline dyes. But the composition of hyaline matter was equally difficult to

determine. Others regarded it as modified fibrin. Without entering into the details of the various theories regarding its nature, it may be said that the first sure advance was made by Krakow,[1] who demonstrated clearly that it is a compound protein, a combination of a proteid (histon) with chondroitin-sulphuric acid ($C_{14}H_{27}NSO_{17}$).

Chondroitin-sulphuric acid in its turn yields chondroitin ($C_{14}H_{27}NO_{14}$), and from this can be gained chondrosin, a reducing substance, of the nature of a nitrogen-containing carbohydrate. Pure amyloid separated from nucleoproteid is an almost white powder, and, like the nucleoproteids, is resistant to digestion with pepsin, though Neuberg found it to be acted upon by trypsin. It is this resistance to peptic digestion that enables us to isolate it from the main mass of proteins.

Amyloid thus comes into the category of the glycoproteins, and, by containing chondroitin-sulphuric acid, is found to be allied in characteristic constituents to cartilage and yellow elastic tissue, both of which yield the same acid. Indeed, from the normal aorta, presumably from its elastic tissue, there can be gained a substance closely allied to amyloid. What we have said regarding the mucins will indicate that they are of an allied group. Like the one group of mucins, and the specific substance of cartilage and yellow elastic tissue, it is an extracellular deposit. How it is formed, how it comes to occupy the position in which it is found, is still a matter of debate. In the first place, it has never been found within the vessels; but the way it is deposited outside the vessels suggests a discharge from the blood. It is most reasonable to assume that one of the eventual constituents, upon diffusing out from the blood, meets with the other outside the capillary walls, and, combining, amyloid is produced. Eden suggests that in local amyloid the lymph vessels and channels play a corresponding part, the conveyance of the one constituent being by the lymph.

Yet another advance in our knowledge of amyloid during the last decade has been the determination that it can be produced experimentally in various animals. The experiments are not always successful, but more particularly in hens and rabbits repeated inoculations of sublethal doses of attenuated pyogenic organisms, or, again, of the sterile fluids of growth, or toxins of pyococci, diphtheria bacilli, etc., will, in a certain proportion, eventually produce amyloid deposits. Pease and Pearce[2] have noted its not uncommon presence in the organs of "antitoxin horses." In the hen the deposits have been found developing as early as ten days. It is in the spleen that these experimental deposits are first noticeable. Nor is it only bacteria and their products that initiate the infiltration; it is developed after inoculations of turpentine. Turpentine, it may be noted, is capable of giving rise to aseptic suppuration, and this association of pus-producing organisms and turpentine might suggest that leukocytic disturbances are factors in the process. For a time this was held by certain investigators, who called attention to the existence of globules reacting

[1] Arch. f. exp. Path. u. Pharm., 40:1897:196.

[2] Journ. of Inf. Dis., 3:1906:619. See also Lewis, Journ. of Med. Research., N. S., 10:1906:449.

with iodine in the leukocytes in cases of suppuration, suggesting that these were the intermediate stage between glycogen and amyloid. Our fuller knowledge of the chemical nature of the latter has demonstrated that there can be no such relationship, nor has investigation shown that the leukocytes play any part in the conveyance and deposit of amyloid matter.

To sum up, the indications are (1) that amyloid material is allied to, but not identical with, certain compounds of chondroitin-sulphuric acid and proteid found normally in cartilage and yellow elastic tissue; (2) that the protein constituent differs from that found in the above-mentioned tissues, but also, judging from analysis, exhibits not a little variation in amyloid obtained from different tissues and cases; (3) that presumably amyloid, as such, is not conveyed by the blood or lymph, but is the result of local interaction between a chondroitin-sulphuric acid moiety (brought by the blood or lymph?) and a modified local protein moiety.

HYALINE METAMORPHOSES.

As already noted, all clear, firm, transparent, homogeneous deposits within the tissues have been in times past grouped together under the common term hyaline. But, obviously, we deal with very different compounds. There are hyaline excretions, as, for example, the hyaline cylinders in the urine or renal tubules in certain conditions of nephritis, and hyaline thrombi, due to conglutination of blood elements. These clearly are of wholly different origin and nature, and differ from what it is now the custom to regard as hyaline proper, namely, interstitial hyaline. Such *interstitial hyaline* is encountered affecting connective tissue and the vessels, more particularly the adventitial coats of the smaller arteries, although the capillaries also may be implicated. The connective-tissue fibrillæ disappear as such, and are replaced by a transparent, homogeneous mass, in which few of the typical attenuated nuclei are to be detected. It is difficult to say whether the disappearance of the fibrillæ is due to a swelling and fusion of the individual fibrils or to the deposit between them of material of the same refractive index. There is, undoubtedly, an increase in volume, whichever way produced, for the interstitial strands of tissue between glandular elements, for instance, become broader than normal. Such hyaline metamorphosis of connective tissue is not infrequent in the framework of the thyroid, in the kidney in chronic interstitial nephritis, and in scar tissue, more particularly in the fibroid areas of so-called chronic interstitial myocarditis. It may affect also the organized fibroid deposits on serous surfaces, deposits which may attain a notable thickness and porcelain-like appearance (*hyaloserositis*). Similarly, the new connective-tissue

FIG. 299

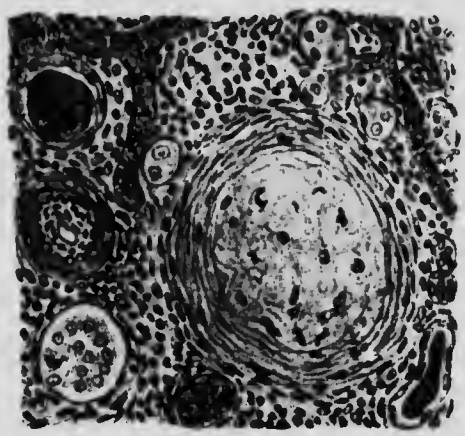
Hyaline degeneration of the membrana propria of two renal tubules, with loosening of the epithelium. (Ribbert.)

growths of tuberculous and syphilitic granulomata are liable to exhibit hyaline change. The same is at times met with in sarcomatous and endotheliomatous tumors, both stroma and cells being involved. This is most marked in the so-called cylindromas.

A region in which hyaline change is common is the ovary, namely, in old corpora lutea (corpora fibrosa). Such become represented by relatively large hyaline masses, whose wavy outline immediately suggests their origin. It is not infrequent in the tubules of the senile or diseased testis.

The hyaline in all these cases appears to be associated with tissue degeneration or malnutrition. In connection with the vessels, this association is not so clear; rather we gain the impression that we deal with deposits of an extracellular type laid down in immediate association with the vessel walls.

FIG. 300



Hyaline degeneration of a glomerulus from a kidney, showing chronic interstitial nephritis.

The outer coats of arteries are a favorite site for the change, notably in the uterus—in old multiparæ; often, though to a less extent, in the heart and kidney.

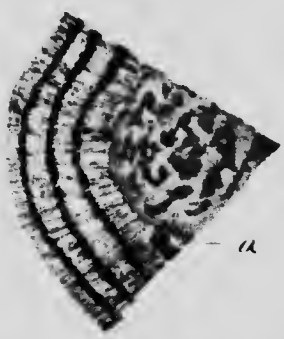
Another well-marked group of hyaline conditions is met with in connection with capillaries; either the walls of the capillaries become converted into thickened hyaline tubes, or the whole capillary becomes converted into a solid homogeneous hyaline mass. The former is encountered occasionally in the capillaries of lymph follicles, and has been noted in those of the brain and thyroid, the latter commonly in old areas of chronic interstitial nephritis; or, again, in old cicatrized infarcts of the kidney, the whole glomeruli becoming converted into homogeneous, transparent nodules. It is these latter cases that more especially recall the capillary changes seen in amyloid disease, and suggest a relationship to that condition, a view which is supported by the fact that cases have been recorded in which deposits have, in part, given the amyloid reaction, in part that of hyaline; as, again, by the observations

of more than one observer, that experimental amyloid may be preceded by a hyaline stage. Lastly, as with amyloid, we occasionally observe the membrana propria of the renal tubules involved in the change. The above description will, nevertheless, have made evident that hyaline metamorphosis tends to manifest itself locally rather than generally, as in amyloidosis; in other words, if the hyaline be allied to the amyloid change, the conditions of deposit correspond more with those determining local amyloid; that it is the result of local disturbance.

Beyond this there is little positive to be said, save that, as regards microchemical properties, both these forms of hyaline, the interstitial connective tissue and the vascular, differ from amyloid in not assuming a metachromatic stain with methyl violet and the other dyes which affect amyloid, nor do they exhibit a specific reaction with iodine. The most that can be said chemically is that such hyaline is *possibly* of glycoproteid nature.

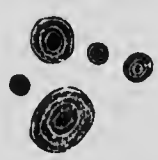
Corpora Amylacea.—Here as an intermediate group may be noted the minute concretions, often showing several concentric layers, which

Fig. 301



Section through a "corpus amylaceum" from a sternal tumor, yet more highly magnified to show the suberystalline deposit of successive layers of closely packed needles of amyloid material. At *a* the needles radiate from a small focus. (Ophüls.)

Fig. 302



Corpora amylacea from brain, to show laminated character. × 250.

may be found in the brain tissue and spinal cord of elderly individuals, in the alveoli of the lungs (most often, it has seemed to us, in the lower lobes in cases of chronic congestion) and in certain tumors. They have the general appearance of hyaline material, and may, or may not, exhibit a certain amount of metachromatism with gentian violet and other aniline dyes, suggesting thus some relationship to amyloid. The observations of Ophüls[1] show that the growth of some, at least, of these is by the successive deposit of layers of obscurely crystalline needles of matter of a protein nature.

Intracellular Hyaline.—More particularly in cancers we are apt to encounter small accumulations within the cells, either globular or of irregular shape, having the appearance and reactions of hyalin. These have been studied more especially by Pianese and Fabre-Domergue. From these studies it is evident that they differ to some extent among

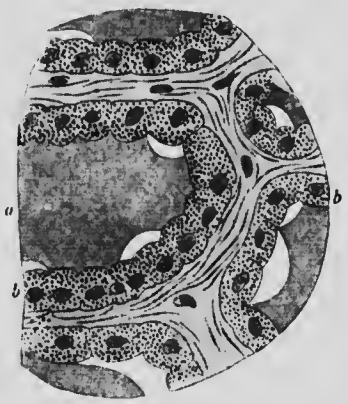
[1] Jour. of Exp. Med., 5[1900] 111.

themselves in chemical composition, for they do not uniformly take on the different stains; some take fuchsin with considerable intensity (Russel's fuchsin bodies). These may occur in chronic inflammations and in enlarged lymph glands, as well as in cancers; and, through degeneration of the cells, may come to be extracellular. Other deposits of a somewhat similar appearance in epithelial cells may be of keratinous nature. While calling attention to these, it has to be admitted that they occur so sparsely that anything of the nature of an exact chemical study of their constitution is out of the question.

COLLOID DEPOSITS.

I am inclined to restrict the use of this term to a single deposit, namely, the material accumulating in the vesicles of the normal, and, to an excessive extent, in those of the ordinary goitrous thyroid. It is more accurate to describe the so-called colloid cancer as a mucoid cancer,

FIG. 303



Section of thyroid gland, showing vesicles with contained colloid: *a*, colloid; *b*, secretory cells with granules. (After Bozzi.)

for the material forming in such cases is of the nature of inspissated mucin. Through inspissation, brownish, solid, colloidal matter may accumulate and fill ovarian cysts, as also isolated and multiple cysts of the kidney. In each case the composition differs from that of the type colloid of the thyroid. The main constituent of the latter is a compound protein, a compound of globulin with an iodine-containing body, iodothyrin, associated with which is a nucleoproteid.[1]

Allied to this, although not identical, is the colloid material of the vesicles of the anterior portion of the pituitary body, to which the researches of Saint-Remy and Benda, and more recently of Schäfer and Herring,[2] have drawn attention.

[1] See more particularly Oswald, Virchow's Arch., 169: 1902: 4 '4.

[2] Quoted by Schäfer. Herter Lectures, Baltimore, 1908 (not yet published).

CHAPTER XXIX.

CALCIFICATION AND CALCAREOUS DEPOSITS.

THERE are few tissues which may not become the seat of interstitial deposits of calcareous salts. The deposits, it is true, most frequently occur in one or other of the connective tissues; in cartilage, in the connective tissue of the vessels, in the stroma of the organs; they are relatively infrequent in the parenchyma of glands, in muscle, and in nervous tissue, but even this last may be affected, the deposits occurring within the bodies of the cells.

In general, these deposits are large enough to be visible to the naked eye as opaque, whitish masses within the affected tissues. Their density varies from a crumbling, cheesy consistency, such as we encounter in caseous tuberculous foci of some little standing, when fine, gritty particles can be detected between the fingers, to a hardness greater than that of bone, as in old calcified fibroids of the uterus.

As in bone, these deposits are composed mainly of calcium salts, but there are wide differences between calcification and ossification. There is, in the former, a want of organization; cells of the nature of bone corpuscles and osteoblasts are wholly wanting. So, too, there is wanting anything resembling an orderly deposition in relationship to the vessels and matrix of the affected area. In bone there is a ratio, constant within relatively narrow limits, between the calcium and magnesium salts and the phosphoric and carbonic acids. The analyses of calcified tissues show no such constant ratio. In calcareous plaques from advanced arteriosclerosis von Kossa could detect no magnesium salts; in experimentally produced calcification of the kidney, no carbonates, though these were clearly present in experimental calcification of the liver, and are met with in normal bone. Kossel also cites examples of calcification in the lungs in which strong acid led to no evolution of carbonic acid.

These statements are refuted by Wells,[1] who, on the contrary, calls attention to the pronounced similarity in composition between examples of calcification, studied by him, and normal bone, as regards calcareous salts. The conditions studied by him were calcified tuberculous masses in man and the ox, a calcified nodule from the thyroid, and a thrombus, the seat of calcification; these are compared with analyses by Zalesky and Carnot of human and ox bone.

[1] Jour. of Med. Research, 7: 1906: 191.

	$Mg_3(PO_4)_2$	$CaCO_3$	$Ca_3(PO_4)_2$
Calcified matter . . .	0.84 to 1.5	7.6 to 13.4	85.4 to 90.6
Normal ossification . .	1.02 to 1.75	9.2 to 12.8	83.8 to 87

The only point of any importance, according to these figures, is that in calcification in general there is apt to be a wider range of variation in the percentage amount of the different salts than in ossification. It must be admitted that Wells' material was of a restricted character, and did not involve the grosser conditions of calcified tumors and serous plates, nor the commonest of all, calcified areas in the aortic wall.

Gierke[1] has called attention to the existence of iron in minute quantities in connection with normal ossification and its frequent but not constant presence in calcified areas. While he found it in psammomas, in a calcified thyroid and a kidney, the seat of experimental calcification, it was absent in the common conditions of arterial and tuberculous calcification. Rarely, traces of calcium oxalate are encountered.

Chemical Reactions.—Treatment with acetic or mineral acid leads to the dissolution of the calcareous salts more rapidly than is the case with bone, more slowly than with pure phosphates and carbonates of calcium. When so dissolved, the extract, treated with ammonium oxalate, gives a heavy precipitate of crystals of calcium oxalate; treated with molybdic acid, a heavy deposit of phosphate. Apparently in all natural, as distinct from experimental, calcification, when of any extent, treatment with mineral acids causes an evolution of bubbles of gas—carbonic acid gas—indicating the presence of calcium carbonate. Sulphuric acid causes solution, followed by the appearance of fine crystals of calcium sulphate (gypsum). Such solution by acids leaves behind an organic matrix.

Microchemical Appearances and Reactions.—Sections examined under the microscope show the salts differing according to the grade of calcification. The earliest appearance is that of a fine dust, scattered through the affected areas; more frequently there are rather coarse, obscurely crystalline or angular particles, highly refractive. They may run together to form solid plaques and masses, or, occasionally, as in brain sand, there are evidences of growth by accretion into globular or polyhedral, somewhat crystalline masses, so as to form small concrements within the tissue. Whatever the size, the granules are insoluble in ether and in dilute caustic potash. They are slowly dissolved by formalin. With rare exceptions—to be mentioned later—upon removal of the salts, the matrix is found to be composed of dead tissue, in which the nuclei no longer stain, and cell boundaries are not to be detected.

In unstained sections, undeprived of their salts, the affected portions have a curiously opaque appearance. The simplest microchemical test

[1] Virchow's Arch., 167: 1902: 318.

is with hematoxylin, with which calcareous masses assume a deep-blue color. Upon treating sections for five minutes with pyrogallic acid (2 parts in 80) to which one part of caustic soda has been added, there is, after washing with distilled water, a decolorization of normal tissues, while the calcified parts stand out as a deep brown, becoming brownish black after the course of a few days. Yet more characteristic, according to von Kossa,[1] is the action for five minutes of a 5 per cent. solution of silver nitrate. This forms a yellow phosphate of silver, and, upon standing and exposure to the air, the salt is reduced and metallic silver precipitated, so that the smallest granules of calcareous salt within the tissues stand out prominently as coal-black dots.

FIG. 304

Section of human aorta of elderly individual, treated by von Kossa' method, to demonstrate calcification of media, and more particularly of the muscular bands. (Klotz.)

Conditions under which Calcification is Found.—It is the custom to divide cases of pathological calcification into two distinct classes of (1) calcareous metastasis, and of (2) necrotic calcification; calcification being held to take place within the living tissue in the former case, in dead tissue in the latter.

Calcareous Metastasis. — In 1855 Virchow called attention to the fact that in certain cases of extreme resorption of bone from extensive caries, from malignant growths within the bone, and (doubtfully) osteomalacia, there may be widespread deposits of calcareous salts in cartilage, in the lungs, in the mucous membrane of the stomach, in the walls of the arteries and capillaries, etc.; the presumption being that the excess of calcareous salts liberated from the destroyed bone becomes metastatically deposited in these other tissues. Such diffuse deposit is very rare. Little more than a dozen cases have been recorded in half a century.

For ourselves, we doubt the existence of this metastatic calcification; or, more correctly, would hold that its existence or non-existence depends upon what we regard as living tissue. We admit that calcareous deposits occasionally occur in tissues which still contain living cells, but those deposits occur *not in the living cells themselves, but in the inert interstitial matter between the cells;* they occur, that is, in dead material,[2] and if the calcareous matter be dissolved out by acid, it is seen that it had been contained in a swollen homogeneous matrix. Living functional cells do not take up and become the seat of deposit of calcareous salts.

[1] Ziegler's Beitr., 29: 1901: 63.

[2] See Appendix B.

There are certain possible exceptions to this statement which are still *sub judice:*

1. Schlüpfer, Virchow, Grohe, and Roth have described cases of calcareous deposit in the outer layers of the mucous membrane of the stomach, rectum, and colon. It is suggested that when there is excess in the blood there is an actual excretion of calcareous salts through the mucous membrane of the intestinal tract, and that excessive excretion is accompanied by the presence of the calcareous salts within the cells. We know of no recent studies in which the modern, more exact, microchemical methods have been employed, whereby it has been determined that the deposits occur in cells retaining nuclear stain.

2. Similarly, calcareous deposits occur in the kidney; while these must frequently show themselves in the contents of small cortical cysts, in old fibroid and hyaline glomeruli, and in the substance of retained casts, occasionally cells of the tubules can be seen containing dust-like, calcareous particles (Beer[1] and others). Most often these cells are loosened and free in the lumen, recognizable rather by their shape than by their nuclear stain; in the rare cases in which the cells remaining *in situ* show the deposits, it is probable that they are already necrosed, or at least necrobiotic. Beer, in his study of one hundred kidneys, from various conditions, demonstrates that macroscopic and microscopic calcification in the kidney is of the same type in cases of extensive disease of the bone and in non-osseous cases—indeed, is apt to be very pronounced in the latter; that such calcification is absent before the twenty-fourth year, constant after the thirty-fifth.

3. The same would seem true of the cases described by Kockel,[2] in which the cells of the capillary endothelium in the lungs have shown the deposit. Kockel shows that the so-called calcareous metastases in the lungs are of infarctous nature, due, when present, to emboli of cancer cells (in cases of malignant bone disease), etc., and identical in histological character with the deposits found in "non-osseous" cases in long-continued passive congestion. In such infarctous areas, as in lung infarcts in general, there is no complete necrosis of all the tissues, but there is lowered vitality and necrobiosis. The lime salts are not deposited in the alveolar epithelium, but in the inter-alveolar fibrous tissue, and more particularly in the elastic tissue of the arteries and in the capillary walls. It is evident from this description that the cells involved are either dead or dying.

Necrotic Calcification.—There is, then, no satisfactory evidence that the process occurring in metastatic calcification is distinct in nature from that which occurs under other pathological conditions. At most, thi is determined, that there may be calcareous infiltration, not merely of necrobiotic and necrotic tissue *en masse*, but also of certain interstitial substances. Of these, more particularly the matrix of cartilage and yellow elastic tissue appear to take up calcareous salts with some readiness. Allied with these, areas of pathological hyaline transformation

[1] Jour. of Pathol., 9: 1903: 225.

[2] Arch. f. klin. Med., 64: 1899: 332.

possess the same tendency. As already noted, such hyaline areas are largely devoid of cells; they, too, are inert. Such deposits are often associated with senile changes.

In those advanced in years there may be very extensive calcareous deposits, and, combined with this, a progressive resorption of bone, so that the individual bones are thin and very light, and their salts greatly diminished in amount. The earliest deposits occur in the cartilages of the ribs, the larynx, and the respiratory system in general, in tissues, that is, which still retain their cells and normal structure, although the deposits are not in, but between, the cells. But with this there are usually deposits in the arterial walls, deposits occurring in definitely degenerating tissue that has undergone necrobiosis. And, in addition, other deposits occur, which may be one or other order, in the interstitial tissues of the thyroid, more rarely in the testes or ovaries and other glandular organs, in the membranes of the brain, the parenchyma of the lungs, the subcutaneous tissues of the shins, etc., and in fibroid areas—scar tissue—the outcome of old inflammatory disturbances.

Many of these are clearly examples of necrotic calcification. Upon histological examination it is obvious that there has been an antecedent necrobiotic change. Examples of such, apart from senile processes, are abundant. The commonest, as already suggested, is in connection with the arteries. In arteriosclerosis (see p. 413) the condition of calcareous atheroma follows hyaline and fatty degeneration and necrobiosis of the media and hypertrophied intima. But also, as Klotz more especially has pointed out, after middle age there may be calcification of the media, not necessarily accompanied by intimal overgrowth, not visible to the naked eye, but very marked when the specific tests are employed for calcium salts. Frequently, also, there is calcification of old tuberculous foci in the lungs, lymph glands, spleen, and other organs. Here, again, calcification follows caseation, and caseation is the outcome of necrobiosis. Other inflammatory processes of the chronic type result often in calcification, notably chronic inflammation of the serosæ. More particularly where there has been chronic suppurative disturbance, with imperfect absorption and resolution, and dense fibroid adhesions are present, the central portion of such adhesions, cut off from adequate blood supply, undergo necrosis. Thus, large calcareous plaques are to be found in the pleura after old empyema. Similar plaques occur in the pericardium, associated with extensive adhesions. The process is not so common in connection with the peritoneum, though here localized areas of calcification may occur in the serosa of individual organs whose capsules have been the seat of chronic inflammation, notably in the capsule of the spleen, less frequently in that of the gall-bladder. In the chronic inflammatory group may be placed the calcification of capsules around foreign bodies, of cysts, etc.

Tumors whose blood supply has been wholly or in part cut off are liable to undergo petrifaction. That which is the commonest tumor of all—the uterine fibromyoma—frequently exhibits it. And we meet with general or localized calcification in other slow-growing and benign

tumors, in fibromas and lipomas; it has even been recorded as occurring in slow-growing scirrhous cancers. One form of tumor, the slow-growing endothelioma of the pia mater, is so apt to exhibit areas of calcification that it has come to be regarded as a special variety, the psammoma.

Organs, or portions of organs, whose blood supply has been cut off may exhibit the process. Thus, we at times encounter calcified infarcts. Individual cells undergoing necrobiosis may exhibit, as, for example, nerve cells after traumatism. According to Durante, calcification of muscle fibers is almost physiological in the herbivora. In man the same may be encountered in the neighborhood of sutures and abscesses and as the result of traumatism; here, again, the calcification, according to Schmjeninoff,[1] is preceded by necrosis. In this connection we may include the impregnation with lime salts of the dead fœtus, the result of extra-uterine gestation retained within the abdominal cavity (lithopedion). Similarly, the cysts of parasites within the tissues, hydatids, trichinæ, etc., are liable to become impregnated.

The Experimental Production of Calcification.—Before discussing the factors at work in the production of calcification, and as an aid to that discussion, it will be well to note the facts gained from experimental observations. These experiments have, it is true, been mainly upon one organ, the kidney, and the process is not, therefore, in all respects parallel with the commoner examples encountered in man, but, notwithstanding, they establish certain points very definitely.

Litten,[2] in 1881, made the first full study in this direction, and pointed out that if, in the rabbit or dog, the renal artery be ligatured for one and a half to two hours, and then the ligature be removed, at first little disturbance is to be detected; the epithelium of the tubules appears uninfluenced. But in twenty-four hours the cortex is found swollen and hyaline; the nuclei in the cells of the convoluted and some of the straight tubules no longer stain, while here and there the cells have fused into cylinders, completely filling the enclosing tube of basement membrane. Some of these cells already show irregular, highly refractile granules, soluble in acid. By the second day the necrosis, the formation of hyaline cylinders, and the deposit of granules within the cells and cylinders is most pronounced. The whole tubule becomes filled with dense granular matter; the deposit becomes more and more intense, until, by the tenth day, the organ is so hard that the razor is notched in attempting to cut it.

Here, obviously, the result of the ligature has been to induce a necrosis, or, more correctly, a necrobiosis of the tubules, and this precedes the deposit of the salts. Litten laid great weight upon the fact that not all forms of necrosis lead to calcification. With the necrosis there must be continuance of an adequate arterial supply. But herein Litten was mistaken; this is not absolutely essential. Complete ligature of all the vessels at the hilus of the kidney may be followed—slowly—by calcifi-

[1] Zeitschr. f. Heilkunde, 18; 1897.

[2] Virchow's Arch., 83; 1881; 508.

cation of the organ. But then the process is somewhat different. It occurs at the periphery, slowly progressing toward the deeper parts. The process, in fact, is of the same type as that which we encounter in the lithopedion, in calcifying caseous tubercles and uterine fibroids. But in both cases, obviously, the results are to be explained by infiltration; where the arterial supply is preserved this takes place from the arteries, and the deposits occur throughout the organ; where it is cut off the infiltration is from the lymph at the periphery of the organ.

A calcification identical in its stages with that produced by Litten had already been observed in sublimate poisoning, by Salkovsky, in 1866; Kaufmann and other observers have since noted it in subacute cases of corrosive poisoning in man, and have produced similar change in the kidney by the employment of neutral potassium chromate, and now a long series may be given of drugs leading to renal necrobiosis and calcification—aloin (Gottschalk, 1882), glycerin (Afanassiew, 1884), bismuth subnitrate (Langhans, 1885), cyanide of mercury (Virchow, 1888), phosphorus (Paltauf, 1888), acetate of lead (Prevost and Binet), copper sulphate, iodine, and iodoform (Von Kossa, 1901), formalin (Putti, 1904), copper acetate (Klotz, 1905).

Kaufmann, in his cases, noted an intense contraction of the renal artery and arterioles, with great venous engorgement; he attributes the necrobiosis to this rather than to the direct action of the sublimate upon the cells. In passing, we may note that these conditions of extensive cell death are conditions which favor autolysis. There would seem to be some relationship between the changes which occur in the cell undergoing such autolysis and the subsequent development within it of calcareous deposits.

Similar appearances are produced in the liver cells of the rabbit by the ingestion of iodoform, calcification being preceded by extensive fatty degeneration.

For all these experiments the rabbit has been found more serviceable than the dog, because its epithelium more easily undergoes necrosis; and, secondly, its blood contains a much larger proportion of calcium salts. Dried rabbits' blood contains from 1 to 2 per cent. of calcium; dried dogs' blood only 0.05 to 0.07 per cent.

We may say in passing that, experimentally, poisoning with oxalic acid (Kobert and Kensner and Neuberger) leads to abundant deposits within the kidney; but these do not stain with hematoxylin; they are deposits of calcium oxalate.

The Causation of Calcareous Deposits.—We are now in a better position to discuss the causation of these deposits.

In the first place, remembering that lime salts are constituents of practically all the tissues and fluids of the body, have we to deal simply with a local change in these salts from the soluble into the insoluble precipitated form, after the manner of Lot's wife? Certainly not. The amount of calcium phosphate and carbonate in the calcified uterine fibroid is very far in excess of the amount present in an ordinary fibroid. As von Kossa has shown, the kidney of a rabbit in which calcification

PLATE XVI

Fig. 1.

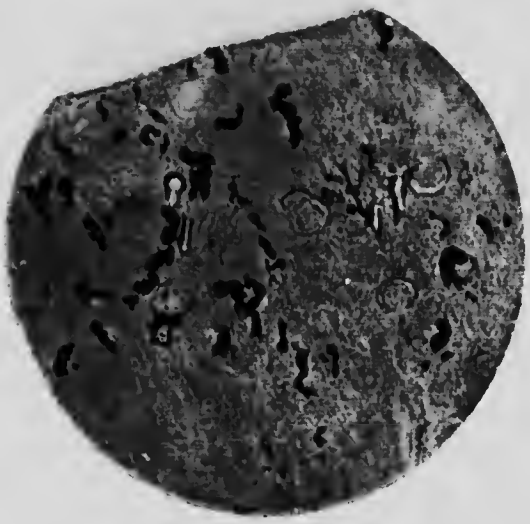


Fig 2.

Two Sections from the Same Kidney of a Rabbit Treated with Injections of Corrosive Sublimate. (Klotz.)

Fig. 1.—Section stained with Sudan III to demonstrate fatty degeneration of certain tubules.

Fig 2.—Section stained with silver nitrate to demonstrate calcareous deposits in the same groups of tubules. (By combined staining it could be shown that the identical tubules took on both the fatty and the calcareous reactions.)

has been brought about by aloin may contain three hundred times as much calcium as does the normal kidney.

Or, in the second place, have we to deal with an alteration of the blood and lymph, so that either (*a*) the actual amount of soluble calcium salts has been increased until saturation occurs, or (*b*), on the other hand, the state of the fluid is so modified that it is unable to hold the normal proportion of salts in solution? There is not a particle of evidence in support of either of these views. We never find the blood so full of calcium salts that these become deposited within the vessels or precipitated after the removal of the blood from the organism. In all cases the amount of calcareous salts in the blood is far below the point of saturation. Cases of calcareous metastasis cannot be explained upon any theory of saturation. At most, this can be said, that, as indicated by von Kossa's analyses, increase in the amount of calcium salts in the body fluids favor the precipitation in certain tissues. There is, indeed, one tissue of elective, namely, the matrix of cartilage. What stands out very prominently is that in the majority of cases a deposit of these salts occurs in dead tissue, and where, as in cartilage, the tissue is not dead, deposits do not occur within the bodies of the living cells, but in the interstitial substance, in matter which is extracellular and is of low vitality, if, indeed, it can rightly be regarded as living (see Appendix B).

We arrive, therefore, at this, that calcification occurs only in dead tissue or in the inanimate, intercellular parts of living tissue, and that it is not a precipitation of salts normally present in the affected areas.

Thus it follows that, for calcification to occur, it is necessary that lime salts be brought to the parts. This can only be through the agency of the blood, or, more exactly, of the lymph. We know that both of these fluids contain calcium salts in solution. As the lymph diffuses into the parts, chemical processes ensue, such that the contained lime salts become converted into insoluble salts, and are precipitated *in situ*. This is very evident from a study of experimental calcification.

But what is the nature of the chemical change leading to the deposit? Here we enter upon debatable ground. While we know that calcium is present in the blood and lymph, we do not know with certainty how it is there combined. The amount is so small that it may be present in the form of ions, or, as Brailsford Robertson[1] has recently shown, it may be combined with protein ions to form an ion-protein compound with some of the proteins of the lymph, resembling the compounds between calcium and casein. That is to say, it is debatable whether calcium exists in normal lymph as definite phosphate or carbonate. Analysis indicates that it cannot all be thus combined.

There are, it will be seen, two possible methods whereby the calcium and magnesium salts become deposited, which may be termed the physical and the chemical, respectively. By the former, the salts are to be regarded as deposited without direct chemical interaction with the matrix, the conditions in that matrix being such as to favor the inter-

[1] Jour. of Biol. Chem., 2: 1907: 317.

action between the components of the salts, so that they join into insoluble forms. Several theories have been advanced along these lines, but none has proved satisfactory.

Thus, Askanazy, to explain calcification in the stomach mucosa and the kidneys, has urged that the deposits occur in parts which secrete an acid fluid, and so are rendered increasingly alkaline; but there are other areas, like the rectum and colon, secreting an alkaline fluid, and, nevertheless, calcification has been recorded in them. Chabrié has suggested that in necrotic areas the CO_2 becomes fixed, and, with its removal from solution, the calcium phosphate and carbonate become precipitated. Irvine and Woodhead, on the contrary, suggest that nascent CO_2 plays the main role, pointing out that in the presence of free CO_2 a solution of carbonate of lime and phosphate of soda yields a precipitate of phosphate of lime. Others, again, have called attention to the special affinity between colloids and crystalline substances, and more particularly the liability for the latter to undergo abnormal crystallization in the former. Certainly, as pointed out by Wells, dead cartilage placed within the tissues becomes rapidly impregnated with calcium salts. This, however, does not explain why functional cartilage remains for long years in the organism continually percolated with lymph without a sign of calcification. Some chemical change must take place in senile cartilage favoring this precipitation.

The evidence in favor of such physical deposit of the salts is thus singularly unsatisfactory. Is there any evidence in favor of deposition through chemical activities in the affected areas, of junction between products of tissue degeneration and the calcium and magnesium brought by the lymph? Here various possibilities may be suggested: (1) that the disintegration of the necrotic tissue supplies the phosphoric and carbonic acid which combine with the calcium and magnesium brought by the blood; (2) that the simpler products of disintegration of the protein substances present combine with the calcium and magnesium, there being formed calcium-protein compounds in the first place, the proteid moiety acting as a weak acid, being subsequently replaced by the stronger phosphine or carbonic acid; or (3) that the fatty acids which make their appearance in degenerating areas play a similar part.

It is along these lines of testing those various possibilities that the most active work is being engaged in at the present time. The first may be dismissed; the amount of phosphoric acid accumulating in, for example, a densely calcified uterine fibroid is far in excess of what could be supplied by the decomposition of the nucleoproteids previously present. The phosphoric and carbonic acids must in the main be conveyed to the part by the lymph.

As regards the second possibility, this cannot be neglected. The affinity of dead cartilage for calcium salts may well indicate an active process of association between the two; the fact, also, that the dissolution of calcareous deposits by acid always reveals a hyaline matrix is at least suggestive, although it does not necessarily imply that the salts have been in direct chemical union with the matrix; they may merely have been adsorbed. Until we know more concerning the compounds between

calcium and protein, or the disintegration products of protein, and have isolated such compounds from areas of calcification, this must remain but an hypothesis.

Theory of Calcium Soap Formation. The third possibility, suggested sporadically by occasional workers during the last fifty years (Weber, Wagner, Diakonow), had received little attention or acceptance until the investigations of Dr. Klotz in our laboratory at McGill brought it prominently to the fore; so that at the present time it may be said to afford the most promising theory so far advanced.

Many years ago Virchow demonstrated the presence of calcareous soaps in a lipoma; more recently, Jaeckle[1] has analyzed a calcifying lipoma in which 29.5 per cent. of the calcium was present in the form of soap. Klotz[2] showed that if celloidin capsules, filled with fat or fatty acid, be inserted into the peritoneal cavity of a rabbit, in the course of a few days these are found to contain amounts of calcium far in excess of that present in the body fluids of the animal. In other words, the calcium, percolating into the sac, becomes fixed. As already noted, calcification occurs, in the main, in areas of necrotic disintegration. By the improved microchemical methods for the detection of fats and calcium salts in the tissues, Klotz was enabled to show that in the atheromatous aorta, the most frequent seat of calcification, as also in calcifying tumors and calcareous plaques of the pleura, and in the experimentally induced calcification of the rabbit's kidney, the process of calcification was in all cases observed to be associated with fatty degeneration. The oldest and densest parts of the deposit did not show this; it was present at the peripheral zone, where the process of deposition was more recent, and here cell bodies could be detected which gave both the fat and the calcium salt reaction. What is more, in this, confirming Fischler, he called attention to the fact that fats and soaps take on a differential stain with Sudan III, globules of the latter assuming a yellower tint. In this way he demonstrated that soaps are present in recognizable amounts in areas of progressing calcification. By Fischler's methods fatty acids and their salts are also to be demonstrated in the areas of calcification. He concluded that the stages in pathological calcification are:

1. Fatty degeneration, with liberation of fatty acids.

2. Combination of these with calcium to form compound calcium soaps.

3. Interaction between the soaps and the phosphates and carbonates brought by the lymph, resulting in the replacement of the weaker fatty acid by phosphoric and carbonic acids and deposit of insoluble calcium phosphate and carbonate in the dead tissues.

His observations led him to regard the soaps thus formed not as simple soaps, but as compounds of fatty acid, calcium, and some protein or product of proteid disintegration. The weak point in the investigation is that Klotz did not determine quantitatively the amount of calcium soap obtainable in his cases; qualitatively such were clearly present, although, obviously, in small amounts. Both Wells and

[1] Zeitschr. f. Physiol. Chem., 36: 1902: 53. [2] Jour. of Exp. Med., 7: 1905: 661.

Baklauf have called attention to the fact that the quantity present is very small; according to Baldauf,[1] it is in general non-existent; but the latter's methods are open to criticism, and Wells[2] would appear only to have studied advanced conditions—not advancing. If the fatty acid play the part of an intermediary body, bringing together successive molecules of calcium and phosphate, a very minute quantity of calcium soap might be present at any one moment. So, also, was Klotz unable to indicate more than vaguely the nature of his presumed compound soap. From our own studies on the myelins, and their relationship to autolysis and tissue degeneration, we are prepared to find that these play an important part in the process. Although the possibility cannot be overlooked that the fatty degeneration and the calcareous deposit may be independent processes, their relationship, as indicated in Dr. Klotz's sections, is so striking that it is difficult to regard it as merely a coincidence. Here, in short, is the simplest and the most satisfactory explanations of the mode of development of calcareous deposits.

CONCREMENTS.

In addition to this deposit of calcareous salts within the tissues, there may be a deposit of the same in the ducts and passages of the body, leading to the formation of solid masses, either round or oval, or assuming the shape of the duct in which they are found. These we term *concrements*, in contradistinction to *calculi*, the latter term being applied to solid accumulations appearing also in ducts and passages, but due to the abnormal precipitation of the *products of glandular excretion*.

The distinction is very far from being complete, for, as may be readily understood, the abnormal conditions which lead to the deposit of calcareous salts in inspissated mucinous matter within a duct may well induce also a precipitation of constituents of the secretion contained within a duct, and the mass be of very mixed composition. The terms, in short, are applied vaguely, and some would regard them as interchangeable, though even these are accustomed to use the term calculus for the agglomerated deposits occurring in the large excretory passages, hepatic, urinary, and pancreatic, and concrement for those containing large amounts of calcium salts occurring in less usual sites. For the sake of convenience only, and as a means of distinguishing what we regard as two orders of pathological processes, we shall employ the distinction noted in the above paragraph, not pretending that it is etymologically correct or wholly adequate.

The concrement, therefore, we regard as a firm and solid mass forming in one of the passages of the body, which, on analysis, furnishes a notable amount of calcareous salts, in addition to varying amounts of other constituents, these calcareous salts being greatly in excess of the quantities usually present in the fluids discharged along the affected passages. On

[1] Journ. of Med. Research, N. S., 10: 1906: 355.
[2] Ibid., 9: 1906: 491 and 12: 1907: 11.

dissolving out the salts, there is constantly left a matrix of proteid or mucinous type, and in general there is an admixture of fatty acids, soaps, cholesterin, and products of proteolysis.

This composition and the clinical history of these cases, in which the development of the concrements can be followed, affords a clue to the mode of their development. We deal, that is, in general, with the results of a catarrhal process—an inflammation—whereby, in the first place, there is exuded into the passage a mucinous discharge, together with exfoliated cells. The disintegration of the latter affords the products of proteolysis and the fatty matters, and in such a matrix, just as in necrotic areas within the tissues, there next occurs a deposit of calcareous salts, through diffusion into the mass of serum of the inflammatory exudate, as, again, of the secretion normal to the passage. Of concretions of this order. the following may be noted:

Rhinoliths are concretions occurring in the nasal passages, most often as the result of chronic ozena and obstruction. Berlioz,[1] as the result of an analysis of four specimens, obtained on the average 17.2 per cent. of organic matter; calcium phosphate, 57.9; calcium carbonate, 13.6; magnesium sulphate, 5.5 per cent.

Tonsillar Concretions forming in the crypts of the tonsil as the result of chronic obstructive inflammation have like characters.

Salivary Concrements.—Formed in one or other of the salivary ducts. The analysis of various specimens has given very varying results—from as high as 83 per cent. of calcium phosphate to as low as 15—the amount of organic matter being correspondingly varied.

Other concrements of the same order are *lacrimal* concrements: *cutaneous* concrements (the latter often multiple, and formed, it would seem, in obstructed and dilated sebaceous glands); *preputial* concrements (found in conditions of phimosis with the accumulated smegma as base); in these there is an admixture of relative large amounts of calcium phosphate with urinary salts, notably the ammonia-magnesium phosphate precipitated by ammoniacal fermentation of the urine; and *appendicular* concrements.

Appendicular Concrements.—The commonest accumulation in the appendix is of semisolid fecal matter with abundant organic and relatively small proportions of calcareous salts. Rarely, large solid concrements are encountered in an obstructed appendix, having abundant calcareous salts.

Intestinal Sand.—With these may be mentioned the true "sable intestinale," small, brownish concretions (from staining with fecal pigment) showing abundant organic matter, but also abundant calcium phosphate, and in some cases abundant magnesium phosphate.[2] These deposits are comparatively rare and small in man, but in cattle huge concretions may form in the lower bowel around retained vegetable foodstuffs; around such a nucleus there may be deposited a thick, solid layer of calcareous salts.

[1] Jour. de Phar. et Chem., 23; 1891; 497

[2] Vide Duckworth and Garrod, Lancet, 1; 1902; 653.

Pancreatic Concrements and Calculi.—Occasionally, concretions form in the pancreatic duct, leading to cyst formation (ranula). The commonest form is the true concrement with matrix of organic matter and mixed cholesterin, and preponderance of phosphates and carbonate of calcium. But here, again, the percentage of the salts exhibits great variations. We would suggest that here, as in the appendix, the age of the concretion is a factor determining variation. A recent catarrhal deposit may show abundant products of cell disintegration, proteins, fatty acids, soaps, cholesterin, etc.; one of long duration, disappearance of fatty acids and soaps, and with preponderance of calcium and magnesium salts.

Phleboliths.—In this category are to be included phleboliths, small oval stones formed occasionally in veins. Their commonest site is in the prostatic plexus in man, the uterine plexus in woman. Every transition may be found, from a recent thrombus in one of the anastomosing branches of such a plexus to extremely dense, pearl-like bodies. We deal, obviously, with the gradual deposition of lime salts in isolated thrombi which have not undergone organization, so that the masses lie free in the lumen of a vein.

We have not seen discussed the conditions under which a thrombus undergoes this characteristic metamorphosis. The necessary factors would seem to be: (1) small size of thrombus; (2) bland, non-infected nature; (3) development in a communicating vein, the thrombosis affecting but one of the series of alternative channels, and leading thus to no secondary disturbance in the nutrition of an area. Under these conditions it would seem that the thrombus undergoes a certain amount of contraction within its bed; some absorption takes place at either extremity, but before this process can be complete there has been an impregnation of its substance by the blood plasma and precipitation within it of calcareous salts, arresting further dissolution. Processes of heterolysis (see p. 339), due to the disintegration of the contained and infiltrating leukocytes, may also be involved to liberate in the thrombus those bodies which fix the calcareous salts.

Calcareous Incrustations.—Deposits upon surfaces may undergo similar impregnation with calcareous salts derived from the body fluids and secretions. The commonest example is *tartar* of the teeth, in which mucinous epithelial debris and foodstuffs form the matrix; in catarrh of the bladder and ammoniacal cystitis a deposit of mixed phosphates not infrequently forms an incrustation upon the vesical mucosa. Incrustations may also form on the surface of foreign bodies gaining entrance into the tissues and cavities of the organism.

Other Concretions.—Concretions not included in the above list, and strictly neither concretions nor calculi, may be briefly alluded to:

Intestinal Concretions.—Besides those already described, showing deposits of calcareous salts, cases are on record of resinous gastric concrements. In certain of the herbivora these are derived from the food eaten—and such form the true oriental *bezoars*, to which, in the East, marvellous healing and preventive properties are still attributed. These

hezoars are said to be obtained from the wild goat. In man there are rare examples of the formation of similar concretions in painters and others, who have taken to drinking spirit varnish for the alcohol therein contained.

In animals also, notably cattle, sheep, and pigs, hair balls (ægagropiles) are not uncommon in the stomach and intestines, derived from licking their own coats and that of their fellows. These form felted masses, which may assume a large size. More rarely, the habit of hair eating is acquired by the human female, and the hair balls growing during the course of months and years may form a cast completely filling the stomach. Our collection at McGill contains two examples. Keenan has collected some thirty cases from the literature. Scotch

FIG. 305

Hair ball of the stomach. The hair forms a complete cast of the stomach and duodenum. (Case of Dr. James Bell, Royal Victoria Hospital, Montreal.)

museums contain examples of oat-hair balls—smaller, finely felted masses, composed in the main of the minute hair-like processes derived from the outer scales of the oat in improperly prepared oatmeal. These are largely absent from modern properly milled oatmeal; but, recalling Johnson's dictum concerning that article of diet, it has to be noted that these oat-hair balls are still to be met with in horses, more particularly those fed on sweepings of flour-mills.

Fatty Concretions.—Besides those mentioned as rarely encountered in the urinary tract (urostealiths), similar soapy masses are occasionally passed in the stools of those consuming large quantities of fat or oil, where they may, at first sight, be mistaken for gallstones. Another familiar example is the accumulation of cerumen which may form in the outer auditory meatus.

CHAPTER XXX.

CALCULI.

Of the calculi proper, as I would term them, the excretions that are produced by precipitates of normal secretions, there stand out two prominent groups: the urinary and biliary calculi. With these must be included one minor form of a different order, the prostatic calculi. This last we may consider first.

PROSTATIC CALCULI.

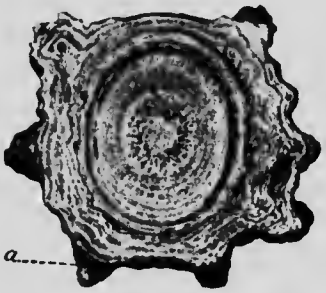
Section through the prostate glands of most men beyond middle age reveals the presence of little dark-colored granules here and there throughout the substance of the organ. Examination of sections shows that these are situated within the lumina of the glands. They are sufficiently soft to be cut with the knife (in paraffin sections), are hyaline in appearance, rounded or polygonal, and exhibit concentric structure. Rarely do they exceed the size of millet seeds. They exhibit imperfectly the reactions of amyloid matter—they may or may not give the iodine reaction, and may or may not take on a metachromatic stain with methyl violet; like amyloid, they are thoroughly resistant to acids and alkalies. They resemble in many respects the corpora amylacea already noted (p. 848), but should perhaps be classed apart as occurring in a normal secretion. Rarely, larger concrements are encountered in the prostate, in which successive layers of calcareous salts have become deposited around a nucleus formed of one of these "amyloid" bodies.

URINARY CALCULI, LITHIASIS.

Normally, the urine contains several salts in solution; abnormally, it may contain yet others, and under certain conditions members of either group may be precipitated in the course of the urinary tract and be deposited, layer upon layer, so as to form urinary calculi. We have to consider not merely what are the different forms of urinary calculi, but what are the conditions favoring their formation. It cannot be said that we have a full knowledge concerning these, but something has been gleaned, more particularly as bearing upon the three more common classes, the uratic (including uric acid and the urates), the calcium oxalate, and the phosphatic. These we will discuss in a little detail, treating the less common forms more briefly.

To prevent repetition, certain features common to all calculi may here be mentioned; and first, it must be pointed out that the calculus is of relatively slow formation, and that it grows by accretion upon the surface. There is a *nucleus* of mucus, cell debris, or foreign matter, such as blood clot, or some body actively introduced into the urinary tract, and in and upon this the salts become deposited. The presence and nature of this nucleus can often be determined by careful observation. As in ordinary crystallization, so here, salts present in solution must have some solid or semisolid as a base upon which to separate out from

FIG. 306



Uric acid followed by oxalate.

FIG. 307

Oxalate, exterior.

FIG. 308

Ammonium urate followed by oxalate and eventually by mixed phosphates. (These three figures from the catalogue of the Royal College of Surgeons.)

solution. The rate of separation and deposition must depend primarily upon the relative amount of salts present in solution, and as the urine varies both as regards amount of contained water and portion of various salts in solution, so the rate of deposition necessarily varies. Periods of relatively abundant deposit alternate with periods of arrest. As a consequence, most vesical calculi are, on examination, seen to be formed of *concentric laminæ*. Not only is this the case, but in a fluid of such varying composition as is the urine, now one, now another salt may be present in relative excess, so that at one period conditions may favor the deposit of one particular salt or combination of salts; at another, the

deposit of other constituents of the urine. As a matter of fact, it is the exception and not the rule to have vesical calculi composed throughout of one constituent. There may be alternate layers of uric acid and calcium oxalate, or often of urates and phosphates. It is very common to have an outer coat of phosphates, this latter deposit being due to the irritation caused by the growing stone having eventually favored the development of infection in the urinary tract, with bacterial fermentation and production of alkaline urine.

But the mere presence of excess of one particular salt is not the only factor. If, by suitable reagents, the salts of one or other order in the urinary calculus be dissolved out, there is left behind a *matrix* of organic matter, of homogeneous, gelatinous, or colloid type, more or less pigmented or yellowish. What is more, if, after the methods of the geologist, calculi be rubbed down until fine sections are obtained, it is seen that, as a rule, they are not formed of well-made typical crystals of one or other order. The nearest approach to such perfect crystalline form would seem to be in cystin calculi; calcium oxalate and uric acid are present most frequently in spheres and dumb-bell shapes. It is worthy of remark that in bone, egg-shell, and other normal deposits of salts, examination shows that these also, in general, are not deposited in a crystalline form. Attention was called to this fact by George Rainey, in 1857, and he formulated a theory of molecular coalescence to account for the peculiar method of deposit of salts in organic material. In 1873 Vandyke Carter[1] applied Rainey's observations to calculus formation. He explained the development of urinary calculi as due to the production in certain states, either in the renal pelvis, the ureter, bladder, or urethra, of a mucous secretion; a colloidal matrix was thus afforded in which the salts were precipitated in an imperfectly crystalline, rounded, or amorphous form. In this way was produced, according to him, the most common type of nucleus, and most often this contained oxalate of lime and uric acid or urates. Once the nucleus is formed, other layers of mucoid material are successively deposited, and in these there occurs a like process of decomposition, the stone in this way gradually growing.

Ord,[2] in 1879, confirmed and advanced these observations by his studies upon change in the form of uric acid and various salts precipitated from saturated solution in albuminous and sugary media. To Ebstein[3] is usually but wrongly given the credit for these observations.

Now, mucin, or, more correctly, a mucinous body, apparently derived from nucleoproteids, is thrown off in abundance in conditions of inflammation of the urinary passages, and the greater the amount of this in suspension in the urine, the greater the liability of salts which would otherwise have remained in solution, to become precipitated in the colloid menstruum. Whether loose combination occurs between the salt and the colloid matter is still an open question. Thus, for the formation

[1] On the Microscopic Structure and Formation of Urinary Calculi, London, 1873.
[2] On the Influence of Colloids upon Crystalline Form and Cohesion, London, 1879
[3] Die Natur und Behandlung der Harnsteine, Wiesbaden, 1884.

of urinary calculi, we recognize two factors: (1) the presence of one or other crystallizable body in relative abundance in the urine, and (2) irritation of some portion of the urinary tract leading to increased discharge of mucinous material.

Moritz[1] has pointed out that an organic base is present in every urinary crystal, whatever its nature, and, as the urine always contains mucinous and other organic material which can serve as a base, Krehl,[2] following him, doubts whether it is necessary to invoke a preliminary local irritation or inflammation. In taking this stand, however, the physical influence of concentration of the colloid material is left out of account.

Such an irritation need not be of bacterial nature. Chemical or mechanical irritation alone, as, for instance, in alkaline urine the presence of ammoniacal salts, is capable of setting up increased mucinous discharge. But infection of one or other part of the urinary tract is also capable of favoring the process, and, once it has begun, the local irritation set up by the presence of the foreign body leads to deposit of a surface layer of mucinous matter, and so the stone grows. The indications are that in the urinary passages, as in the gall-bladder, low forms of infection, notably by the B. coli, initiate the process in a large number of cases, but not necessarily in all. Without infection the urates precipitating in the collecting tubules of infants can set up a very definite irritation.

Uric Acid and Uratic Calculi.—Uric acid may be a constituent of a stone, either as the acid or in the form of amorphous urates. The first of these is the more common. Calculi formed mostly of urates are soft and of grayish-yellow color, and are found chiefly in children. Combined uric acid and urates are fairly common at all ages, the uric acid predominating. In fact, uric acid is the commonest constituent of calculi, whether as the main constituent or forming the central portion of the stone. Frequently there is some admixture with oxalate of lime. Uric acid calculi may be found either in the pelvis of the kidney or in the bladder. The typical vesical uric-acid calculus is of flattened, rounded, or oval shape; its surface is smooth or finely mammillated; the color varies from pale fawn to a brick red, according to the amount of associated pigment (uroerythrin) which is brought down in the urine when uric acid separates out. Upon section the individual laminæ are well recognized. Frequently the calculus is solitary, but they may be multiple, in which case the individual stones may exhibit smooth, facetted surfaces.

These calculi apparently originate in the pelvis of the kidney, and, instead of being arrested in the bladder, they may, while still small, be voided in the form of *gravel*. These little calculi have a smooth surface of reddish tinge. On the other hand, the calculus may never pass beyond the pelvis of the kidney, and here it may grow until it forms a large "stag-horn" mass, forming a mould of the dilated pelvis. These calculi may be found at any period of life, but their frequency in early years is noticeable.

[1] Cong. f. inn. Med., 1896: 532.

[2] Path. Physiologie, Leipzig, 1898.

Uratic Inspissation of Infancy.—The liability for the development of uric acid and uratic calculi in the young appears to be intimately associated with another condition, that, namely, of the formation of so-called *uric-acid infarcts*—a term which, while old established and etymologically correct as regards usage of the term infarction, is unfortunate, since our ordinary employment of that term is for a totally different process. Nor do these infarcts contain crystals of uric acid. *Uratic inspissation* would be a much more satisfactory term.

Autopsies upon infants a few weeks old not infrequently afford kidneys in which the calices and a considerable part of the medulla have an opaque, dirty whitish appearance, and, upon examination, this is seen to be due to the obstruction of the collecting tubules with abundant small spherical masses lying in a mucinous matrix. These are doubly refracting under the Nicol's prisms. Chemically these masses have all the properties of amorphous urates—quadriurates. The urine of the newborn contains normally twice as much uric acid as does that of the adult. Why this should be so is a matter of debate. Woods Hutchinson explains it as due to the breaking down of the nucleated red cells, which, present in the fœtal blood, rapidly disappear upon birth. Fry's observations indicate that these deposits may only occur some days, or even weeks, after birth. The acute disturbance of metabolism, the tissue destruction following upon birth, and, more particularly, the leukocytosis of the newborn, appear to afford a more satisfactory explanation. So grave is the disturbance which this obstruction of the tubules may set up that, as Fry[1] and Martin point out, there may be developed not merely a coincident albuminuria, but a definite condition of infantile uræmia. This excessive discharge would appear to be the origin of the uratic calculi in the young. Occasionally in young children, in the pelvis of the kidney, more rarely in the bladder, we encounter small, soft agglomerations of the same type having a mucoid matrix containing these spherical grains of quadriurates, and examination of fully formed uric-acid calculi shows, most often, a nucleus of this nature.

Both in the young and in adults who are the subjects of gravel and calculus, the urine passed is characterized by its high acidity and by the deposit, on standing, of a brick-dust precipitation of urates, from which uric acid gradually crystallizes out. While, as already pointed out, freshly passed urine rarely contains free uric acid, these stones are formed mainly of this substance. We are led to conclude, therefore, that, in the process of decomposition in the mucoid matrix, the quadriurates are broken down, uric acid is precipitated, and the alkaline urates are set free.

The usual teaching is that lithiasis—the condition in which there is this passage of urine containing precipitated urates—exhibits increased discharge of urates. Such increased discharge does occur, but it is, we think, more than debatable whether this is essential for calculus formation, or even for many cases of lithiasis, for, in a large proportion of

[1] Trans. Amer. Pediatric Assoc., 1903 150.

cases, brickdust deposits in urine are due not to increased discharge of urates, but to a concentrated and more acid state of the urine than is normal. There is frequently to be noted a relationship between gout and lithiasis such that those afflicted with gout have been liable to show abundant urate deposits, or to pass gravel, or, again, some members of the family are gouty, the others the subjects of lithiasis. But it is not the amount of the uric acid so much as the condition determining relative solubility that forms the main factor in lithiasis, and the relationship to gout suggests that, in some cases at least, the actual amount of uric acid formed may be below rather than above the normal.

Calculi of this nature may remain in the system for years, setting up relatively little disturbance; or, on the other hand, may, by their passage, cause obstruction in the ureters, the orifice of the bladder, or the urethra (renal colic). There has been much debate as to whether they ever become spontaneously dissolved, for uric acid is, to some extent, soluble in alkaline solutions. As a matter of fact, the evidence seems to be conclusive that, through keeping the urine alkaline through long periods by giving sodium bicarbonate, alkaline soaps, etc., not merely is gravel arrested, but the stones within the bladder, after such treatment, show clear evidence of erosion. In examining any large collection of uric acid calculi obtained in the postmortem-room, etc., certain specimens have a rugged, wormeaten appearance, and, upon section, are found loose in texture, with evidence of lamination very indistinct. Upon analysis such calculi are apt to yield relatively considerable amounts of quadriurates. These calculi, it seems to us, are clearly undergoing slow solution, and the quadriurates are an evidence of the action of the alkaline urine upon the uric acid. Sometimes, also, relatively large calculi undergo spontaneous fracture. We had two well-marked examples of this in the collection at McGill University before it was destroyed, and it has been noted ever since the time of Hunter. With such breaking up, the individual smaller pieces may be voided in the urine.

CALCIUM OXALATE CALCULI.

Calculi formed in the main of calcium oxalate are of three types. The commonest and the most characteristic is the so-called "mulberry calculus." In general solitary and occurring in the bladder, this form is relatively the heaviest of all calculi, densest and most resistant to fracture. The main feature is the heavily bossed or mulberry-like appearance. The color tends to be brown, or even brownish black. Often there is an incrustation of phosphates secondary to the great mechanical irritation induced by their presence in the bladder. Upon section the appearance is also characteristic. The outlines of the concentric laminæ recall the plan of a fortress, with bastions and reëntering angles.

More rarely we encounter white, colorless oxalate calculi. These, upon fracture, have a more crystalline appearance, are relatively pure, and their surface shows small crystals of the salt. There may also be

a condition of oxalate gravel. The minute concretions then are in the form of small, smooth, round bodies, blackish or dark gray in color.

A greater or less proportion of uric acid is usually present in these oxalate calculi. The nucleus also is frequently of uric acid or urates. This combination can be easily understood when it is remembered that, like the urates, calcium oxalate is deposited from acid urine.

Regarding the conditions under which these are formed, it may be recalled that oxalic acid is normally present in the urine to the extent of some 50 milligrams daily. In certain conditions this amount is greatly increased, and that during long periods, so that a definite condition of *oxaluria* and the oxalic-acid diathesis is to be recognized. What is the essential cause of this is little understood. Under normal conditions it is found that vegetable food containing oxalic acid (rhubarb, etc.) causes an increased discharge, but this does not explain persistent oxaluria. This oxaluria has been found in certain conditions of dyspepsia of a somewhat neurotic type, in confirmed obesity, and in association with diabetes. Excess of cane sugar has also been noted to cause it. According to E. G. Smith,[1] there is often a condition of hyperchlorhydria. It may, therefore, be that some perverted metabolism of the carbohydrates plays a part in the development of this state. Once formed, it would appear that oxalates are not easily dissolved.

PHOSPHATIC CALCULI.

Two, or probably three, forms of phosphatic calculi are to be recognized, namely: (1) those in which the phosphate is only in the form of calcium phosphate; (2) the mixed phosphatic or fusible calculus in which ammonium magnesium phosphate is the main ingredient, and in which calcium phosphate is also present; and (3) the pure ammonium phosphate calculus. The second of these is by far the commonest. All these are thrown down from alkaline urine, but the form of salt precipitated depends upon the cause of the alkalinity. It is where the urine is secreted in an alkaline state, the alkalinity depending more upon sodium salts, that calcium phosphate is precipitated. It is where the urine has become secondarily alkaline through fermentation and the bacterial breaking down of the urea into ammonia and carbonic acid gas that the triple phosphate is thrown down.

As a matter of fact, while calcium phosphate is freely precipitated in ordinary alkaline urine, it then shows relatively little liability to accumulate in the form of stones, and there may be, for months or years, a passage of such precipitated phosphates without any symptoms pointing to calculus formation. It may be pointed out that, under these conditions, the urine is not irritating, so there is no stimulus to the production of any excess of mucoid material to form the matrix, so that pure calcium phosphate stones are definitely rare. When found, they are white,

[1] Ref. Handbook Med. Sci., article upon Calculi, 1903.

rather firm—much firmer than the form about to be mentioned—and they rarely attain to large size. The mixed phosphates, on the other hand, are relatively loose and friable, the different layers splitting apart with relative ease, and they may attain to an enormous size. It is almost unknown to find such mixed phosphates as a nucleus of a calculus; the salts are usually deposited around other stones, or, again, around foreign bodies introduced into the bladder. It is rare also to find that other salts form the outer layer of phosphatic calculi, the reason being that, once cystitis is set up, where such stones are present, it continues, so that urine very rarely becomes once more acid. It is generally stated in text-books that these stones are not absorbed, and this because of the difficulty in rendering the urine acid by therapeutic means. With our knowledge that cystitis and the alkaline fermentation of the urine are of bacterial causation, and the recent production of drugs like urotropin, which are capable of sterilizing the urine, the possibility is certainly open that these calculi may become dissolved in the organism.

In such cases of cystitis, not only are we apt to find stones within the bladder or pelvis of the kidney, but on the inflamed mucous membrane there may be deposits of the phosphates.

OTHER URINARY CALCULI.

Outside these three main groups above mentioned, other forms of urinary calculi are distinctly rare. Of these, one of the most interesting is the *cystin* calculus. These are of a honey-yellow color, becoming green upon exposure to light; they have a radiate structure, and, upon fracture, a peculiarly transparent brilliancy, like that of beeswax. They are soft, so that they can be indented with the nail, and are usually pure. Sometimes they are large and single, but a condition of cystin gravel also occurs, in which the patient, from time to time, over long periods, voids minute calculi of this nature. The collection at McGill contained a set of eighteen small calculi passed by one patient in this way.

Cystin is an abnormal constituent of urine. It contains a relatively large amount of sulphur (as much as 26 per cent.), and dissolves in liquor ammoniæ. From this solution, as the ammonia evaporates, beautiful six-sided tablets separate out along with some square prisms, the substance being dimorphous. (See Fig. 135, p. 346. Its formula is $C_3H_7NSO_2$, and thus it is not far removed from that of taurin.

What leads to its appearance in the urine is wholly unknown, save this, that it tends to be formed by more than one member of a family, and that the condition of cystinuria may show itself for long years without any impairment in health or obvious change in the other constituents of the urine, the only serious danger being a tendency to form calculi (see p. 345). Sometimes a tendency to lithiasis accompanies this.

Still rarer are *xanthin* calculi, first noted by Marcet, of London, in 1817. Altogether, little more than half a dozen cases are on record of

the formation of these calculi, which are of pale-yellow color, and exhibit a waxy lustre when rubbed. Their main constituent is xanthin, and nothing is known with regard to the conditions leading to extensive discharge of this alloxur body. In cattle, somewhat parallel calculi of *guanin* have been encountered. Yet rarer, again, are the concretions termed by Heller *urostealiths*. These are formed of fatty and soapy matter, lime soaps being apparently their main constituent. While some, obtained from the bladder, have been explained as due to the passing in of soapy medicaments, others have been found actually within the kidney, and so must have been derived from fatty matter discharged from this organ.

Lastly there are at times to be met with small, firm, *fibrinous* concretions, more or less blood-stained, which clearly are secondary to hemorrhage in the urinary tract.

BILIARY CALCULI; CHOLELITHIASIS.

The composition of the calculi which may form in the gall-bladder and bile passages differs widely from that of the urinary calculi, and,

Fig. 309

Cholesterin calculus, cut and polished to show radiate crystalline structure. (Naunyn.)

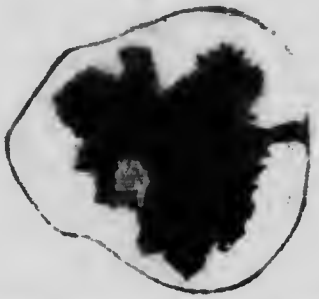
Fig. 310

Section of common mixed bilirubin calculum gallstone. (Naunyn.)

Fig. 311

Pure bilirubin calcium calculi: bile gravel. (Naunyn.)

Fig. 312



Section of "amorphous" cholesterin gallstone exhibiting central cavitation. (Naunyn.)

as a body, they are characterized by being less dense and much lighter in weight. The main constituents are the modified pigments of the bile

and cholesterin; a third constituent present not infrequently as an admixture, but rarely as a predominant constituent, is calcium carbonate. We thus distinguish the following varieties of gallstone.

1. **The Common Gallstone.**—This may be single and large, when it is often barrel-shaped (as though other stones had previously been present in series, and had compressed and facetted the two ends); or there may be two to four relatively large stones facetted in their opposed aspects, and forming together a cast of the gall-bladder; or multiple small facetted stones, from a score or so to several hundred in number, relatively equal in size. It is more uncommon to meet with an admixture of large and small stones. The facetted surfaces are smooth; the larger stones, where the surfaces do not oppose, are usually finely nodular. The external color varies from a deep brown that is almost black, through reddish brown (bilirubin), to green (biliverdin). Or, again, it often is pale yellow, through surface layers of cholesterin, or, rarely, is white, from a surface layer of calcium carbonate. On section, such calculi exhibit a characteristically concentric structure of alternate layers of varying depth of color, according to the extent of admixture of cholesterin with the calcium salt of bilirubin or of biliverdin. The nucleus may be either of cholesterin or of bile pigment, or, as Naunyn points out, may be represented by a cavity.

Such calculi, it will be seen, are mixed; the main constituents are cholesterin and bilirubin calcium, although biliverdin another higher oxidation form of bile pigment, may take the place of bilirubin; with these may be minute quantities of Cu and Fe, apparently in combination with the bilirubin calcium. Calcium carbonate is a not uncommon constituent, laid down in minute nodules throughout the mass of a calculus; more rarely, inconsiderable quantities of calcium sulphate and phosphate have been detected.

Of these mixed calculi Naunyn distinguishes three classes: (1) The "common" multiple gallstone, having a laminated firm crust, covering a relatively large, soft, pigmented nucleus. (2) The "mixed bilirubin calcium" calculi, constituting the large single calculi, or the groups of three or four, laminated and firm throughout, having a nucleus of cholesterin. In these the percentage of cholesterin may be as much as 25. (3) The "laminated cholesterin," resembling the last group in general characters, but having a predominance of cholesterin, which may be present in broad zones. The cholesterin in these varies from 75 to 95 per cent. All these are mixed calculi, the bilirubin calcium being predominant in the first, the cholesterin in the last.

2. **Pure (or Almost Pure) Cholesterin Calculi.**—These are characteristic stones, most often single and oval, most often, also, of pale yellow, waxy exterior, with finely nodulated surface. But multiple and slightly facetted stones are encountered, as also those having a distinctly brownish color. If colored, these have a distinctly radiate crystalline surface; if sawed through and polished, an obscurely crystalline, rather nacreous surface with little or no sign of stratification. There

may be a small nucleus of pigment. It is, in short, rare to obtain a calculus of pure cholesterin, but from 90 to 98 per cent. of the total contents may be of this substance.

3. **Pure Bilirubin Calcium Calculi.**—These most often are present as what may be termed bile gravel—multiple blackish granules, averaging about 1 mm. in diameter, lying in a distinctly mucoid bile. When fresh they are very soft, easily crumbling between the fingers. They are difficult to dry and preserve, in consequence of shrinkage and fracture into small fragments. Frequently, through the mucus in which they are embedded, they agglomerate into small mulberry-like masses. Naunyn describes another firmer form, with metallic lustre, which we have encountered but once and that doubtfully.

Calculi of this class are composed almost entirely of the calcium salts of the bile pigments, with but a trace of cholesterin. In addition to the bilirubin salt, there may be large proportions of bilihumin calcium (bilihumin being the most oxidized of the bile pigments).

4. **Calcium Carbonate Stones.**—Stones formed almost entirely of calcium carbonate are rare and small in man; among the herbivora they are more common, and may attain a considerable size. Naunyn differentiates two forms in man—the one brown and spicular, the other pale and smooth, both of relatively great hardness. As already noted, nodules of calcium carbonate may occur more especially in connection with biliverdin calcium.

Another rare form is what may be termed cholesterin gravel—fine deposits or accumulations of what Naunyn regards as amorphous cholesterin. This is the first stage of stone formation; later, the cholesterin becomes crystalline.

Etiology.—There have been abundant theories regarding the causation of gallstones; these have been largely forgotten since Naunyn's classical work gave a foundation of more thorough knowledge.

It had for long been recognized that gallstones are more common (1) in middle and advanced life; (2) in females, rather than in males; (3) in those of sedentary, as distinct from active, habits. Frerichs more particularly laid down that stagnation of the bile is the main factor leading to their formation, holding that through this stagnation certain of the salts of the bile become reabsorbed, whereby the bile becomes more acid and its pigment more particularly becomes precipitated. The cholesterin both he and Gmelin regarded as discharged by the liver.

Naunyn, in the first place, demonstrated that the cholesterin is not excreted in any amount by the liver. Feeding animals with cholesterin did not lead to increased cholesterin in the bile, while, on the other hand, he showed that sputum and other catarrhal products contain relatively large amounts of cholesterin, this also being present in pus and many conditions of cell disintegration. The cholesterin, he showed, was derived from the mucous membranes of the gall-bladder and bile passages, but more particularly from the former. This view has been sub-

stantiated by Herter[1] and Wakeman, who gained increased cholesterin in the gall-bladders of dogs by injecting into their bladders phenol, corrosive sublimate, etc.

In catarrhal conditions of the bladder Naunyn saw the epithelial cells filled with double-contoured myelin droplets, and in association with the disintegrating cast-off cells found clumps of "amorphous cholesterin" becoming precipitated, which, upon treatment with acetic acid, become converted with the well-known plates of cholesterin crystals.

That these views of Naunyn are correct is evidenced by the fact that it is in cases of obstruction of the cystic duct we find the purest cholesterin calculi in the gall-bladder, lying in a fluid free from any trace of bile.

I have encountered a case in which the obstruction was caused by a stone blocking the entrance to the cystic duct. The greater part of this stone projecting into the gall-bladder was colorless, composed of pure crystalline cholesterin; the smaller portion lying in the cystic duct was pigmented, a mixed calculus. The specimen was in the museum at McGill prior to the fire.

These observations of Naunyn have recently been materially advanced by Aschoff.[2] As shown by Aschoff and myself,[3] among the bodies which are normal constituents of the organism, and possess the power of double refraction at the room temperature and the properties which are associated with myelin (see p. 828), is cholesteryl oleate. This is a normal constituent of the blood. Aschoff found that the cells of the mucous membrane of the gall-bladder, noticed by Naunyn to contain myelin bodies, contain doubly refractive globules. These he regards as cholesteryl oleate, and urges that the simplest explanation of the appearance of cholesterin in the alkaline bile is that, with disintegration of the cells, the myelin is set free, and under the action of pure alkalies the cholesteryl oleate is dissociated. Its oleic acid moiety combines to form relatively soluble soaps, the cholesterin becoming precipitated. It is interesting to note that Naunyn, in his earlier analyses, called attention to the presence of fats and soaps in the bile. It is true that he regarded them as keeping the cholesterin in solution. Aschoff's view appears to us more inherently probable, namely, that the fats are liberated and the soaps formed and absorbed from the gall-bladder when the cholesteryl oleate is disintegrated. It has still to be determined whether this appearance of myelin globules in the biliary epithelium is purely degenerative, or is a normal secretion. We are inclined to the latter view; the observations of Naunyn show that the amount of cholesterin which constitutes roughly 1 per cent. of the dry matter obtained from normal bile (0.35 to 1.18) is unaltered when increased cholesterin is introduced into the system either subcutaneously or by the mouth; that it is independent of hepatic activity. But it has to be recognized that the amount

[1] Trans. Cong. Amer. Physicians, 6: 1903: 158.
[2] Verhandl. d. deutsch. path. Gesell., 10: 1907.
[3] Proc. Roy. Soc. Lond. B., 78: 1906: 359.

present in the bile is greatly increased in catarrhal conditions. We then reach the conclusion that *the cholesterin of gallstones is derived from the mucous membrane of the bile passages, and more particularly of the gall-bladder; that the increased production is associated with a catarrhal condition; and that the presence of fats, soaps, and cholesterin in the bile in conditions of catarrh is due to the dissociation of cholesteryl oleate.*

It is deserving of note that so long ago as 1845 Budd[1] reached a like conclusion regarding a fatty degeneration of the mucous membrane of the gall-bladder as affording the cholesterin. Bristowe[2] also regarded it as derived from secretion from the mucous membrane. We have suggested[3] that what Naunyn describes as "amorphous cholesterin" is a fused mass of myelin, and that the crystallization that this undergoes, and is induced outside the body by the action of acids, is due to the separation out of the cholesterin. The disintegration of cholesteryl oleate and abstraction of the fatty acid in the form of soluble soaps would explain the cavitation and central softening of those stones in which such a mass formed the nucleus. (See Fig. 307.)

The same catarrh which leads to the production of cholesterin favors also the discharge of calcium salts into the bile and the interaction of those with the bile pigments to form precipitated bilirubin calcium and other calcium composed of the bile pigments. As Naunyn points out, the calcium of the bile has the like origin to the cholesterin, namely, from the (inflamed) mucous membrane. He found, further, that calcium salts added to normal bile led to no precipitation; that we have, in short, the same phenomenon that we dealt with in other calculi and concrements, the favoring action of a colloid substratum.

Thus, where catarrhal inflammation is present, whether in the unobstructed gall-bladder or the bile ducts, we encounter deposits of both bilirubin calcium and cholesterin. It is, in our experience, a sure sign that cultures from the bile will be positive when, instead of being clear, thin layers of the fluid removed from the gall-bladder show flocculi more or less pigmented.

As already noted, "pure" cholesterin calculi are encountered in cases of obstruction of the cystic duct, and again, we may add, where stones develop in pockets cut off from the main cavity or passages. What the conditions are under which "pure" pigment calculi are produced have not as yet been surely determined, nor why we obtain the great variation in the relative amounts of pigment and cholesterin in the different layers of a mixed calculus. It may be that this depends upon the proportion of soaps present in the bile at different periods. As shown more particularly by Brockbank, these are present normally in bile, and possess a great solvent power for cholesterin. Whether these soaps —and fats—alone are answerable is still undetermined. Cholesterin placed under aseptic conditions in the gall-bladder of healthy dogs undergoes slow dissolution.[4]

[1] Lectures on the Liver.
[2] Lancet, February 19, 1887.
[3] Address, Buffalo Academy of Medicine, February, 1906
[4] Harley and Barratt, Jour. of Physiol., 29:1903:341.

As to the agents setting up the low forms of inflammation necessary for the production of gallstones, Gilbert and Girode, and Naunyn, independently, indicated that the B. coli communis is the most frequent agent in the production of cholecystitis. Naunyn, in 1892, had isolated it from five cases of cholelithiasis by puncture of the gall-bladder during life. These observations have been abundantly confirmed, one other agent having been found also to play an important role, namely, the B. typhosus.

Dufort, in 1893, found a history of a previous attack of typhoid in 19 cases of cholelithiasis, in 12 of which the first attack of biliary colic came on within six months after the fever.[1] The same year Chiari[2] called attention to the presence of typhoid bacilli in the gall-bladder in 19 out of 22 cases. Pure cultures of one or other organism have been gained from the centres of a large number of gallstones by various observers. It has been found that cultures of one or other form introduced into the unobstructed gall-bladder or biliary passages may have no result; they are liable to be washed out by the bile flow. If by ligation obstruction be produced, cholangitis is set up and precipitation occurs in the bile. In this way Cushing[3] was able to produce gallstones experimentally by the injection of B. typhosus into the gall-bladder.

How these microbes reach the gall-bladder is still a matter of debate. The usually accepted view is that they travel up the stagnant bile from the duodenum. Against this view is the fact that the duodenum is the part of the intestine which is freest from bacterial flora; the typhoid bacillus more particularly is rarely to be encountered there. We do not recall a single case in which it has been isolated therefrom. Some years ago Natter demonstrated that ligation of the common bile duct is followed by cholangitis and growth of the B. coli in the gall-bladder. In such cases the blood seems to afford the more natural channel of infection. Our own studies upon apparently normal bile afford us frequent growths of an attenuated B. coli (the method being employed of dilution in broth rather than smears upon solid media). There have, however, been equally positive observations by capable workers negativing these views. The matter must thus be regarded as still *sub judice*.

To sum up: *The commoner forms of gallstones owe their origin to the interaction of two factors:* (1) *the stagnation of the bile;* (2) *bacterial infection of the same, with the development of a low form of cholangitis and catarrh of the biliary mucous membrane.* The onset of such a cholangitis may be relatively acute, with much epithelial discharge. This would explain why, in general, the stones are characteristically of like size and apparent age. Following upon this, a certain amount of tolerance or latent infection is established. Years after an attack of typhoid fever the B. typhosus may be obtained from the affected gall-bladder,

[1] Rev. de Méd., 1893: 274.

[2] Präger med. Woch.

[3] Johns Hopkins Hosp. Bull., 10: 1899: 166. (With bibliography.)

and no matter how large and well formed the stones, and how long the history of cholelithiasis, the gall-bladder in the majority of these cases affords cultures of either the B. coli or the B. typhosus.[1]

URATIC DEPOSITS IN THE TISSUES.

Gout and the so-called uratic infarcts of the newborn are discussed at some length elsewhere (pp. 342 and 868). It is but necessary to recall here in due order the fact that there exist deposits of urates of sodium within the tissues, and these of two orders. In gouty states these are in the form of closely packed, fine, needle-like crystals of sodium biurate. The seats of election are primarily the cartilages of the joints and particularly of the more distal joints, so that where gouttiness is suspected a routine examination should be made *post-mortem* of the metatarso-phalangeal articulation of the great toe. In the more advanced conditions there may be accumulations or nodules of the deposit (*tophi*) outside the joints, either in cartilage elsewhere—*e. g.*, in the pinna of the ear, or around synovial sheaths and tendons. We may possibly compromise over the long-standing debate as to whether tissue necrosis precedes (Ebstein) or follows the deposit (Garrod and others) by laying down that the infiltration is *never primary in the living cells*, but occurs in the inert intercellular matrix, and that as indicated by the experiments of His[2] once laid down the crystals act as irritants or slow poisons, setting up eventual death of the surrounding cells.

The deposits in the medulla and collecting tubules of the newly born are totally different in appearance. They occur in the form of spherules of minute, doubly refractive spherocrystals[3] or spheroliths, present both in the collecting tubules and in their investing cells. What is the exact composition of these is still a matter of debate. We incline to the view that they are identical with the similar so-called amorphous urates of the urine, which have the same globular character, and according to Sir William Roberts are quadriurates of sodium (p. 345). Somewhat similar deposits have been produced in the dog[4] and in the rabbit by feeding[5] with adenin, but according to Nicolaier[6] these are neither uric acid nor urates but amino-dioxypurin, a body not present in human urine.

[1] The most important monographs upon cholelithiasis giving the literature are Naunyn, Klinik der Cholelithiasis, Leipzig, 1892 (English translation by A. E. Garrod, New Sydenham Soc., 1896), and Brockbank, E. M., on Gallstones, London, 1896. Of the former a new edition is on the point of being issued.

[2] Deutsch. Arch. f. klin. Med., 63: 1899: 266.

[3] Adami and Aschoff, Proc. Roy. Soc. B., 78: 1906: 367.

[4] Minkowski, Arch. f. Exp. Pathol. u. Pharm., 41: 1898: 428.

[5] Schittenhelm, Ibid., 47: 1902: 432.

[6] Zeitschr. f. klin. Med., 45: 1902: 359.

CHAPTER XXXI.

PIGMENTATION AND PIGMENTARY CHANGES.

THE property possessed by various chemical compounds of being colored affords no adequate ground for bringing them together into one common class. The colored state is an accident to this extent, that, so far as we can see, it connotes no common underlying physiological feature. Bodies as wide apart as elements like iodine, and coal-tar products, like the aniline dyes, are equally colored. Thus, at first sight, it would seem unscientific to bring together into one common group the various pigmentary changes occurring in the organism. There is, however, a certain usefulness in so doing, for the more numerous and the more pigmented bodies present in the system, under both normal and abnormal conditions, are closely allied, while the remainder are so varied that it is not easy to group them according to any other scheme.

ENDOGENOUS PIGMENTS.

With this understanding we would proceed to redivide the colored substances of the body appearing under pathological conditions into two broad sub-groups: (1) *endogenous pigments*, the direct products of cell metabolism or disintegration; and (2) the *exogenous* colored matters foreign to the organism and absorbed from without. The endogenous we may further divide into (*a*) hemoglobin and its derivatives; (*b*) other metabolic pigments. Each main sub-group contains two orders of bodies, namely: (1) soluble; (2) insoluble or precipitated pigments.

It is usual in works dating from the days when morbid histology was considered as pathology to exclude very largely the first of these, and in this connection to discuss more particularly the pigmentary deposits. Such a distinction only leads to confusion.

Abnormal Pigmentation Due to Hemoglobin and its Derivatives.—Hemoglobin and its derivatives are so fully studied in works upon physiology and physiological chemistry that it is unnecessary here to do more than recall its presence in a soluble condition, not only in the blood corpuscles, but also in the muscles; its remarkable chemical properties; its constant liberation from dying red corpuscles, more particularly in the portal system (including the spleen); its disintegration, more particularly through the agency of the liver cells, with discharge into the bile of the iron-free portions of the pigment as bilirubin and other bile pigments. It is probable, though this is not wholly determined, that the urinary pigment, or urochrome, is likewise a derivative of the normal

disintegration of hemoglobin. Certainly, under pathological conditions, the liver and the kidney are the two organs through which hemoglobin and its compounds are discharged from the blood.

It is further deserving of note, as contributing to a natural classification of metabolic disturbances, that hemoglobin is a conjugated protein after the type of the nucleoproteins and the glycoproteins recently discussed. It is a compound of a nitrogenous coloring matter—*hematin* ($C_{32}H_{32}N_4FeO_4$), with the basic protein *globin*.

Experimentally, by various means—injections of large amounts of water, dilute glycerin, potassium chlorate, arseniuretted hydrogen, toluylenediamin, certain acids, and by the transfusion of the blood or blood serum of another species of animal—it is possible to cause the red corpuscles to break up and liberate their hemoglobin, which then becomes free in the blood plasma, and may diffuse out of this into the various tissues, and, indeed, undergo absorption by various orders of cells. Similar destruction of the corpuscles may be brought about by severe thermal changes.

In disease we have numerous examples of a similar liberation, and may either encounter this hemoglobin in the unaltered state or find it modified. A somewhat frequent example of the former condition is seen in *hemoglobin*, or, as it is often termed, *postmortem imbibition*. Here we find the heart valves and the intima of the aorta and larger arteries assuming a bright rose-pink color. This occurs more particularly in cases of general sepsis. But two conditions, it seems to us, have to be distinguished. In hot weather, with the rapid onset of decomposition, the staining of the intima may show itself, which is distinctly a postmortem change. In acute sepsis the same process is seen, even when the autopsy is performed within an hour after death. Here it is not merely postmortem, but, through the extreme toxic state, there has been destruction of the erythrocytes during the last hours of life, and it is a combination of antemortem and postmortem diffusion of the hemoglobin which leads to this characteristic appearance.

Certain poisons—some of them already mentioned—are apt to cause, in man, a similar rapid liberation of the hemoglobin, notably potassium chlorate, certain poisonous mushrooms, and snake venoms. Where the destruction of the red cells occurs in the systemic circulation, the liberated hemoglobin may be discharged, unaltered, through the kidneys (*hemoglobinuria*); slightly altered, as after potassium chlorate (*methemoglobinuria*). Methemoglobin, it may be added, is apparently of the same composition as oxyhemoglobin, but the oxygen is more firmly combined, and the reaction is acid. The modification occurs often in the bladder rather than in the system before excretion. Where the destruction of the red cells has occurred, not in the blood stream, but in the tissues and cavities of the body, the pigment before discharge may undergo still further change into hematoidin or urobilin (*urobilinuria*).

Care must be taken to distinguish between these different states and *hematuria*, in which we have to deal, not with the mere excretion of

blood pigment, but with escape of blood into any portion of the urinary apparatus and the consequent presence of all the constituents of blood in the blood-stained urine.

Hemoglobin, as Miss Adams first demonstrated, may be discharged through the glomeruli of the kidneys, or also, as Afanassiew was the first to show, may be taken up by the cells of the convoluted tubules. In the latter case it is clearly modified, being present in these cells, not merely in a diffused form, but also in the form of fine brownish granules. These granules are iron-containing, with the iron in looser combination than occurs in hemoglobin proper.

Paroxysmal Hemoglobinuria.—A very remarkable condition, associated with liberation of hemoglobin, deserves more than passing notice. This is the condition first described by Dessler (1854) and by Dr. George Harley (1865), to which Pavy has given the name of *paroxysmal hemoglobinuria.*

In this condition there is a sudden appearance of urine, tinged, or, it may be, deeply colored, by the presence of hemoglobin. For an hour or two what urine is passed is thus colored, and the next passage may be perfectly clear and limpid. This little understood condition is not in itself fatal, even though two or three attacks per diem may occur over a considerable period. Patients have been known to be affected from time to time for as many as eleven years. When the condition first manifests itself it is noted that the paroxysms come on after slight exposure to cold, as, for example, the chilling of the body upon rising in the morning, and first and other attacks are most frequent during the winter months. In inveterate cases they occur during the summer also, and frequently without obvious cause. Yet it has been observed that, in these severe cases, living in a warm climate prevents the paroxysms. There is, indeed, a certain relationship between this condition and cyclical albuminuria. As Copeman points out, such cyclical albuminuria also follows chills, and is truly a globulinuria, and not an albuminuria; while, in the condition we are now discussing, a condition of globulinuria, associated with a rapid reduction in the number of red corpuscles in the circulating blood, may precede the appearance of hemoglobin in the urine. In both conditions the red corpuscles appear to be abnormally sensitive to temperature changes, and a feeling of coldness and shivering in the extremities frequently precedes the paroxysms.

Vasomotor changes, therefore, affecting the cutaneous vessels appear to be very intimately connected with the development of the condition. That it is due to a liberation of hemoglobin from the corpuscles was first fully demonstrated by Küssner, in 1879, by withdrawing blood from the peripheral circulation during a paroxysm, and finding that, after coagulation, the serum was distinctly colored by hemoglobin. Yet clearer demonstration was afforded by Ehrlich, who showed that, after ligaturing the finger of a patient subject to these attacks, and dipping it in cold, and then in hot, water, not only had the serum become tinged, but, among the corpuscles, numerous shadows of red cells, which had lost their hemoglobin, could be distinguished. It is possible

that the more recent studies upon hemolysins, and upon the development in the system of substances which lead to the disintegration of red corpuscles, may throw some light upon this curious disease; so far no adequate explanation has been afforded.

A similar but more severe and more paroxysmal hemoglobinuria is seen in horses, and here also exposure to cold has been noted to play a part. This condition is sometimes spoken of as *azoturia*.

Infective Hemoglobinuria.—But not all the hemoglobinurias in cattle and in man are of this same obscure origin. Some undoubtedly are due to the effects of blood parasites, sporozoa. The organisms of ague or malaria, for example, would appear to be the essential cause of "blackwater fever" in man, though, according to Koch, an idiosyncrasy toward quinine, taken to ward off the ague, has also to be invoked. In Texas fever in cattle, the piroplasma similarly leads to a dissolution of the erythrocytes and the discharge of hemoglobin.

Modified Hemoglobin.—Free hemoglobin undergoes extensive modifications in cases in which there is prolonged destruction of the red corpuscles; and, again, where there is localized hemorrhage in the tissues. As indicated by the succession of tints assumed by subcutaneous hemorrhage—in a "black eye," for example—there is a succession of modifications of its pigment constituent, the *hematin*, leading to eventual deposit in the tissues of two, or, more correctly, three substances—*hematoidin*, *hemosiderin*, and *hemofuscin*. Of these, hematoidin is a pigmented, rather ruby-red, iron-free substance, which may be present either in the form of definite, rhombic crystals, or in a more granular state, with occasional faint indications of crystalline structure. This, it has been noted, occurs more frequently in relatively large hemorrhages, or, more correctly, in the more central portion of hemorrhagic areas; it may be found in cerebral hemorrhages, or in the hemorrhagic contents of corpora lutea. It is soluble to a slight extent, and is supposed (see p. 890) to be the cause of the yellowish pigmentation of the skin that accompanies severe paroxysmal hemoglobinuria and other conditions like pernicious anemia, in which there is extensive destruction of the red corpuscles. Chemically it is identical with bilirubin and closely allied to urobilin.

Hemosiderin, on the other hand, is always amorphous, in the form of fine granules, and is iron-containing, so that it can always be recognized by certain microchemical tests. By treating sections with ammonium sulphide, the granules appear brownish black, through the formation of sulphide of iron (Quincke's test). The more beautiful test is the so-called Perl's test, which consists of treatment of sections with moderately dilute solutions of potassium ferrocyanide, followed by treatment with weak hydrochloric acid. By this test the iron granules become converted into cyanide of iron (Prussian blue), and each granule has then a characteristic rich blue appearance. Deposits of this hemosiderin are regularly to be encountered, more particularly in the outer zone of hemorrhagic areas, both free and in leukocytes or other cells. Cellular activity appears to be necessary for its development. It occurs

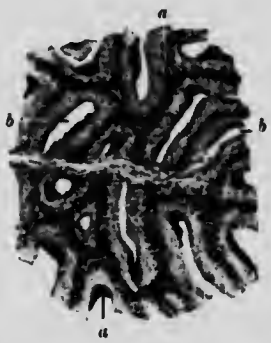
also in various organs of the body after repeated hemorrhages, or where, from one cause or another, there has been extensive destruction of red corpuscles—in the spleen, liver, pancreas, lymph glands, walls of the intestines, etc. More particularly under such conditions do the liver cells come to contain relatively great quantities of hemosiderin. This is particularly noticeable in pernicious anemia, and here, as Quincke, Hunter, and others have pointed out, the liver may contain as much as ten times the normal amount of iron. In addition to pernicious anemia, there may be large deposits of hemosiderin in the liver and other tissues in the condition known as *hemochromatosis*.

What is the cause of this condition is still a matter of debate. Von Recklinghausen was the first to call attention to it and point out that, in the slighter stages, it is to be noted in the walls of the small intestines, which, as a consequence, assume a yellowish or light-brown tint. In more advanced cases it is associated with cirrhosis of the liver, fibrosis of the pancreas, and, not infrequently, with diabetes, in the condition known by the French as *diabète bronzé*. As Kretz has pointed out, and as Dr. Maude Abbott has confirmed,[1] a considerable proportion of cases of cirrhosis of the liver show an excessive deposit of iron-containing pigment in that organ. Dr. Abbott found this in not less than nine out of sixteen cases of portal cirrhosis studied in Montreal. But what is the cause remains doubtful. The condition occurs more commonly in men; indeed, Dr. Abbott's case is the only one so far recorded in the female. Opie[2] is of the opinion that hemochromatosis is a specific disease. This we are somewhat inclined to doubt, for, as already indicated, a large proportion of cases of ordinary cirrhosis show slight grades of the condition. This, however, I think must be admitted, that the deposits of the pigment indicate, as in pernicious anemia, a

FIG. 313

Rhombic plates and needles of hematoidin. × 500. (Ziegler.)

FIG. 314



From a section of the liver from a case of pernicious anæmia, treated by Perl's test to demonstrate the iron-containing pigment lying in the liver cells close to the bile capillaries *a*, and away from the blood capillaries *b*. (After Ribbert.)

[1] Journ. of Pathol., 7: 1901: 55. [2] Opie, Journ. of Exp. Med., 4: 1899: 279.

destruction of the red corpuscles extending over a long period, and the heaping up of the pigment, more particularly in the liver, as an indication that the cells of that organ are incapable of dealing adequately with the iron-containing portion of the hemoglobin, which thus remains in a fixed state in the liver cells and other cells throughout the organism.

The indications are that this hemosiderin is an albuminate of iron in which the iron is relatively loosely combined. In livers containing a considerable amount of the hemosiderin turning blue by Perl's test, other granules can be seen of the same size and general appearance, which, however, are unaffected, remaining of a yellowish brown. These granules are known as *hemofuscin*, and, as pointed out by Dr. Abbott, employing the Perl test, with heat and somewhat stronger acids a certain proportion of these now take on a blue color. The probability, therefore, is that hemofuscin represents an albuminate of iron in which, as in hemoglobin itself (which also does not react to Perl's test), the iron is in a more stable and firmly fixed combination, though other observers regard it as hemosiderin which has lost its iron. Such hemofuscin is found also in other conditions—in extravasations of blood at a late stage; similar brownish-yellow granules have been noted in certain gland cells of the stomach and intestines, of mucous and sweat glands. Whether these granules are all of the same order is debatable. We are inclined to regard them, with von Recklinghausen, as, in the majority of cases, clearly derived from hemoglobin.

The nature of the pigment seen within the muscle fibers in brown atrophy is still a matter of debate; from histological considerations, regarding the atrophy of the fibers with which the pigmentation is associated, it is most natural to regard the pigment as a product of dissociation of myohemoglobin. Lubarsch[1] and others have regarded it as a lipochrome (see p. 894), and undoubtedly from the heart with brown atrophy there can be dissolved out a certain amount of such fatty pigment. But Taranonkhine[2] cannot recognize that it is either a derivative of hemoglobin or a lipochrome, although he regards it as a proteid derivative. Yet it is deserving of note that Rosenfeld,[3] studying the pigment of the muscles of the small intestines (the pigmentation which von Recklinghausen has regarded as the first stage of hemochromatosis), found in this so large a proportion of sulphur that he regarded as more essentially allied to the melanins.

As against this view we would point out the impossibility of adequately isolating this pigment; and secondly, the ease with which sulphur, in the form of sulphuretted hydrogen, diffuses from the bowel, and so is liable to be taken up and absorbed by the surrounding tissues and their constituents.

Pseudomelanosis.—In this connection we may note that a marked grade of pseudomelanosis is occasionally to be met with. Where there has been breaking down of red corpuscles, with liberation of hemo-

[1] Centralbl. f. Path., 13:1902:881.

[2] Roussky Arch. patol., 10: 1900:441; ref. in Lubarsch-Ostertag Ergebnisse, 1901.

[3] Arch. f. Exp. Path., 48:1900

globin and formation of hemosiderin, and, further, the presence of sulphuretted hydrogen, an iron sulphide is formed and the tissues become black. Such liberation of sulphuretted hydrogen occurs most often in the stomach during digestion and fermentation of the food. Thus, at autopsy it is most frequently the stomach walls and the organs in the immediate neighborhood—the liver and the spleen—that exhibit the change. But sulphuretted hydrogen may also be liberated by bacterial activity in suppurating wounds, gangrenous extremities, etc., and a similar pseudomelanosis be so produced. Mere postmortem decomposition rarely seems adequate to induce the change; more often there has been during life local or general hemolysis, with setting free of hemoglobin.

Hematoporphyrin and Hematoporphyrinuria.—Like hematoidin, hematoporphyrin is an iron-free derivative of hemoglobin, or, more truly, of hematin. It is not, to our knowledge, found within the tissues, but minute quantities have been recognized in normal urine, and in certain conditions of disease the amount in the urine may be notably increased; acute rheumatism and sundry hepatic conditions are liable to be accompanied by a slight grade of hematoporphyrinuria. The greatest discharge is liable to occur after the injection of certain drugs, such as sulphonal, whose acid constituent is supposed to be liberated within the system, and then to act upon free hemoglobin.

JAUNDICE; ICTERUS.

That there is a constant, if somewhat intermittent, excretion of bile is easily realized. It is more difficult to realize that the abundant pigment of that bile is derived from the never-ceasing destruction of red corpuscles. This is surely the case. The individual erythrocytes have but a short life period, apparently not exceeding four weeks; either they die in the blood stream—fade away, their hemoglobin dissolving out, and the colorless shadows later breaking up and dissolving in the blood plasma—or the corpuscles are taken up in a moribund condition by the phagocytic cells of the spleen and liver. Other endothelial cells, notably those of the lymph glands, possess the same property, although they exercise it to a less extent. The hemoglobin from these corpuscles, whether in an unaltered state or modified, is absorbed by the endothelium of the hepatic capillaries, is passed on to the liver cells, and is, by them, broken up. The exact stages of this breaking up process, first demonstrated by Kühne in 1858, have not been followed; the result is that the iron-free portion of the pigment is discharged into the bile capillaries in the form of bilirubin, the pigment of the bile. What becomes of the iron-containing moiety under normal conditions is a matter of conjecture rather than of precise knowledge. It may be returned direct to the blood; it may pass into the lymph channels. Compared with the amount of bile pigment discharged, the amount of iron present in the washed-out liver is relatively small. There

is no great storage of iron in a combined state in this organ; the amount in the bile is so small as not to be worth consideration. Evidently the iron of hemoglobin is a valuable asset, and is not lightly parted with by the organism. If discharged into the bile, it is capable of being absorbed again in the small intestines where, as Macallum, of Toronto, has demonstrated, albuminates of iron are taken up by leukocytes which have wandered on to the free surface and are, by them, conveyed into the blood and lymph stream.[1]

Any disturbance of the regular discharge of altered blood pigment leads to a more or less definite grade of jaundice, by which we understand a condition in which the bile pigment, failing to be discharged duly from the liver, accumulates in the [illegible]e until it regurgitates into the lymph and bloodvessels, and so, being carried, in a soluble state, to the other tissues of the body, it is [illegible] by those tissues, causing them to assume a bile-stained appe[illegible]. It is this staining that is the essential feature of jaundice (F[illegible], *jaunisse; jaune*, yellow); the accompanying symptoms, itching of the skin, slowing of the heart, mental depression and melancholy (literally, *black bile*), etc., while due to hepatic incompetency and regurgitation of other constituents of the bile, must be regarded as subsidiary. They may not show themselves in the milder stages of the condition, and will be discussed later when treating of the general pathology of hepatic disturbances. That this staining is due to bile pigment is easily proved. The blood, the urine, and the tissues give, upon analysis, the chemical reactions for bilirubin, or, in some cases, for its more oxydized modification, biliverdin. That in all cases of true jaundice the liver is the organ in which this pigment is formed, if not wholly, at least in preponderating quantities, is shown by the fact that this organ is the first to be involved, and may exhibit a greenish color when other parts of the body are but slightly involved. Microscopically, also, it can be made out that the pigment is present in excess within the liver cells. There is clearly regurgitation or passage of this soluble pigment from the liver into the circulation, and when it passes into the blood it is taken up by and stains the various tissues.

Distribution.—These are effected variously. At a very early stage the bilirubin may be detected in the blood serum, and at an early period also the kidney takes on a distinctly yellow color; for it is by the kidney that the excess pigment of the blood tends especially to be discharged, and it is the convoluted tubules, or certain portions of the same, which take an active part in this process. The cells of these loops are not only diffusely pigmented, but contain yellowish brown granules, which are either granules of inspissated bilirubin, or, by some observers, are thought to be the small granules of the cell deeply pigmented. But clinically, the condition is first noticeable in the sclerotics of the eye, and next in the mucous membrane of the mouth, being more particularly capable of detection over the hard palate. Then the skin becomes

[1] For a discussion upon the fate of the iron liberated from hemoglobin, see also Morishima, Arch. f. exp. Pharm. u. Path., 41:1898:291.

involved, taking on a pale-yellow tinge. From this period onward, upon postmortem examination, it is found that the ordinary connective tissues throughout the body are especially affected. The spleen takes on a pronounced stain, as do also the vessel walls. Certain tissues are relatively unaffected, noticeably cartilage, the cornea, the brain, and nervous tissues (save in the very young). In the brain the perivascular lymph may be relatively deeply stained, but the nervous tissue proper remains colorless. The lungs also are not greatly involved, save where there is intercurrent pneumonia, when the pneumonic areas and the expectoration become jaundiced. The bile pigment passes into several of the secretions; first and foremost is the urine; next in importance is the sweat, whereby the underclothing of the patient becomes stained yellow. The saliva is not unfrequently affected, the milk more rarely; the tears are said to be free from pigment even in the most advanced cases, and, as evidenced by the pale color of the feces in those cases in which there is complete obstruction of the common bile duct, there is very little, if any, discharged from the glands of the stomach and intestines.

The tint of the skin varies according to the intensity and duration of the condition, from pale yellow, through an obtrusive sulphur yellow, to olive green, or, in advanced cases, to a dirty greenish black. In those cases in which the cause of the jaundice passes away, the pigment becomes again discharged from the tissues; but this not immediately; it may be present, slowly fading, for weeks afterward.

Etiology.—What, now, is the exact nature of this process? Are all the conditions we include under the term jaundice due to staining with bile pigment; or, more exactly, is it essential that, when bodies of the nature of bile pigment cause a staining of the tissues, they have been formed in the liver itself? Or, on the other hand, can bodies of this nature be formed by the breaking down of the hemoglobin in the circulation, and thus there be a hematogenous as well as a hepatogenous jaundice? As regards hepatogenous jaundice, how does the bile pigment gain entry from the liver cells into the circulation? Is it discharged or diffused backward from the liver cells, through the vascular endothelium into the portal capillaries; is there a process of distension of the bile capillaries and bile ducts, ending in the rupture of the same into the portal vessels; or does the pigment enter the blood outside the liver by way of the hepatic lymph vessels and the thoracic duct?

We will endeavor to answer these questions, if not in the order here given, at least in such a way as to give a clear indication of their relationship and importance. There can, in the first place, be no question that pronounced cases of jaundice are due to the production of bile pigment in the liver and passage of the same from the liver into the blood, for in these cases not only is the liver the organ which, to the naked eye, shows the earliest and most advanced pigmentation, but the microscopic appearances also fully bear out this conclusion. There is here abundant evidence of the obstruction of the outflow of the bile. *All true jaundice, in fact, is of an obstructive nature*, with regurgitation of pigment and other bile constituents into the circulation. We can distinguish the following:

1. *Obstructive jaundice* pure and simple (hepatogenous jaundice), with no primary blood disturbance. Cases of this order may be due to any one of the many causes which lead to complete or partial obstruction of the bile channels in any part of their course, from the hepatic lobule down to the duodenal papilla; congenital absence or narrowing of the main bile ducts; inflammatory swelling of their walls, with narrowing of the lumen (catarrhal jaundice); growths within the passage; presence of foreign bodies within the lumen, such as gallstones or parasites, enlarged lymph glands, new-growths, or inflammatory cicatrices compressing the bile ducts from without; spasmodic stricture of the ducts. This is, as it were, but the skeleton of the many causes which have been found operative in leading to obstructive jaundice.

In these cases, not only do we have indications of distension of the bile channels and the filling of the same with bile, within the liver, but the liver cells show a diffuse pigmentation, together with the presence of deeply stained masses of pigment. And careful examination in advanced cases shows that this pigment deposit within the liver cells has a definite and characteristic arrangement. As first shown by Nauwerck,[1] of Königsberg, and independently, a few months later, by Fütterer,[2] of Chicago, this pigment lies in and injects a system of intracellular channels which are in direct connection with the bile capillaries. This network encloses the nucleus of the cell, but never enters it.

How, then, does this pigment enter the circulation? The more usual method was first demonstrated by Saunders in 1809.[3] He ligatured the common bile duct, and then was able to trace the lymphatics of the liver, distended with bile, up to their junction with the thoracic duct. It has also been clearly demonstrated by Vaughan Harley.[4] If two dogs be taken, and in both dogs the common bile duct be ligated, and in one, in addition, the thoracic duct be also closed, in the one bile pigment appears in the urine (discharged from the blood) in the course of a few hours; in the other, with the thoracic duct closed, it may be eight or even fourteen days before there is any such discharge.

Clearly, the normal path by which the bile reaches the circulation is by way of the lymphatics. There is here a certain analogy between what occurs in the liver and what has been observed in the pancreas after obstruction of the pancreatic duct. When the pancreatic duct becomes overdistended, the pancreatic juice makes its way into the lymph spaces round about the ducts, and there leads to very definite disturbances. There would seem to be a similar passage out of the distended bile capillaries and ducts into the lymphatics. But, on attempting to repeat Vaughan Harley's experiment, it does not succeed in every case. At times, although the operation has been performed most carefully, bile may appear in the blood and in the urine within a

[1] Deutsch. med. Woch., 1895, and Münch. med. Woch., 1897.

[2] Medicine, Chicago, June and July, 1898.

[3] The Structure, Economy, and Disorders of the Liver, London, 1809.

[4] Arch. f. Anat. und Physiologie, Physiolog. Abt., 1893.

day or two, and Ziegler demonstrated very clearly that, in advanced grades of obstructive jaundice, there may be rupture of the distended bile capillaries into the neighboring bloodvessels. This is probably what occurs in the exceptional cases above referred to. And lastly, there is the possibility to consider, that even within the liver cells there may be a diffusion or reverse discharge of the bile pigment into the blood capillaries of the lobules, and this would seem to be favored by a second series of extremely fine intracellular channels communicating with the blood capillaries. The existence of such was indicated by Nauwerck and, even more definitely, by Browicz; their actual existence and connection with the lobules has been shown by Professor Schäfer, of Edinburgh, in the rabbit's liver. It may well be that reverse currents might thus be set up in the liver cells themselves, with discharge through these fine channels into the blood. But of such a *parapedesis* we have no positive evidence. The prolonged period which may supervene before bile appears in the blood when the thoracic duct has been ligated would seem to contra-indicate any such reversal of secretion, at least in cases of simple obstruction.

2. A second form of jaundice is secondary to extensive breaking down of the red corpuscles in the circulation, with, as a result, overloading of the liver cells and excretion by them of a concentrated or inspissated bile, whereby the *fine bile channels* become blocked, and the bile pigment now makes its way into the general circulation. This we may term, with Afanassiew, *hemohepatogenous jaundice*, or, as it is frequently now termed, *toxemic*. It may be manifested in all those conditions which lend to excessive destruction of the red corpuscles—in acute septic disturbances, for example.

In these cases the jaundice is not so severe as in the preceding group; there is not complete obstruction, the feces remain colored, and the gall-bladder may contain a thick, intensely black bile. Experimentally, the condition can be produced, as Hunter and others have pointed out, by the employment of toluylenediamin and other drugs which set up great destruction of the erythrocytes.

3. A similar grade of jaundice is set up in another group of conditions, namely, in acute yellow atrophy of the liver, phosphorus poisoning, and acute infectious jaundice, or Weil's disease. It is questionable where to place this group. There is here, clearly, an acute toxic condition chiefly affecting the liver cells and not affecting the blood. Probably it should be included in the purely hepatogenous group, for the disturbance or obstruction is in the liver cells themselves, or in the finest capillaries.

4. Lastly, there are cases on record of the rapid supervention of jaundice after severe shock and nervous disturbance. The condition develops so rapidly that it is difficult to suppose that it is due to any spastic contraction of the ducts, and there must either be rapid concentration of secretion, with blocking of the finer channels, or reversed circulation, as already indicated when discussing the intracellular passage in the liver cells.

Urobilin Pigmentation.—We have still to inquire if bilirubin or any allied derivative of hemoglobin can be produced in the circulating blood outside the liver, and this to such an extent that the tissues become pigmented. We know that hematoidin, which, as Neumann has shown, is identical with bilirubin, can be formed in tissues (see p. 882). We know that it has been detected by Naunyn and Minkowski, Löwit, and others actually within the circulating leukocytes. We recognize, also, that in cases of known destruction of the red corpuscles within the vessels—in paroxysmal hemoglobinuria, in pernicious anemia, in hemochromatosis, in hepatic cirrhosis, in sepsis, etc.—the skin is apt to assume not, it is true, a frank jaundiced hue, but at least a distinct tinge, varying from pale lemon yellow to ashen or bluish gray (as in advanced hemochromatosis). Whether we are dealing with one and the same substance in all these cases is, perhaps, doubtful; but it is evident to every clinical observer that in this group of cases we have pigmented changes which appear to form a distinct group by themselves. And in this group of cases, when we come to make postmortem examination, the liver *in general* is not jaundiced, and, when examined microscopically, its cells exhibit no excess of bile pigment. We say "in general," because there is a certain proportion of such cases of more acute type in which the livers exhibit the characters associated with toxemic jaundice. The ordinary septic liver, for example, is not jaundiced, even though the skin be of a lemon tinge; but in some cases of sepsis we have all the indications of an acute hepatitis, with disturbed secretion and accumulation of bile pigment within the cells.

Now, in this group of cases, judging from the blood counts, there is abnormal and continued destruction of the red corpuscles, and the urine tends to be high colored and to contain urobilin, which analysis shows is a modified form of bilirubin, a reduction product of the same, closely allied to, if not identical with, hydrobilirubin (bilirubin = $C_{32}H_{36}N_4O_6$; hydrobilirubin = $C_{32}H_{40}N_4O_7$). While urinary urobilin in some cases may be absorbed from the intestines, and in others directly produced in the liver, it is also admitted that it may be due to production from blood pigment in the organism independent of the agency of the liver.

But, these facts notwithstanding, the accepted teaching of the present day is that all these conditions of pigmentation are also hepatogenous, and that the pigment is derived from the liver. We believe that this teaching is wrong. It is based upon certain apparently most decisive observations of Naunyn and Minkowski (1886) upon the goose, of Stern upon the pigeon (1885), and on other confirmatory observations upon the frog. In these animals not all the portal blood passes through the liver; there is a collateral vessel carrying a portion directly into the inferior vena cava. It is thus possible to close off or extirpate the liver without completely arresting the portal circulation. An animal so treated may, under favorable conditions, continue to live for a length of time sufficient to make observations about its metabolism. Naunyn and Minkowski found that if, for instance, they allowed geese so treated to inhale arseniuretted hydrogen (which ordinarily brings about great

destruction of red corpuscles), no jaundice was set up. And, further, no bilirubin or urobilin was excreted from the kidneys. Hemoglobin alone was discharged. In other words, for the formation of these pigments the liver is indispensable.

The more recent observations by Croftan[1] appear to explain this non-appearance. According to him, the breaking up of hemoglobin to bilirubin within the system is brought about by tryptic ferments in the presence of a carbohydrate (glycogen or dextrose). It is in the liver, he points out, that this combination of ferments with carbohydrate and hemoglobin is most liable to occur. If the liver be removed, any excess of glycogen or carbohydrate within the blood or tissue is immediately utilized. Hence the above experiments do not demonstrate that all bilirubin is formed within the liver. The liver, it is true, is a factor, and, when it is present, bilirubin may be formed within its cells. But it may be formed in other parts of the organism—wherever, in fact, free hemoglobin is present along with dextrose and trypsin. And trypsin has been detected within every organ.

This explanation harmonizes the data in our possession. There may be a true hematogenous pigmentation of the tissues with urobilin derived from hemolysis within the vessels, without any participation by the liver, save that this organ supplies to the blood the carbohydrate necessary for the conversion. This is not jaundice proper; for want of a better term, we may speak of it as *urobilin pigmentation*. If the hemolysis be more intense, then the overstimulation of the liver cells leads to a disturbance of their function, obstruction of the finer bile channels, and regurgitation into the circulation of the bilirubin produced within the liver cells (toxic or hematogenous jaundice). And lastly, and this is the most pronounced form, there is the purely hepatogenous or obstructive jaundice developed without any primary blood disturbances.[2]

OTHER ENDOGENOUS PIGMENTATIONS.

Melanotic Pigmentation.—Of the autochthonous pigmentations not derived from hemoglobin, the most important is melanin. Melanin—or, perhaps more correctly, the melanins, for the divergent analyses suggest that we have to deal with not a single body, but with a group—is characterized by absence, or minimal quantity, of iron and, with rare exception, by relatively considerable sulphur contents.

The variation in the sulphur present is striking; as high as 10 per cent. has been recorded in the melanin from some cases of melanotic sarcoma. Abel and Davis[3] found from 2 to 4 per cent. in that from skin and hair, but that from the choroid of the eye has been found free from sulphur. As regards the iron, it would appear that the more the melanin is purified the less is the amount of iron detectable.

[1] Phila. Med. Jour., 9: 1902: 75 and 142.

[2] For a fuller study of jaundice, Hunter's article in Allbutt's System, vol. 4, may well be recommended.

[3] Jour. of Exper. Med., 1: 1896: 361.

According to Abel and Davis, to whom we are indebted for the most thorough study of the pigment of the negro's skin and hair, melanin granules are insoluble in dilute alkali, dilute hydrochloric acid, alcohol, or other solvents, in the order here named, although after treatment for some days with dilute hydrochloric acid, dilute alkali now causes them to give up their pigment, leaving behind fine shadows of an organic substratum. What is more, these observers detected a definite amount of silicates in the granules, from both the skin and the hair. It exists normally in the choroid coat of the eye, in the deeper cells of the Malpighian layer of the skin, as also in certain cells—chromatophores—of the upper layers of the corium, and is found also in the membranes of the brain, more particularly in the neighborhood of the choroid plexus. Its coloring power is intense. Abel and Davis calculate that the entire skin and hair of the negro do not contain more than 1 gram of the substance. In melanotic growths, however, it is present in great quantities; from the affected liver alone in a case of melanotic sarcoma as much as 300 grams have been gained. It may be recalled that it is not only in the colored races of mankind that it is present in the skin, but in all human beings, with the exception of Albinos, as those are termed who exhibit an inherited lack of melanin formation.

What we regard as the normal production of melanin in members of the human family varies within wide limits, the fair-haired Saxon and the swarthy negro representing the extremes. What we regard as abnormal is, with the one striking exception, not very extreme. A physiological increase in the pigmentation is observed in pregnant women in the increased color of the areolæ around the nipples; this pigmentation, or *chloasma uterinum*, affects also other areas already pigmented, and is most marked in those having already dark skins—brunettes. A somewhat similar pigmentation, but of irregular distribution, is observed in many cases of exophthalmic goitre and certain neurotic states (*melasma*). What is generally regarded as a pigmentation of the same order, and still more marked, is encountered in Addison's disease. But the most extreme abnormal development of melanin is associated with the development of new-growths and of melanotic tumors (see p. 759). Where these are extensive and rapidly developing, there is an escape of pigment into the blood (*melanemia*) and discharge through the kidney (*melanuria*). This excretion may be either of the fully formed melanin or of its chromogen, the urine, at first relatively colorless, taking on a dark-brown color on standing or after treatment with certain reagents. Among the domestic animals, notably the horse, a condition has been described not found in man, namely, a diffuse melanosis in which pigment-containing cells are found throughout the tissues. Such melanosis and the presence of melanotic tumors have been found to affect white and not dark-colored horses.

Von Fürth,[1] to whom we are indebted for the fullest recent study upon

[1] Centralbl. f. Path., 15: 1904: 617; see also v. Fürth and Schneider, Hofmeister's Beiträge, 1: 1901: 229.

the nature of melanin, has brought forward an ingenious and plausible theory regarding the nature and origin of melanin. French observers, more particularly, have called attention to the existence of oxidases within the living tissues, through whose action certain proteins are darkened. It has, for example, been shown that the browning of the cut surface of an apple is due to this process, while, similarly, the conversion of the relatively colorless juice of certain Japanese plants into black lacquer by exposure to air[1] has been found to be due to the presence of oxidases which act upon the tyrosin and other aromatic products of protein decomposition. Experimentally, also, it can be shown that the action of strong acids upon proteids produces a dark-brown substance—"artificial melanin"—which is regarded as produced from the tryptophan, tyrosin, and other aromatic bodies resulting from proteid decomposition by the addition of oxygen. Von Fürth would regard melanin and the melanoid bodies as developed by the action of intracellular oxidases ("tyrosinase") upon the aromatic or chromogen groups of the protein molecule. In favor of this view is the fact that a tyrosinase has been shown to be present in the ink sacs of cuttlefish, the pigment developed in these sacs, sepia, being allied in composition to melanin. And he would regard both the sulphur and iron as combined secondarily. It is somewhat against this view that tyrosin is not one of the products gained from the decomposition of melanin, although indol and skatol are obtained. Indol, therefore, and the allied bodies, rather than tyrosin, would appear to be involved in the process.

Independently what would seem to be a striking support to this view has been adduced by W. L. Halle.[2] He has demonstrated that, under the influence of an enzyme contained in the adrenal, tyrosin is converted into adrenalin. We would point out that it is when the adrenal or its secretion is deficient that the characteristic pigmentation—bronzing—of Addison's disease shows itself. If the above view be correct, that pigments of the melanin group are of the nature of members of the aromatic series of derivatives of the protein molecule, then the bronzing gains its explanation: it is due to the want of conversion of the tyrosin and allied bodies in the relative absence of the adrenal and to their consequent accumulation in the tissues, and we would add that the greater darkening of the superficial parts most exposed to light and air gains its explanation from the more active oxidation of these "aromatic" bodies in these regions.

In the section upon neoplasms the nature of the cells containing the melanin has already been discussed (p. 763).

Melanin, or the melanins, are also the cause of the color of the hair. We do not encounter pathological—as distinguished from artificial—excess of hair pigment, but the opposite condition of loss of pigment—

[1] Vide Duclaux, Microbiologie, 1.

[2] Hofmeister's Beitr., 3 Chem. Physiol. u. Pathol., 8: 1906: 276. I owe this reference to Professor Schäfer's lectures upon the adrenal, Brit. Med. Jour., 1908: i: 1281. These and Dr. Rolleston's address, Montreal Med. Jour., 36: 1907: 671, give an admirable summary of the present status of knowledge regarding the adrenals.

turning gray, or *canities*—is common. According to Metchnikoff, this process is essentially brought about by the increased phagocytic activity of the epidermal cells of the medullary layer of the hair, cells which Metchnikoff terms *pigmentophages*. We cannot but regard this as at most a partial explanation. It may well explain certain cases of loss of color, but some cases of white hair, like leukoderma of the skin, are surely due to failure on the part of the cells of the hair bulb to assimilate or elaborate the melanin. Following von Fürth's theory, it may be suggested that there is in these conditions a lack of intracellular oxidase or tyrosinase, whereby the chromogen or melanogen is not converted into melanin. In this connection it is suggestive that Spiegler[1] has isolated from white hair and wool a body closely related to melanin, which he regards as a white chromogen or melanogen.

Ochronosis.—Possibly allied to the melanins—although its nature is still a matter of debate—is the pigment which, in very rare cases, causes a striking blackish discoloration of cartilages. In the sixties Virchow described the first case noted; since then scarce half a dozen cases have been recorded. The tendons, tendon sheaths, and synovial membranes may also be involved. The pigment is iron-free.

Hansemann's[2] case had associated with it the conditions of melanuria; Hecker and Wolff and Pick have added other cases, if not of melanuria proper, at least of darkening of the urine upon standing; and the latter, in a very thorough study of the condition, comes to a conclusion closely allied to that of Von Fürth regarding melanins, namely, that the pigment in ochronosis is derived from aromatic compounds through the action of tyrosinase.

Lipochromes.—There is a little understood series of colored fatty bodies occurring in normal tissues. In the human body these more particularly give the color to the fat of the organism, and one of them —lutein—is present in considerable abundance in the cells of the corpora lutea. The pigment that accumulates in the nerve cells in advancing life, and under certain pathological conditions, would seem to belong to this order of bodies; as also, according to some observers, that of brown atrophy of muscle cells, though, possibly, in this last case we have to deal with combinations between fat and derivatives of hemoglobin. What is apparently a true lipochrome is the light-yellow, fatty body present in the cells of *xanthomas* (p. 666).

There is yet another form of neoplastic growth—the *chloroma*—in which the characteristic (green) pigmentation is evidently of fatty nature. We have discussed this elsewhere (p. 679), and here would only note that, according to Dock and Huber, the pigment is dissolved by ether and alcohol. On exposure to the air it loses its color.

We have encountered a pale greenish discoloration of a fatty tumor, of another order, not to be mistaken for chloroma proper, namely, in the neighborhood of a trocar puncture into a large abdominal lipoma. The discoloration here was evidently secondary to hemorrhage.

[1] Hofmeister's Beiträge, 4: 1903: 40.

[2] Berl. klin. Woch., 1892; Pick, ibid., 1906: 478.

EXOGENOUS PIGMENTATIONS.

Of the exogenous pigmentations, three main groups are to be distinguished:

1. Colored substance gaining entrance into the organism in a solid state and becoming deposited here and there as collections of colored particles.
2. Colored substances entering in a state of solution, becoming absorbed by the cells of one or other tissue, and so staining them.
3. The colored derivatives or decomposition products of substances themselves not colored, absorbed by the organism.

The most familiar example of the first of these groups is exhibited in the widespread practice of *tattooing*, in which insoluble particles of colored matter—charcoal, vermilion, etc.—are rubbed into fine punctures of the skin in such a way as to produce designs or patterns in varying degrees of crudeness or elaboration. In this way there are deposited in the outer layer of the corium collections of isolated particles. Though the tattoo marks may last a lifetime, they gradually become paler, there being a slow transposition of the particles along the lymph spaces and channels by the agency of the leukocytes. The pigment is always to be found in the nearest lymphatic glands. It is further possible to cause almost complete disappearance of the marks by inducing a cutaneous inflammation of some duration. That inflammation causes an active determination of leukocytes to the part and accelerates the removal of the pigment.

Of more serious import is the group of inhalation pigmentary deposits, the so-called *pneumonokonioses*, deposits in the lung tissue or elsewhese of colored particle inhaled in the form of dust (*κονις*, dust). The commonest of these is *anthracosis*, the deposit of coaldust or of soot, present to a moderate degree in the lungs of every adult town dweller, and present to an extreme grade in the lungs of miners working in the dusty soft-coal mines. These deposits, it is needless to say, are coal black. Of a more grayish color are the deposits of siliceous particles in the lungs of quarrymen and workers in granite and other hard stones (*chalicosis*—*χαλιξ*, a pebble—or *silicosis*). The lungs of knifegrinders, glasspolishers, and others subjected to iron or iron oxide dust, take on a rusty red (*pulmonary siderosis*); workers in the potteries, inhaling kaolin or claydust, obtain similarly dirty white deposits in the lungs (*aluminosis*); workers in tobacco obtain rusty brown lungs from the tobacco dust (*tabacosis*), etc.

By causing animals to inhale air laden with one or other of these dusts, and by studying their lungs at successive periods, as, again, by an examination of sections of the lungs of human beings affected by these disturbances, the process by which the deposits are formed can be well followed. Where the air is full of dust, not all the particles are arrested by the moist lining of the nasal passages and the pharynx. As a result some particles are conveyed into the pulmonary alveoli. Unlike the

bronchi and bronchioles, in that it is not ciliated, the epithelium lining the air sacs is unable to expel these solid particles, which would remain within the sacs were it not for the phagocytic activity of the epithelium and, more particularly, of scavenging leukocytes, which make their way from the vessels into the air sacs. Free cells can be seen in the alveoli laden with these foreign particles. While some of these wandering cells make their way into the bronchioles, and so are discharged with the sputum, others wander back into the lymph spaces of the alveolar wall and from thence to the lymph channels. In either of these positions the leukocytes may break down and the contained pigment be taken up by the endothelial connective-tissue cells of the region; or the breaking-down process, with liberation of the particles, may not occur until the lymph glands are reached at the root of the lungs. It is along the course of the lymph channels that the interstitial deposits mostly occur, namely, in the interlobular lymphatics and in those around the bronchi and the pulmonary vessels. There is also a peculiar liability for the pigment to be deposited where the interlobular lymphatics approach the surface of the lung to join the subpleural network of the lymph channels. As already stated, it can be seen that the endothelium of the air sacs also takes up these foreign particles. What happens to these has not been so clearly followed.

In support of the contention now urged by not a few workers (we think excessively) that pulmonary tuberculosis is most often secondary to the taking up of tubercle bacilli from the intestines, Calmette has recently published observations to the effect that the pneumonokonioses are due not to the direct inhalation of particles into the lungs, but to a swallowing of the same and selective collection of the same in the lung tissue through the agency of the leukocytes. A large number of French and German observers have been thus stimulated to researches on the subject, with the result that Calmette's conclusions cannot be accepted, and the mechanism here laid down has become more surely established.[1]

The foreign particles act as mild irritants. Certain cells of the connective-tissue type seem particularly to take them up, and become, as a consequence, enlarged. Eventually there is a development of new connective tissue in their neighborhood, with fibrosis or interstitial pneumonia. This may be both diffuse and nodular, so that masses of new tissue resembling tubercles may be formed around larger accumulations of the particles. It is noteworthy, in some districts, at least, that these changes are frequently followed by tuberculosis proper, so that a combination of anthracosis, or stonemason's phthisis, with true tuberculosis, is often encountered. Nor are these deposits confined to the lungs. At times, even in the absence of adhesions, they may be observed in the parietal pleura, the pigment having evidently been conveyed by the leukocytes across the pleural spaces. And, in advanced cases, they are to be detected in other organs. Thus, we have encountered clusters of silicious particles with an obscure development of fibrous tubercles around them in the liver of a stonemason.

[1] Vide Calmette, Ctes. rend. Soc. de Biol., 62: 1907: 1050 and previous volumes.

2. The second group, that, namely, of absorption of colored matter in solution, with staining of the different tissues, is of only experimental interest. As first shown by Daddi, certain of the aniline colors, such as Sudan III, used commercially to color waxes and fats in candle-making, when given by the mouth are absorbed, and, gaining entrance to the circulation, they color fat cells *intra vitam*. Recently, in his studies upon trypanosomiasis, Ehrlich has found that trypanroth, given to rats, while destroying the trypanosomes in their blood, at the same time colors the skin and other tissues of the animal a very distinct red.

3. In the third group of pigmented decomposition products the commonest example is a blue line on the gums in cases of chronic lead poisoning. Lead may enter the system either through the *digestive tract*—as in drinking soft water which has been conveyed in lead pipes; through the *respiratory system*, as in a series of cases observed recently in the Royal Victoria Hospital, in which several members of a family became the victims of acute lead poisoning as the result of using old white lead barrels for fuel in a defective stove; or, it would seem, by absorption through *the skin* of workers in lead and lead paints. The blue line, when examined after death, is found to be due to a deposit of fine, brownish-black granules in clusters in the subepithelial connective tissue of the gums. The clusters apparently indicate endothelial and other cells. In those with clean mouths and well-brushed teeth the blue line is often wanting. It is more pronounced at the bases of decaying teeth, or, where the teeth are badly kept, near the accumulations of debris of food at their bases. What happens in these cases is that the sulphuretted hydrogen liberated from the food material diffuses into the tissues of the gums and acts upon the soluble salts of lead which have diffused out of the blood into the lymph spaces of the gums. The granules are a precipitate of insoluble sulphide of lead.

Another metallic deposit is seen in *argyria*. Thirty years or so ago a treatment for epilepsy came into vogue, consisting of rather small doses of silver nitrate. This mode of treatment ceased when it was found that the unfortunate patients assumed an earthy—or unearthly—bluish-gray color, and this of a most unfortunate permanency; for those who have survived their epilepsy and the treatment are today as blue, or almost as blue, as they were at the expiration of a few months. Experiments upon the lower animals to determine the cause of the phenomenon have demonstrated that soluble silver salts given by the digestive tract and absorbed into the circulation pass into the lymph. In the ground substance of the tissues the salts are reduced with the deposit of excessively fine granules of metallic silver. The process, in fact, is the same as that which occurs when we employ silver nitrate to make silver preparations of the tissues for histological purposes. The epithelial and glandular tissues are unaffected; the brain also remains free, but connective tissues are the seat of the deposits, notably the connective-tissue framework of the medulla of the kidney, the papillæ of the skin, the intima of the larger arteries, and serous membranes.

CHAPTER XXXII.

NECROSIS.

Under the term necrosis are included all those conditions of local death of cells, of tissues, and even of parts of the organism composed of many tissues, the organism as a whole continuing to live.

Causation.—All those classes of noxæ, mechanical, physical, chemical (including the bacterial), which may set up disease and cell degeneration, may induce necrosis when they act more intensely upon local cell areas. It will thus be recognized that there are all grades of cell disturbance, from the slighter degenerative conditions, through graver degenerations leading to eventual cell disintegration, to sudden death of the cells and tissues. It is usual to make a distinction between this intermediate form of gradual death, and necrosis in the narrower sense; it is spoken of as *necrobiosis*, and in the discussion of many of the degenerations we have made frequent reference thereto. Every one of the degenerations, if sufficiently severe, induces necrobiotic changes; among these even the physiological atrophies, such as the constant wearing out and death of the outer layers of the epidermis, and the physiological degenerations, such as the fatty changes and disintegration which accompany the formation of milk and sebum.

We have discussed in some detail the various mechanical, physical, and chemical causes of disease in the second part of this work, and there indicated how these may induce cell death. It is unnecessary here to do more than refer to what is there written. It is necessary, however, to refer in somewhat fuller detail to those conditions of necrosis set up by circulatory and nervous disturbances.

Circulatory Disturbances.—Two different orders of disturbance tend to produce cell and tissue death: (1) arrest of blood supply; (2) deficient or perverted quality of the blood, with, as a result, deficient nutrition.

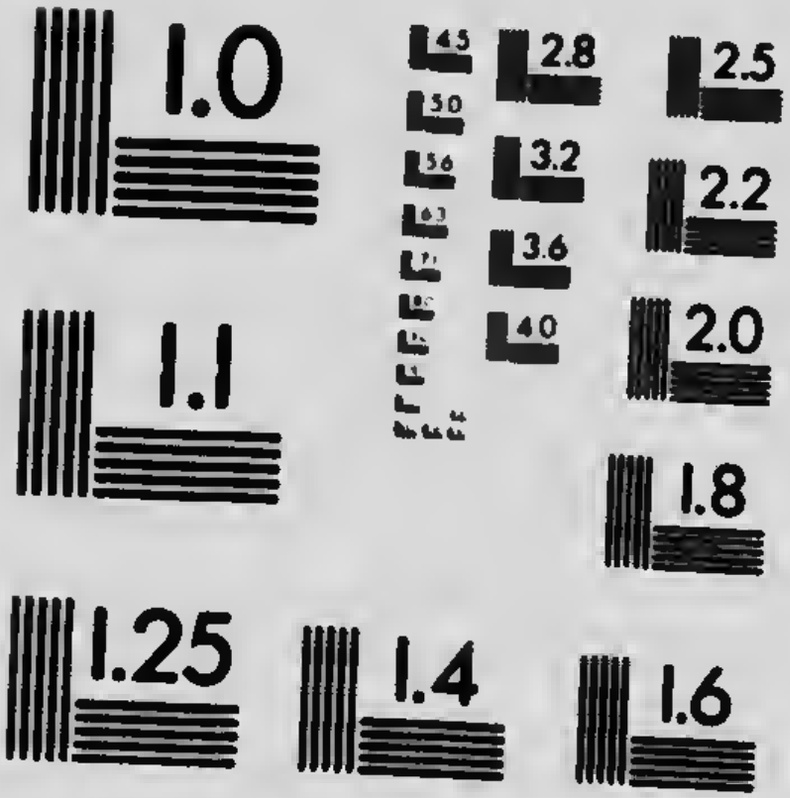
Many orders of local disturbance may cause the arrest of the blood supply to a part—ligation of the nutrient artery; ligation of the efferent veins; pressure upon the vessels by tumors, cysts, etc.; *thrombosis*, or coagulation of the blood within artery or vein; *embolism*, or obstruction of certain types of artery by foreign bodies, which, from their size, become blocked in the course of the vessel; the direct constricting and obliterating action of a poison, such as ergot; lowered action of the heart, so that the pressure within the vessels is unable to propel the blood onward; lastly, actual disease of the arterial wall, with proliferation of the intima, leading to occlusion.

Of these, widely different as are the effects upon the vessels of the

part, occlusion of the afferent arteries and occlusion of the efferent vein both lead to the same death of the tissues of the part; the result is the same whether the blood be cut off from the region, or whether it can pass into the region but cannot leave it. In both cases there is developed a lack of oxidation of the tissues. The subjects of thrombosis and embolism will be found treated in detail in the second volume of this work. Here it is necessary to remind the reader that obstruction of an artery or of a vein only leads to necrosis in those cases in which there is an inadequate collateral circulation; provided that where an artery is blocked nutrition can be gained from blood provided by other arteries, and that where a vein is blocked the blood can drain from a region through collateral veins; a sufficient circulation may be maintained to preserve the vitality of the cells of a tissue or part. It is only where vessels are what is termed absolutely or relatively *terminal* that necrosis ensues; it is only under these conditions that we have developed the state of *infarct*, using this term in its broadest sense, and such infarct may be either *anemic* or *hemorrhagic*. In this connection may be recalled the fact that the infarctous state may be brought about either by arterial obstruction (the more common) or by venous. According as to whether there is sudden obliteration or gradual, so do we have either necrosis or necrobiosis.

Inadequate Nutrition.—Under this heading we include more particularly cases of general malnutrition and cachexia. Associated with these there is weakened heart action and inadequate blood supply. In all these cases the result is not so much a sudden necrosis as a progressive condition of necrobiosis; and in this the different orders of cells react differently; the more highly differentiated cells, such as those of glandular epithelium, are more easily influenced by nutritional disturbances than are the more lowly cells of connective-tissue type. In this way not all the cells of an affected area are necessarily involved.

Nervous Disturbances.—There has been, and there continues to be, much debate as to whether central stimuli proceeding from the higher nervous centres can in themselves induce necrosis, as also whether the removal of nervous influences is a direct factor. There are undoubted cases of impoverished nutrition and local anemia, more particularly of the extremities, which can only be referred to functional or hysterical conditions. In general, it is becoming more and more accepted that, while vasomotor influences, by constricting the vessels of a part, may induce necrosis, loss of nerve supply, while it may lead to cell inanition, does not of itself set up necrotic conditions. To produce these some other factor is regarded as necessary; thus, to cite a familiar example, it used to be held that section of the fifth nerve led to necrosis and ulceration of the cornea, and that there existed a definite condition of neurotrophic keratitis. It is now well established that, after such section of the nerve, provided that the surface of the eye be protected from light and dust and coarser injury, no inflammation and no necrosis show themselves. The section of the nerves supplying a part affords an important *predisposing* but not a direct inciting cause of cell death. A like



explanation is to be given for the so-called perforating ulcers of the sole and other regions associated with Charcot's joint disease and advanced cases of locomotor ataxia.

Here may be recalled what has been stated (p. 802) regarding inanition atrophy and the gradual shrinkage and the gradual death of cells which have been cut off from receiving the normal nervous stimuli. The necrobiosis in these cases is so gradual as to be almost imperceptible. We would not, however, have it believed from the above paragraphs that loss of function does not eventually lead to the death of, more particularly, more highly differentiated cells.

Forms of Necrosis.—It is difficult to make a wholly rational and satisfactory distinction between the forms of necrosis and the resultant changes that take place in a necrosed area. It is, however, possible in the first place to distinguish between (1) the necroses affecting individual cells; (2) those affecting small groups of cells—focal necroses; (3) those affecting circumscribed areas of one tissue—as result of vascular obstruction—infarcts; (4) necroses involving parts rather than tissues—mortification.

FIG. 315

b *a*

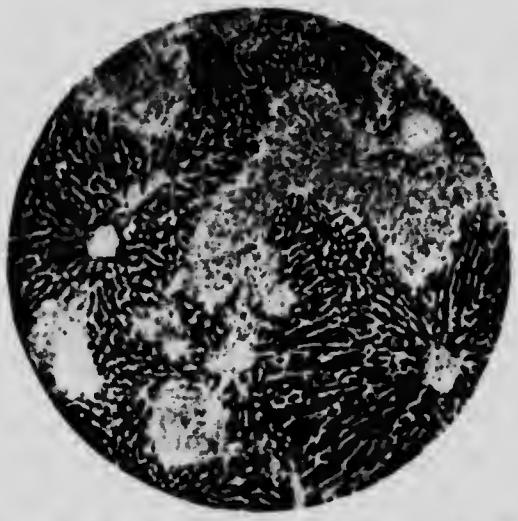
Wax-like degeneration of muscle fibers (*a*, *b*) seventeen hours after temporary ligation of the same. In *b* there is already some accumulation of leukocytes. (Oberndörffer.)

1. **Necrosis of Individual Cells.**—Apart from the conditions of local atrophy and fatty degeneration and necrobiosis which have already been referred to, certain rather characteristic necrotic changes in individual cells deserve mention. Of these, the most characteristic is that known as *Zenker's degeneration*, or waxy degeneration of muscle. In this condition individual muscle fibers are found which have lost all their striation and have become converted into masses of a waxy, almost glassy, appearance, lying within a still intact sarcolemma. The condition is found most frequently in the muscles in typhoid fever, and more particularly, as first pointed out by Zenker, in the recti muscles of the abdomen. This is, however, by no means the only condition; it may be induced in individual muscle fibers by sharp blows, or by trauma; it has been noted in the skeletal muscle fibers in the neighborhood of tumors, as also in the heart muscle in cases of diphtheria (Ribbert). Opinion is divided as to the exact nature of the change; apparently it is of the nature of a coagulation of the muscle substance, a coagulation associated with the death of the same, for the waxy matter may undergo disintegration or absorption, and is not involved in the new regenerative process. Wells and Mathews suggest that the relatively abundant acid

present in muscles leads to a swelling of the coagulated muscle substance similar to that of fibrin under the action of acids.

2. **Focal Necroses.**—More particularly in certain cases of severe infections there are encountered in different tissues minute areas of necrosis scarcely visible to the naked eye. Such, for example, are present in the lymph follicles in diphtheria and typhoid, as, again, after severe burns (Bardeen, J. McCrae). The most common example is, however, seen in the liver in typhoid fever, though similar conditions have been recorded in cases of sepsis, of scarlet fever (Pearce), and even in the more chronic states of tuberculosis and glanders; the most extreme are in the liver in cases of puerperal eclampsia.

FIG. 316



Multiple focal necroses in the liver of a rabbit subjected to experimental glanders. (Duval.)

Experimentally, in addition to injections of sundry bacteria and their toxins, focal necroses of many organs may be produced by abrin and ricin, by the toxic substance present in dogs' blood serum,[1] and by hemolytic agents in general (Pearce[2]).

Studying these cases, it is noted that small capillary areas are involved, and that here the cells in the first stage lose their nuclear stain, undergoing karyorrhexis and chromatolysis. They thus, in stained specimens, contrast strongly with those of the surrounding tissue. Later, there is an attraction of leukocytes to the part, with disintegration and eventual absorption of the dead cells, the appearance suggesting that of early abscess formation. Nevertheless, careful staining for microorganisms shows that in the majority of cases these are characteristically

[1] Flexner, Johns Hopkins Hosp. Rep., 6: 1897: 259.

[2] Journ. of Med. Research, N. S., 7: 1904: 329

absent. Only, to our knowledge, in the focal necroses of tuberculous marasmus has Le Count[1] detected the presence of bacilli, and attributed the condition to the local action of toxins diffused from these. In the allied necroses seen in chronic glanders Duval[2] has found no such relationship.

There has been much debate regarding the mode of causation of these focal necroses—nor can the matter be regarded as definitely settled. The probability is that there is more than one mode of formation. The following solutions have been advanced:

1. *Local* diffusion of toxins by bacteria *present in the tissues.* This as a possible cause is indicated by Le Count's observation, but is clearly the exception, and not the rule.

2. That soluble toxins *circulating* in the blood are directly responsible (Flexner and Opie). It is suggested that stasis of the blood in restricted capillary areas permits these toxins to affect the capillary endothelium, and, diffusing into the tissue cells of this area, produce upon them more severe and fatal effects.

3. That the causation is embolic. Schmorl more particularly called attention to the productions of capillary emboli by placental cells in cases of puerperal eclampsia, and Mallory has demonstrated experimentally that if the spleen of the guinea-pig be compressed so as to drive some of the splenic cells (endothelial) out of the sinuses into the splenic vein (or if active contraction of the spleen be induced by passing an electric current through the upper abdomen), within a few minutes capillary emboli of splenic corpuscles may be obtained in the liver.

4. Thrombotic causation. There is so extensive a collateral circulation in the hepatic capillaries that it is difficult to realize that capillary emboli alone are able to induce focal necroses. And Mallory[3] has suggested, in connection with the typhoidal focal necroses, that the enlarged and proliferated endothelial cells seen in this disease, reaching the liver as emboli, there undergo degeneration and disintegration, lead to the local formation of thrombi extending along the capillaries, arresting the nutrition of the surrounding cells, and so leading to their necrosis.

Studying Dr. Duval's specimens of the liver in experimental glanders, while in some instances we detected what appeared clearly to be capillary cell emboli, in the majority of cases the existence of hyaline capillary thrombi without recognizable cell emboli was very evident.

It is possible that Flexner's and Mallory's theories may be harmonized by the determination that in one series of cases the toxins act directly on the capillary vascular endothelium, and, by destroying it, lead to the development of capillary thrombi; in the other, the thrombus is induced by the disintegration of cells within the capillary lumina.

In a careful examination of some 40 cases at the Royal Victoria Hospital, by Dr. McCrae and Dr. Klotz,[4] they were unable to convince themselves that cell emboli played any active part in association with the

[1] Jour. of Exp. Med., 2: 1897: 657. [2] Trans. Assoc. Amer. Phys., 22: 1907: 398.
[3] Jour. of Exp. Med., 3: 1898. [4] Journ. of Pathol., 12: 1908: 279.

focal necroses; on the other hand, they found frequent evidences of hyaline thrombi.

5. That the thrombi are due to a primary hemolysis. As an explanation of these hyaline masses within the liver capillaries, the more recent observations of Pearce and his associates appear to afford valuable indications. These observations show that the toxins associated with the formation of these necroses exhibit, one and all, a very definite action upon the red corpuscles *in vitro*. Many of them are markedly agglutinative, but, what is more important, the more marked the production of focal necroses, the greater the hemolytic activity of the toxin. Thus, Pearce suggests that hemolysis takes place throughout the system, and that small masses of broken-down erythrocytes become arrested in the liver capillaries, there giving rise to hyaline thrombi. As a confirmation of this view, Benno Schmidt, of Zurich, has recently shown that disintegrated masses of red blood cells can be recognized in the capillaries of the spleen and other organs, and this more particularly in the course of typhoid fever. We are thus inclined to hold that, whereas at times the endothelial and other cells may block the hepatic capillaries, more frequently the focal necroses are due to hemolytic action. It is quite possible that this hemolytic action may be (1) general, from the action of some agent in the circulating blood; or (2) local, the hemolysin being generated or discharged from disintegrating endothelial or other cells.

Fat Necrosis.—The condition of fat necrosis was first described by Balser, in 1882, but to Fitz, of Boston, we owe the first recognition of its intimate relationship to pancreatic disease or disorder, and other observers in the United States (Opie, Flexner, Williams, Wells) have been foremost in establishing our knowledge of the condition and its causes, although to Langerhans is due the credit of first establishing experimentally the relationship.

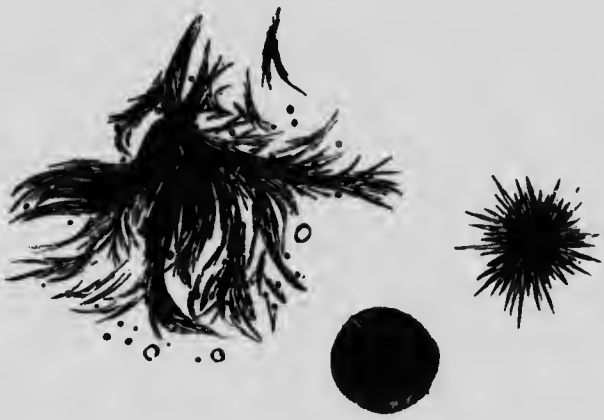
Fat necrosis reveals itself by the striking appearance of opaque whitish yellow areas or islands of small size—a few millimeters in diameter—in the fatty tissues of the organism, standing out prominently against the surrounding more translucent yellow fat or zone of hemorrhagic tissue. Most frequently it is the fat upon and in the immediate neighborhood of the pancreas that is involved. In more advanced cases the omentum, mesenteric fat, appendices epiploicæ, and subperitoneal fat have these little areas scattered through them extensively. In the most advanced cases the mediastinal and pericardial fat are recorded as having been involved.

Microscopically, examining sections which have been frozen and not treated with alcohol or clearing fluid, collections of fat cells are seen having a greatly altered appearance. Their outline may still be determined, but instead of clear contents, many present clusters of "margarin crystals" (a combination of palmitic and stearic acids), while others are filled with a granular debris which, according to Langerhans, is composed largely of calcium soaps detectable by microchemical means.

It is noticeable that frequently the affected fat cells take on little or no stain with osmic acid, although the surrounding normal fat cells assume the usual dense black. As osmic acid stains only oleic acid compounds, this would appear to indicate that the olein, in dissociation, passes rapidly into a diffusible modification, leaving the more insoluble palmitic and stearic acid compounds behind.

If careful examination be made of the peripancreatic fat at autopsies, it is not unusual to distinguish an isolated area or two of fat necrosis, and this in cases affording no history indicative of pancreatic disturbance and showing no obvious lesion of the organ. To these slight cases reference will be made later. But any extensive manifestation of the condition confirms Fitz's observation that there is associated pancreatic lesion. In the majority of cases hemorrhagic pancreatitis is present; not infrequently there is actual gangrene of the organ, which may lie

Fig. 317



Fat crystals (margarin). × 250. (Perls.)

almost dissected from the surrounding tissues. It is deserving of note that suppurative disorders of the organ are rarely accompanied by fat necrosis.

The numerous experiments that have been made upon the subject, from Langerhans onward, demonstrate that the condition is due to the escape into the tissues of the fat-splitting ferment, normally present in the pancreatic juice. Thus, fat necroses have been observed to follow:

1. The injection into the fat tissue of rabbits and dogs of an aseptic infusion of rabbits' pancreas (Langerhans).

2. The introduction into the peritoneal cavity of one animal of pieces of fresh pancreas taken from another (Jung).

3. The ligature of the tail of the pancreas with ligation of its veins (Hildebrand, Flexner, Williams), or by multiple ligatures (Katz and Winkler).

4. The temporary obstruction (20 min.) of the circulation of part of the organ (Blume).

5. Ligation of the pancreatic ducts (Opie).

6. The escape of the pancreatic juice from the divided duct into the surrounding, or into the subcutaneous, fat (Milisch, Opie).

7. Severe injury to the pancreatic tissue, as by injecting into the duct, or the tissue direct, turpentine, artificial gastric juice, etc. (Hlava, Körte, Oser, Flexner).

8. Injection of steapsin (the fat-splitting ferment) into fatty tissue (Flexner).

9. Injection of steapsin plus trypsin (Wells).

The evidence is thus abundant that the pancreatic juice and its constituent steapsin induce fat necrosis. Nevertheless, it has been objected (1) that a remarkably large proportion of experiments fail to produce the disturbance; and (2) that the experimental necroses are not nearly so extensive as those occasionally met with in man. The explanation, according to Opie, is that (*a*) suppurative complications prevent the development; and (*b*) that time is not usually afforded for extensive diffusion of the pancreatic juice. In some of Opie's experiments, in which the animals died or were killed at the end of two to three weeks, necroses as extensive as those in man were obtained. Wells, in addition, doubts whether, under ordinary conditions of experiment, steapsin alone will induce necrosis; there must be coincident action of trypsin.

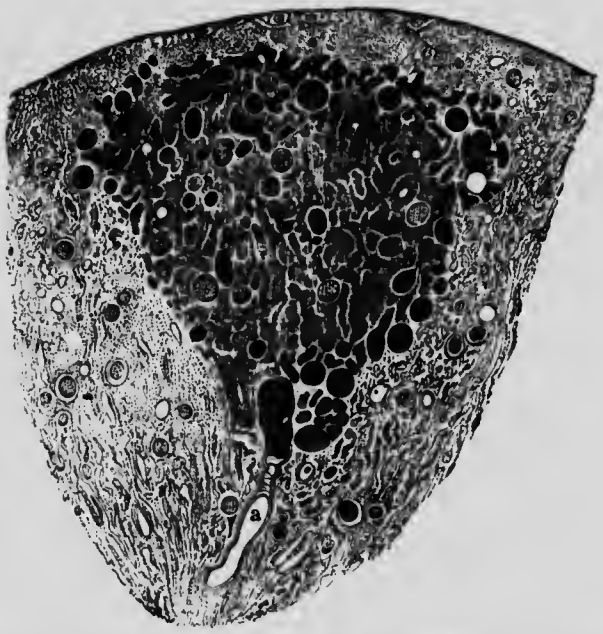
Chiari has afforded what appears to be an adequate explanation for the cases of slight fat necrosis unaccompanied by obvious pancreatic disease. Such constantly exhibit postmortem self-digestion of the organ, and must be due to diffusion outward of the juice from the cells undergoing this form of autolysis into the surrounding fat. He is inclined to the opinion that such self-digestion may at times be agonal. The observations of Opie, Flexner, and Halsted suggest the mechanism whereby hemorrhagic pancreatitis would seem most often to be brought about, namely, by injury to the walls of the duct, or pressure within the duct sufficient to permit a transfusion of the excreted juice into the surrounding tissues, with digestion of the same. Opie more particularly has pointed out that obstruction of the ampulla of Vater by a gallstone, or of the termination of the duct by cancer of the head of the pancreas, reproduces the conditions developed in his experiment. Similar obstruction of larger and smaller ducts may be induced by chronic interstitial pancreatitis.[1]

Infarcts and Coagulation Necrosis.—The mode of formation of infarcts, their relationship to embolism and thrombosis, and the varieties, will be discussed in the second volume. Here only must be taken into account a characteristic form of necrosis which accompanies some, but not all, cases of infarct formation, a form to which

[1] For a fuller discussion of this subject with literature, see Opie's Diseases of the Pancreas; Wells' Chemical Pathology, Lippincott, 1907, gives the more recent literature.

Weigert gave the name of *coagulation necrosis*. The condition is best seen in anemic infarcts of the kidney and spleen; the affected areas become firm, pale, and relatively swollen, in the early state projecting distinctly above the surrounding surface. Under the microscope the nuclei have wholly lost their chromatin, and the cells have a hyaline appearance, with loss of sharp outline, the whole area appearing to be converted into a solid, somewhat homogeneous mass, as though coagulated uniformly. In some cases, by the use of Weigert's fibrin stain, actual fibrin can be recognized, laid down here and there in filamentous form. The comparison may be instituted between this con-

FIG. 318



Anemic infarct of cortex of kidney to show coagulation necrosis, with surrounding zone of congestion; a, artery. (Orth.)

dition and thrombus formation, in which the coagulation of the blood, while often leading to the production of a fibrinous network, may also be of the hyaline type, with coagulation or conglutination *en masse*. Weigert regarded the process as essentially of the nature of a fibrinous coagulation, the dying cells liberating a fibrin ferment, the lymph and fluids of the area, together with the cell bodies, affording substances of the nature of fibrinogen. That the whole mass of cells forming the infarct becomes a mass of fibrin may well be doubted. Rather we must admit that blood fibrin is but one of a group of coagulated proteins, and compare the process with what obtains in muscle in Zenker's degeneration, where the myosinogen becomes converted into coagulated

myosin (p. 900). The process, it may be noted, does not attack all tissues, as might reasonably be expected were it the result of reaction between the protein-containing fluids diffusing into those tissues and enzymes liberated in the death of the cells. Anemic infarcts of the brain do not exhibit it, but instead, a form of colliquative necrosis.

Colliquative Necrosis.—Two distinct processes are often confused under this term, namely, *colliquative necrosis* proper, due to the liquefaction of the dead tissue as a process of self-digestion unassociated with any bacterial decomposition, and *putrefactive necrosis*, due to a not dissimilar liquefaction brought about by the proteolytic activities of bacteria. The latter we shall refer to later. Colliquative necrosis proper can only be regarded as autolytic in nature; the dead area softens, the cells undergoing a granular disintegration, with production of myelin, fat, cholesterin, etc. It is well seen, as above noted, in connection with infarcts (both anemic and hemorrhagic) of the brain. A fluid granular debris is the result, containing a certain number of migrated leukocytes, which become engorged with fat in the form of small fatty globules, forming large characteristic granule cells, or Gluge's corpuscles. Some of these migrate into the tissue immediately surrounding. According as there is more or less blood present and involved in the necrotic area, so do the fluid contents assume different colors (see p. 882).

Similar colliquative necrosis occurs in other tissues and conditions apart from obvious circulatory disturbances, though in all cases, strictly speaking, we deal with a primary cutting off of the blood supply to the affected areas. The atheromatous softening of the deeper layers of the intima in one stage of the arteriosclerotic process is of colliquative type. A similar colliquative necrosis may involve the central parts of tumors and lead to eventual falling in and umbilication, or to cyst formation (see p. 7[illegible] also, old standing thrombi, more particularly the sessile th[illegible] heart cavities, undergo a central colliquation, and may be [illegible]y a shell of fibrin inclosing a turbid fluid.

Caseati[illegible] connection another type of necrosis may be noted, in which [illegible]osed a[illegible] exhibits neither coagulation nor colliquative change, but, undergoing a slower necrobiotic change, the cells exhibit a change akin to fatty degeneration, become granular, and break up into fatty granular debris, in which no sign of the earlier cellular structure can be recognized. The area thus becomes converted into a mass of the appearance and consistence of a rather dry cream cheese; hence the term caseation. The change characteristically occurs in connection with tuberculous new-growths. Tubercles are, from their mode of development, extravascular; but the cutting off of the blood supply, while tending to produce necrobiosis and necrosis, would not produce this special type of change. That must be attributed to the action of the tuberculous toxins and their effect upon the cells. Through inspissation of pus, produced by other bacterial agents, we occasionally encounter similar caseous accumulations.

Gummata.—That toxins are factors is indicated by the fact that gummata, or syphilitic tubercles, which, histologically, are of closely allied

formation, although due to the presence of microbes of very different type, do not exhibit caseation proper. Their necrotic centres, while showing, similarly, no trace of cell structure, are "gummy" rather than caseous. There is not the same abundant fat present. Beyond this little is known of the exact constitution of the gummatous necrotic matter.

Mortification and Gangrene.—The death of large areas of tissue and of parts composed of many tissues may be brought about by very many causes: by vascular obstruction and arrest of the blood supply to a part, or of the outflow from a part; by enfeebled circulation; temporary stoppage of the circulation of a part or organ, as in Litten's experiment on the kidney (p. 855); acute infection (as, for example, phlegmonous cellulitis, hospital gangrene, and emphysematous gangrene, due to the growth of B. Welchii); by burns, intense cold (frostbite), action of chemical agents (caustics and acids), and of physical (electricity, *x*-rays, radium).

The Results of Necrosis.—This description of the different forms of necrosis prepares us to find that the results vary widely. (1) Where the necrosed area is small and there is no infection, *absorption* occurs. By autolysis the cells undergo disintegration and more or less solution. Leukocytes attracted to the area, by their phagocytic activity aid the process, and not only may there be absorption, but this may be followed by regeneration. Even where the necrotic process has been very extensive such regeneration may tend to show itself, as, for example, in those cases of very extensive necrosis of the liver cells which are met with in acute yellow atrophy and chloroform poisoning, in which the specific cells of the liver are in the main involved. In such cases where death has not been brought about within a few days, proliferating liver cells can be recognized advancing into the spaces left by the autolysis and dissolution of the preëxisting liver cells.

(2) More often, where the area of dead tissue is a fair size, and where, again, there is no infection, we encounter a *cicatrization* as the result of organization. This is especially well seen in the latter stages of the non-infected infaret. The death of the cells and diffusion outward of their products of disintegration leads to the production of a surrounding zone of inflammation, with well-marked congestion of capillaries and migration of leukocytes into the dead area. As in the previous case, these leukocytes reinforce the autolytic processes and aid in the removal of the dead matter, but with this the surrounding capillaries send new vascular loops into the region, and what is truly a granulation tissue is developed, which gives place eventually to well contracted cicatricial fibrous tissue. A similar process of organization is the end result in many cases of intravascular coagulation of the blood and thrombosis.

(3) Where, as in the brain, the tendency is toward colliquative necrosis, there the end result of the autolytic process is *cyst formation*, rather than organization and cicatrization, though small necrotic foci in the cerebellum may give place to a complete organization.

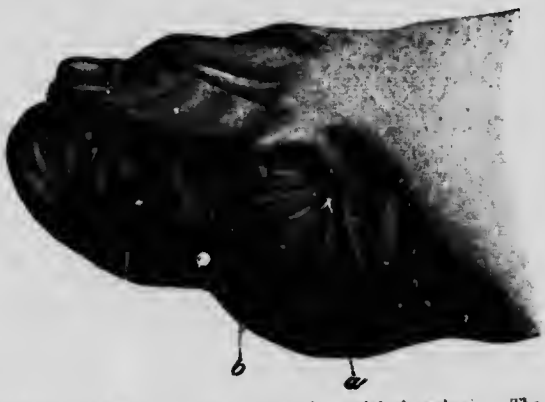
(4) Where, as in bone, the tissue is so dense that disintegration of the

dead matter is a long-drawn-out process, there, through leukocytic action more particularly, the surface portions of the dead area may be disintegrated and loosened from the surrounding more healthy tissue, and in such cases the still unabsorbed necrosed mass remains as a *sequestrum*, lying in a more or less well-defined cavity or tract, and bathed in a fluid of purulent nature.

(5) Another sequel to colliquative change is *inspissation*, the fluid portion of the dead material draining away, leaving thus a more or less cheesy accumulation. Indeed, in caseation proper, as seen in tuberculosis, there is a certain grade of inspissation present. Such cheesy, inspissated matter is especially prone to become the site of calcification (p. 854).

In the condition of gangrene, according to the extent of blood entering the dead part from the vessels, and the rate of evaporation of fluid from the surface, so do we have developed either the condition of (6) *moist*

FIG. 319



Senile gangrene of the great toe, from a case of arterial thrombosis. The toe is shrunken and its epidermis is being exfoliated. At the line of demarcation the skin has retracted (*a*) and the deeper parts are separating (*b*).

gangrene or *sphacelus*, or of (7) *mummification* or *dry gangrene*. It is in the extremities and the ears that the latter condition alone can show itself. The necrotic portion becomes shrunken, wrinkled, and assumes the dark brownish-black color, the appearance, in short, of mummy flesh. As in an infarct formation, so here, at the zone of junction of the dead and living tissue, there develops an intense zone of inflammation, the so-called *line of demarcation;* and, as in infarct formation, leukocytes passing beyond this aid in the solution of the dead matter, whereby the mummified and living matter become separated and the former becomes eventually detached.

Where, as in the lung and the intestine, and in the extremities of those cases in which blood is still able to enter the dead area, evaporation cannot take place, there, on the contrary, the dead matter becomes waterlogged, and inevitably putrefaction sets in, through the entrance from

the surface of various microbes. The appearance in these cases is striking; the affected tissue becomes greatly swollen and livid; on the skin large blebs may form filled with œdematous fluid; the discharge from such blebs becomes foul and stinking through bacterial growth; through the same putrefactive agents the blood corpuscles become broken down, and their pigment becomes diffused through the tissues. So, also, the various soft tissues become decomposed and deliquesce, a foul fluid resulting, filled with fatty globules, pigment, and various products of proteolysis.

Both in dry and in moist gangrene any bony portions involved are the last to undergo decomposition.

CHAPTER XXXIII.

DEATH.

In this life of ours, with all its uncertainties, there stands out one certainty—that we shall die. Sooner or later death comes to all men. It is as inevitable as that on this rotating world of ours night follows after day; nor can any care on our part, any precise regulation of the course of our days—can science or prescience—ward it off for more than a few years. There is no *elixir vitæ*.

This supreme fact has profoundly affected all human thought, and has been the pivotal point of all philosophies; nay, more, the various religions of the world may be regarded as the evidence of man's determination to rise superior to the dissolution of his body. Mere philosophy, however, cannot tell us why death is inevitable; we can only find an explanation by the study of living matter and its attributes. Making such a study, it is seen that death is not inherent in living matter as such; that it is the price paid for advance and increased power over Nature. For death is not inherent in the constitution of the simplest unicellular organisms. With such relative constancy of environment as Nature provides—within the natural limits of heat and cold, of dryness and moisture—the schizomycete microbe assimilates and grows and divides, and if, over long periods of time, the environment undergoes slow change, the property of adaptation, to which we refer at length in our opening chapters, permits the organism to adjust itself surely to the new conditions. At each division each half carries on the flame of life. There is in such a process no inherent death; at most, there may be accidental death by temporary lack of nutrition, by desiccation, by physical and chemical bactericidal agents in general. In like manner, with unicellular organisms higher in the scale, death is only apparent; when, for example, the nuclear matter of the hematozoon of malaria undergoes division and becomes distributed into numerous spores, and those spores break away, leaving behind a collection of fine pigment granules and debris to represent what had been the previous single individual, there is to the eye, it is true, a cessation of individual existence, but in reality the living matter, far from being dead, is, on the contrary, increased in amount, and is given the occasion to increase itself still farther. There has been no destruction of the nucleoplasm, the essential living matter, but a multiplication of the same; each spore carries on the life.

It is with the appearance of the metazoon, of the multicellular organisms, that natural death enters into the world. Multicellularity connotes division of labor among the component cells, specialization of function

and increased capacity of the individual as a whole. Certain cells, the germ cells, become set apart to carry on the living matter which shall develop into new individuals. In these germ cells, then, death is not inherent. It becomes inherent in the somatic cells, and this through the functional differentiation that they have undergone. An ideal cell republic might be imagined, in which the division of labor and function among the constituent cells was so allotted that each nourished and contributed to the exact needs of the other, all developing their powers simultaneously. In such a case there would be no need for somatic death. As a matter of fact, this ideal state has not been attained, nor, under the conditions of development, is it even possible. The individual, that is, undergoes growth and development, and this process of growth demands that different orders of cells are required to be mature and active at different life periods. Herein, it seems to us, is the essential explanation of somatic death.

Take, for example, the case of man himself: Even in the embryo, organs are developed—such as the yolk sac—which are of merely temporary use; they perform temporary service until other parts are developed which are of greater value; and when they become useless, their cells tend to atrophy and disappear; a new equilibrium has to be established. And so, throughout fœtal life there is constant change in the relationship and interaction of parts. Of all embryonic and fœtal organs of active function which have this temporary character, the placenta stands out preëminent. Postnatal existence affords abundant examples of the same order. The individual tissues have periods of development to full activity and maturity *which are not synchronous.* Some, like the heart and kidneys, are fully functional before birth; subsequent increase in size and activity are of the nature of adaptations to the increased work thrown upon them by the growth and increase of the body in general. Others, like the thymus and the lymphoid tissues of the organism, are at their maximum in the early years of life, and already show diminution and atrophy before the adult state of the organism as a whole has been attained. Others, like the brain, attain their full anatomical development in childhood. Yet other organs and tissues lie latent, showing little signs of development for years. Such are the genitalia and accessory organs of generation, the mammary glands, etc., and these, again, like the ovaries, may, from purely physiological causes, have a period of active life shorter than that of the organism as a whole.

If these various organs in the performance of special functions not only extract from the blood the materials necessary for their growth and nutrition, but afford internal secretions to the same which are of definite service to other tissues and to the organism as a whole, it will be seen that the atrophy and disappearance of the same induces not only loss of special function, but leaves the blood and remaining active tissues impoverished in one or other direction. Up to a certain point there may be an internal adaptation; it would seem there is always a tendency thereto, other tissues taking on certain of the functions of those that have

disappeared. But, at the same time, this assumption of additional activity throws additional strain upon them and brings the still active cells nearer to the margin of their reserve force, nearer to the point at which these in turn become exhausted and undergo atrophy.

By such processes of continually modified equilibrium and of increased strain thrown upon the surviving cells and tissues the period is reached at which disintegrative changes in the organism exceed the assimilative, at which, also, the reserve force of the surviving cells becomes diminished, and in this way inevitably the time is reached when sundry cells, unable through loss of this reserve force to respond to stimuli, bring about the condition of somatic death. As Bichat long ago pointed out, most of the tissues and even parts of the organism may be destroyed and yet life still persist. There is, however, a triumvirate of organs—the circulatory, the respiratory, and the nervous—each one of which is indispensable, and any one of which, if injured in particular regions, alone may bring about the state of somatic death. The researches of the last half century, and more especially of the last few years, have impressed upon us that other organs play an almost equal part. While those which for the race are of the foremost importance—the ovaries and testes—may be removed without in any way influencing the span of life of the individual whose "by-play," to quote Sir Michael Foster, may still continue, certain small and hitherto little regarded organs cannot be removed without death being the inevitable result. Such are the adrenals, the minute parathyroids, and, as Paulesco, Harvey Cushing, and others have shown within the last few months, the yet smaller pituitary body. Insignificant in size, as it is, remove this last and death (at least in the laboratory animals so far tested) supervenes within forty-eight hours.[1] The results are not so immediate, it is true; but in physiological death, such as that here suggested, it must be that certain cells in one or other of these fail to react, and so bring about arrest of function and cessation of life.

Rarely do we encounter this natural death—the passing of the quiet sleep of exhausted old age imperceptibly into death. More frequently in those who have attained great age what happens is that the resisting and protective powers of the organism more particularly show signs of exhaustion, with the result that sundry pathogenic organisms normally present upon the surface of the body, but normally prevented from gaining entrance into the tissues through the agency of the protective cells, eventually, despite slight virulence, gain entrance into the tissues, multiply, and set up a *terminal infection*. Such terminal infections are the immediate cause of death not merely in old age, but in all the states of progressive disease with progressive sapping of the reserve force of the individual. It is the prevalence of the terminal infections that gives force to Dr. Osler's dictum, that the individual rarely dies of the disease

[1] As Schäfer and Herring point out, the active portion of the pituitary is not the posterior neuroglial lobe, but the anterior with its contained glandular vesicles, and it may be also the glandular *pars intermedia*. (Herter Lectures, Baltimore, April, 1908, not yet published.)

from which he suffers, save, it may be added, when that disease is in itself of the nature of an acute infection.

We have thus to recognize two orders of death—the *physiological* and the *pathological;* of the latter the terminal infection is the most common cause, though there are abundant others that will lead to the same end. Just as it has been pointed out that all the causes of disease may lead to local cell death when acting with a certain intensity, so, without exception, acting with greater intensity or acting directly upon one of the three vital organs, mechanical, physical, chemical, and bacterial agents may induce somatic death.

This somatic death may briefly be described as the cessation of function of the three vital organs, followed by the signs of disintegration and decomposition of the tissues in general. It is difficult to describe the state otherwise, inasmuch as it is not necessarily accompanied by the immediate death of all the component cells of the body.

Examples confirmatory of this statement are abundant and familiar. The head may be cut off a snake and the body for long continue to wriggle actively. We have ourselves seen the heart of the tortoise removed and a strip of the cardiac muscle still exhibiting spontaneous contractions eight days after such removal.[1]

The so-called "ueberlebendes," cat's heart, or mammalian kidney wholly removed from connection with the body, will similarly, under favorable conditions, continue to function for hours. Perhaps the most striking example of all is the epidermis removed from a dead animal, or, again, human epidermis cut off from any skin surface, if kept in the dark in a cool and moist place; even after several weeks, if placed upon a granulating surface, this has been found capable of growth and of the formation of new skin.

The Signs of Death.—These are discussed fully in text-books of medical jurisprudence; here it is but necessary to refer to them briefly. They are many in number, and from a medico-legal point of view are of different value as affording indication of the period that has elapsed since death occurred. Among the more important may be mentioned:

1. Cessation of respiration, so that a cold mirror held in front of the nostrils does not become moistened and dulled.

2. Stoppage of heart beat. Neither this nor the preceding are absolute signs, as it has been shown experimentally that after poisoning a dog with chloroform until both heart and respiration have stopped, transfusion of saline fluid or defibrinated blood under pressure may be followed by resumption of the heart beat and gradual recovery. They are, however, the first signs for which one looks. They are corroborated by—

3. Loss of transparency of the cornea. The pupils usually dilate at the moment of death; the eyes stare directly forward; the cornea in a short time becomes cloudy.

4. The development of *rigor mortis*. Of those parts of the body which can be observed and studied without section, the eyelids are the first to pass into a state of rigidity with contracture, leaving the eyes to

[1] This in Dr. Gaskell's laboratory at Cambridge, in 1884.

remain open. According to Fuchs, the heart ventricles are the first muscles to become rigid, and certainly in those cases in which a post-mortem is performed within an hour or two after death, the ventricles are constantly found firmly contracted, so as to suggest to those ignorant of this rapid rigidity the presence of the so-called "concentric" hypertrophy. There is great variation, however, in the period of onset of this change in the muscles of the body. In those engaged in active and violent exercise, it may be practically coincident with death. Strychnine poisoning and tetanus also exhibit rapid rigidity. On the other hand, prolonged wasting conditions, with muscular atrophy, may exhibit a rigidity only showing itself after many hours; the same is true in cases of death from asphyxia and hemorrhage. The duration of the rigidity also varies very greatly.

The nature of the rigidity would appear to be that of a coagulation of the *myosinogen* of the normal muscle, *myosin* being the term given to the coagulated product. This coagulation would appear to be brought about chiefly by the lactic acid of the muscle. The passing off of the rigor mortis would appear to be due to development of autolytic changes.

5. *Cadaveric Lividity.* Through gravitation of the blood to the dependent capillaries, the under or lower parts of the dead body show within a few hours a livid reddening, or, where the blood is more venous, a bluish-purple color. Where there has been cyanosis with great distension of the superficial capillaries before death, as not infrequently happens in the vessels of the face and neck where death has occurred from asphyxial disturbances, a similar, and even more intense, lividity may be present over surfaces that are not dependent. Where there is pressure, as upon the nates and over the shoulder-blades, the mere weight of the body prevents the filling of the capillaries, and such regions of pressure remain pale.

6. *Decomposition and Putrefaction.* Decomposition of the organs shows itself most frequently first over the abdomen, as a greenish discoloration. The onset is very variable, it being delayed or completely arrested by great cold and materially hastened by warmth. Those organs and parts which normally are moist and contain abundant bacteria exhibit the putrefactive changes earliest; thus it is that the intestinal canal is most markedly affected. There are, however, other factors: Cases of acute infection and of bacteremia are especially apt to early decomposition, not merely, it would seem, through the action of the specific pathogenic organisms, but because in the course of the infection the protective substances of the organism have been exhausted, and there is no inhibition to the growth of putrefactive bacteria. A similar rapid decomposition has been noted after snake poisoning, in which, also, there is a rapid destruction of antibodies. Arsenical and certain other intoxications may very materially delay the onset.

Other slighter signs of death are:

7. Relaxation of sphincters; and

8. Loss of tissue elasticity. The latter would seem to be largely due to solidification of the subcutaneous fat, so that the position assumed by the surface tissues at the moment of solidification tends to become fixed.

APPENDIX.

APPENDIX A.

PROTEIN NOMENCLATURE.

REFERENCE has been made (p. 820) to the recommendations of the two Committees upon Protein Nomenclature.[1] The provisional recommendations of an American committee, appointed by the American Society of Biological Chemists and the American Physiological Society have appeared while this volume has been passing through the press. These are very similar to the earlier English recommendations, but more precise. We print them here, as they give succinctly the modern views regarding protein constitution, relationships, and nomenclature.

The recommendations are as follows:

First: The word *proteid* should be abandoned.

Second: The word *protein* should designate that group of substances which consists, so far as at present is known, essentially of combinations of *a*-amino acids and their derivatives, *e. g.*, *a*-amino acetic acid, or glycocol; *a*-amino propionic acid, or alanin; phenyl-*a*-amino propionic acid, or phenylalanin; guanidin-amino valerianic acid, or arginin, etc., and are therefore essentially polypeptids.

Third: That the following terms be used to designate the various *groups of proteins:*

I. **Simple Proteins.**—Protein substances which yield only *a*-amido acids or their derivatives on hydrolysis.

Although no means are at present available whereby the chemical individuality of any protein can be established, a number of simple proteins have been isolated from animal and vegetable tissues which have been so well characterized by constancy of ultimate composition and uniformity of physical properties that they may be treated as chemical individuals until further knowledge makes it possible to characterize them more definitely.

The various groups of simple proteins may be designated as follows:

(*a*) *Albumins.*—Simple proteins soluble in pure water and coagulable by heat.

(*b*) *Globulins.*—Simple proteins insoluble in pure water, but soluble in neutral solutions of salts of strong bases with strong acids.[2]

[1] See also Jour. of Physiol., 34: 1907: xvii for the British recommendations.

[2] The precipitation limits with ammonium sulphate should not be made a basis for distinguishing the albumins from the globulins.

(*c*) *Glutelins.*—Simple proteins insoluble in all neutral solvents, but readily soluble in *very* dilute acids and alkalies.[1]

(*d*) *Alcohol-soluble Proteins.*[2]—Simple proteins soluble in relatively strong alcohol (70 to 80 per cent.), but insoluble in water, absolute alcohol, and other neutral solvents.[3]

(*e*) *Albuminoids.*—Simple proteins which possess essentially the same chemical structure as the other proteins, but are characterized by great insolubility in all neutral solvents.[4]

(*f*) *Histones.*—Soluble in water and insoluble in very dilute ammonia, and, in the absence of ammonium salts, insoluble even in an excess of ammonia; yield precipitates with solutions of other proteins and a coagulum on heating, which is easily soluble in very dilute acids. On hydrolysis they yield a large number of amino-acids, among which the basic ones predominate.

(*g*) *Protamins.*—Simpler polypeptids than the proteins included in the preceding groups. They are soluble in water, uncoagulable by heat, have the property of precipitating aqueous solutions of other proteins, possess strong basic properties and form stable salts with strong mineral acids. They yield comparatively few amino-acids, among which the basic amino-acids greatly predominate.

II. **Conjugated Proteins.**—Substances which contain the protein molecule united to some other molecule or molecules otherwise than as a salt.

(*a*) *Nucleoproteins.*—Compounds of one or more protein molecules with nucleic acid.

(*b*) *Glycoproteins.*—Compounds of the protein molecule with a substance or substances containing a carbohydrate group other than a nucleic acid.

(*c*) *Phosphoproteins.*—Compounds of the protein molecule with some, as yet undefined, phosphorus-containing substance other than a nucleic acid or lecithin.[5]

(*d*) *Hemoglobins.*—Compounds of the protein molecule with hematin or some similar substance.

[1] Such substances occur in abundance in the seeds of cereals, and doubtless represent a well-defined natural group of simple proteins.

[2] The British committee recommends for this class the less cumbrous name *Gliadins*, after the principal member of the group.

[3] The sub-classes defined (*a*, *b*, *c*, *d*) are exemplified by proteins obtained from both plants and animals. The use of appropriate prefixes will suffice to indicate the origin of the compounds, *e. g.*, ovoglobulin, myoalbumin, etc.

[4] *Scleroproteins* of British report. These form the principal organic constituents of the skeletal structure of animals and also their external covering and its appendages. This definition does not provide for gelatin, which is, however, an artificial derivative of collagen.

[5] The accumulated chemical evidence distinctly points to the propriety of classifying the phosphoproteins as conjugated compounds, *i. e.*, they are possibly esters of some phosphoric acid or acids and protein. The British committee in their second report take exception to this and would class casein and its allies with the simple proteins on the ground that the cleavage products still contain phosphorus.

(*e*) *Lecithoproteins.*—Compounds of the protein molecule with lecithins (lecithans, phosphatids).[1]

III. **Derived Proteins.**—1. *Primary Protein Derivatives.*—Derivatives of the protein molecule apparently formed through hydrolytic changes which involve only slight alterations of the protein molecule.

(*a*) *Proteans.*—Insoluble products which apparently result from the incipient action of water, very dilute acids or enzymes.

(*b*) *Metaproteins.*—Products of the further action of acids and alkalies whereby the molecule is so far altered as to form products soluble in very weak acids and alkalies but insoluble in neutral fluids.

This group will thus include the familiar "acid proteins" and "alkali proteins," not the salts of protein with acids.

(*c*) *Coagulated Proteins.*—Insoluble products which result from (1) the action of heat on their solutions, or (2) the action of alcohols on the protein.[2]

2. *Secondary Protein Derivatives.*[3]—Products of the further hydrolitic cleavage of the protein molecule.

(*a*) *Proteoses.*—Soluble in water, uncoagulated by heat, and precipitated by saturating their solutions with ammonium sulphate or zinc sulphate.[4]

(*b*) *Peptones.*—Soluble in water, uncoagulated by heat, but not precipitated by saturating their solutions with ammonium sulphate.[5]

(*c*) *Peptids.*—Definitely characterized combinations of two or more amino-acids, the carboxyl group of one being united with the amino group of the other, with the elimination of a molecule of water.[6]

APPENDIX B.

IS INTERCELLULAR SUBSTANCE TO BE REGARDED AS LIVING MATTER?

THE long-established conception of the constitution of the multicellular organism is that it is of the nature of a community of individual cells

[1] Omitted by British committee on the ground that the nature of these bodies is not yet determined, whether true chemical combinations or adsorption compounds.

[2] The British Committee object as regards (*a*) and (*c*) that they see no object in singling out for special mention a few of the infinite varieties of insoluble modifications which proteins exhibit.

[3] The term secondary hydrolytic derivatives is used because the formation of the primary derivatives usually precedes the formation of these secondary derivatives.

[4] As thus defined, this term does not strictly cover all the protein derivatives commonly called proteoses, *e. g.*, heteroproteose and dyspiroteose.

[5] In this group the kyrins must be included. For the present we believe that it will be helpful to retain this term as defined, reserving the expression peptid for the simpler compounds of *definite* structure, such as dipeptids, etc.

[6] The peptones are undoubtedly peptids or mixtures of peptids, the latter term being at present used to designate those of definite structure.

which remain united for mutual benefit. This *communal*, or, as the Germans term it, "*Baustein*" (building-stone), theory has more particularly during the last ten years received considerable criticism. It is unnecessary to repeat our objections or to quote again the "decentralization" theory propounded on p. 34. But it is to be noted that there are those whose opposition strikes deeper, and, indeed, is directed against the very being of the cell theory. The most recent and fullest attack is by Professor Martin Heidenhain,[1] of Tübingen, whose elaborate work upon *Plasma und Zelle* has come into our hands too late to notice in its proper place, but whose views are so much opposed to those here expressed, and whose reputation as a cytologist is so great, that his contentions must be noted.

As Heidenhain points out, the cell theory, as usually expounded, demands that all living matter is concentrated within the cell. If, therefore, it can be demonstrated that there is living matter in the multicellular organism which is external to the cell boundaries, then the theory, if not wholly upset, demands very material modification. Forthwith he proceeds to demonstrate that the fibrils of white connective tissue, the fibers and sheets of yellow elastic tissue, the matrix of cartilage, and the lamellæ of bone—all of them extracellular in their completed form—are actually living matter. According to him, these exhibit metabolism, growth, formative energy, and perhaps, also, a definite grade of functional activity. The fibrils of connective tissue and the coarser deposits of elastin in yellow elastic tissue begin in general within the cell. This we freely admit. Later they come to be extracellular and freed from the cell body proper; they increase in length and also in bulk. A similar origin is upheld for the cartilaginous matrix; that, according to Schaffer, begins as a modification of the ectoplasm of the cartilage cells, and as the cells shrink and this modified ectoplasm, derived from one cell, fuses with that of neighboring cells, so does the matrix become a homogeneous mass in which are embedded what are now sharply defined cells. Nay, in this matrix is also living matter of another order, since study shows running through it fine fibrils of connective-tissue type. The living matter of the bony matrix, he admits, has not been the subject of adequate study, but that it exists he has no doubt.

To this it may be replied with, I think, considerable force:

1. That, from a chemical and physical point of view, the albuminoids, and scleroproteins, which form the characteristic constituents of matricial matter—collagen, elastin, and chondrin—are of all the proteins of the body the most inert; in characters they are most nearly allied to the coagulated proteins, which are obviously "dead;" that, knowing their insolubility in various reagents, and the difficulty with which they are dissociated, it requires a severe stretch of the imagination to conceive these bodies as possessed of the power of recurrent satisfaction and dissatisfaction, which has been pointed out as the prime attribute of living matter.

[1] Plasma und Zelle, Part I, Fischer, Jena, 1907.

2. That, physiologically, interstitial matter is strikingly inert, exhibiting nothing that we can regard as a direct reaction to irritation; what reaction shows—dissolution, etc.—is obviously determined by the enclosed cells, *i. e.*, it is in the immediate neighborhood of cells showing obvious reaction that changes are first to be noted in the matrix as the result of irritation.

3. That because the fibrils, the cartilaginous matrix, etc., show their earliest signs of development within the cell body, that does not, *ipso facto*, make them living matter, any more than intracellular fat globules are to be regarded as living matter.

4. That, as regards actual growth of the connective and yellow elastic fibrils upon which Heidenhain lays so much emphasis, we obtain, as Leo Loeb has shown (see p. 391), "growth" of a curiously similar type outside the body in lymph or blood subjected to strain. When a drop of uncoagulated lymph is placed between two glass slides, the mere act of pulling the one slide over the other leads to the appearance of fibrils, which grow in length and bulk; which, like those of connective tissue, are not only intracellular, but actually traverse cell bodies situated in their path; which show themselves first in immediate connection with these cells, the cells, as we now hold, liberating an enzyme that determines the modification of the more soluble protein into a precipitated or coagulated modification. But the lines of this precipitation are evidently along the lines of strain. And so identically do we observe that the direction of the individual connective-tissue fibrils in a tendon, a fascia, etc., bears a direct relationship to the strain to which the tissue is habitually exposed.

5. That if cartilaginous matrix is to be regarded as living, then also the hyaline and amyloid deposits in pathological conditions are to be regarded as living. But among these we have every transition to conditions of deposit in successive layers, to conditions clearly of precipitation, and not of growth by intercalation or progressive building up of new molecules in immediate association with the old; the process is of a passive, not an active type; nay, more, as Ophüls has shown, it may take on the type of deposit of successive layers of needle-like crystals of hyaline matter.

In his *Cellular Pathology* (1858, p. 23), Virchow laid it down that the intercellular substances had not life of their own, "but borrowed or obtained vital properties at second-hand from the (associated) cells." Heidenhain, with justice, points out that here is a basal mistake. The concept of life is that it is something inherent, something automatic. There is no such thing as one individual instilling or breathing life into inanimate matter. Nevertheless, Virchow, despite his illogicality, was, it seems to me, nearer the truth than is Professor Heidenhain. We come back, that is, to the problem stated but not answered on p. 65—a problem which, so far as I can see, Heidenhain does not touch upon, namely, what is to be our primary postulate regarding the essential distinguishing property of living matter. If we lay down that it is growth—is the inherent power of assimilating other molecules, of so

arranging them as to build up like proteidogenous molecules, possessing, therefore, like properties—then it must be held that intercellular substances have not this property, and are not living. If, on the other hand, we declare that growth is not essential, and recognize three orders or grades of living matter, then, with Virchow, we can well admit that the cells discharge living molecules of the order of enzymes which act upon and modify the surrounding matrix. But in this case it is not the matrix itself that is living, as claimed by Heidenhain, but the discharged cell molecules, which act upon substances present in the surrounding lymph. And it has to be admitted that molecules of the same order acting within the cell can similarly act upon assimilated substances of the same order, and lead there to the production of the like precipitum.

APPENDIX C.

NUCLEOLAR MATTER, AND ITS RELATIONSHIP TO CELL ACTIVITIES.

In the description given of the histology of the cell little stress was laid upon the presence of the nucleolus or nucleoli, and this—to be honest—because when that chapter was written I was not prepared to make definite statements regarding the function thereof. To have given the various conflicting theories regarding nucleolar function would have tended only to confuse the student. At most, attention has been drawn from time to time (pp. 29, 40, 41, and elsewhere) to the discharge of nucleolar matter into the cytoplasm in connection with certain cell activities. Those conflicting theories still exist, but of late so many observations have been published calling attention to nucleolar changes, that it is timely to indicate what would seem to be the trend of these studies.

Briefly, it may be stated that the nucleoli are spherical bodies, apparently fluid or colloidal, and exhibiting no structure; at most, the peripheral and central portions may stain with different intensity. They vary greatly in size; in some orders of cells they are single, in others multiple. They may be of relatively great size; thus, in the oocyte of *Antedon bifida* (a crinoid "starfish"), the single nucleolus may be half the diameter of the nucleus (Chubb). Or, on the other hand, there may be multiple minute nucleoli situated at points of intersection of the chromatin network. Of these, there may be as many as 300 (Montgomery: unicellular glands of *Piscicola*). Whatever theories they may hold regarding their function, all recent observers agree in recognizing that they are intimately related to the chromatin. Thus, as M. Heidenhain points out, they are absent from the feebly staining nucleus of the young cell immediately after cell division, but grow *pari passu* with the development of the nucleus and appearance of increased chromatin. They are not

chromatin proper, that is, in general they take on a differential staining with nuclear dyes; at times, however, while showing no trace of organization, they take on the same stain. The main opposing views (1) that they are waste products of chromatin activity (Häcker); (2) that they supply nutriment to the chromatin (Flemming, Bambeke, Korschelt, Lubosch); (3) that they are the means through which the unorganized

Fig. 320

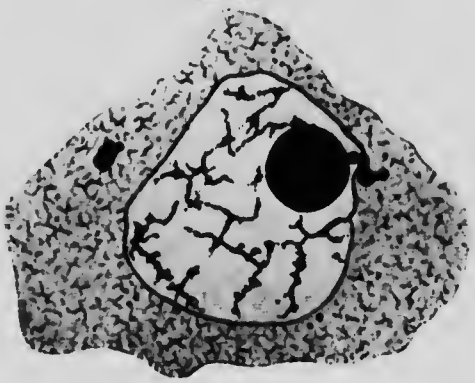


Fig. 321

Fig. 322

Developing eggs of *Antedon bifida*, showing extrusion of nuclear matter.

Fig. 320.—Young oocyte, the nuclear chromatin in the form of scattered branching threads. The deeply stained nucleolus is at In the act of extruding spherules into the cytoplasm. (× 2000.)

Fig 321.—Nucleolus from an adult egg, showing discharge of nucleolar spherules from the unstained area of the nucleolus into the nuclear substance. (× 1000.)

Fig. 322.—A relatively young oocyte, showing discharge of spherules from the unstained area, with accumulation of spherules previously discharged to form first stage of the "yolk nucleus"—*yn;* other spherules scattered through the cytoplasm. (× 1000.) (Chubb.)

chromatin assimilated from the cytoplasm is converted into the organized chromatin of the nucleus (R. Hertwig); and (4) that they represent the dissociation product, rich in albumin but devoid of phosphorus, of the nucleo-albumins taken up from the cytoplasm to provide the nucleoproteins of the chromatin (M. Heidenhain[1]). All these may be har-

[1] For bibliography, see Chubb, Phil. Trans. Roy. Soc., B. 98: 1906: 447, and M. Heidenhain, Plasma und Zelle, p. 212.

monized by regarding the nucleolus as store or reserve material, from which, on the one hand, assimilated material is withdrawn to provide (by dissociation) the chromatin needed by the growing or regenerating nuclear network, and to which, on the other hand, are passed the products of chromatin degeneration or disintegration. We must, that is, accept for the nucleus as far the cytoplasm, the general principle noted repeatedly in these pages, that protein matter tends to pass through identical stages and present like intermediate products in the opposed conditions of integration and of disintegration.

Chromatin, as such is not discharged from the nucleus, save in the rare cases of aberrant mitosis, as in cancer cells, when aberrant chromosomes may become free in the cytoplasm. What is discharged is this intermediate nucleolar matter. This is clearly the outcome of the more recent studies. Any statements to the contrary contained in the main body of our work must be modified to this extent. This admission, however, in no wise invalidates our contention that the nucleus supplies matter which is of controlling influence in the development of the specific granules and secretions of the cell body. Only we must realize that it accomplishes this through the intermediation of the nucleoli.

On the ground that in the course of his long and exact studies upon the cell he has never determined this passage of nucleolar or of nuclear matter out into the cytoplasm, M. Heidenhain strenuously denies that the nucleus plays any part in the secretory activities of the cell. He considers the nucleus as the conservative agent in the cell, unconcerned in the specific cell activities, but carrying on the specific cell properties from one generation to another.[1] Our discussion of the cell from every aspect, chemical, physiological, and morphological, will show that we cannot accept this view. The abundant observations of other microscopists—botanists, zoölogists, and pathologists—upon nuclear extrusions must, we think, overbalance the personal experience of even so excellent and experienced a cytologist as is Professor Heidenhain.

Of such discharge of nucleolar matter numerous instances may be afforded over and above those cited in the text of this work. More particularly attention may be called to the studies of Montgomery,[2]

[1] Macallum has recently (Royal Society of Canada, Ottawa, May 1908) enunciated somewhat similar views regarding the colloidal nuclear membrane as a protective mechanism whereby the manifold substances present in the cytoplasm are prevented from diffusing into the nucleus and so from acting upon the nuclear matter, which thus is conveyed from cell to cell with the minimum of change in constitution and properties. With this view I am largely in sympathy. Nevertheless, the active growth in size of the young nucleus, and the variations undergone in the course of cell function indicate that the nuclear matter is far from being inert: that if some orders of substances cannot pass through the nuclear membrane to affect the chromatin there are others that are diffused and assimilated with great readiness. The nucleus in short is not merely the (inert) bearer of inherited properties but in addition exerts throughout the life of the cell certain orders of activities, both anabolic and katabolic.

[2] Journal of Morphology, 15: 1898.

upon *Pisicola*, in which the discharge is extreme; of Chubb, on the oocytes of the crinoid, *Antedon;* and especially to the researches of R. Hertwig[1] and his pupils on nuclear discharges in certain protozoa, and their relationship to the development of pigment granules of melanin-like nature in the cytoplasm; this in certain abnormal states of the cell (see also p. 765). Hertwig calls attention to the frequent presence of *chromidia*, *i. e.*, of minute particles of chromatin-like nature present in the cytoplasm and derived from the nucleus, or present as a fine filament or network in the immediate neighborhood of the nucleus. Both he and Goldschmidt describe discharges from the nucleus giving origin to this chromidial matter, which appears to be identical with the *mitochondria* of Benda,[2] seen in spermatocytes and oöcytes.

Here a final word may be said regarding the relationship of these plasmosomes or chromidia to the development of secretory granules in the cytoplasm. Reading the various descriptions of the various observers, one feature stands out in a striking manner. With scarce an exception, it is noted that the granules which, when first extruded, and in the immediate neighborhood of the nucleus, take on a stain approximating to that of the nuclear material, as they pass outward into the cytoplasm lose that stain, while farther outward there appear the specific globules taking on their particular dye or other properties. They may, in fact, wholly disappear as such, becoming swollen, fused, and modified into such intracytoplasmic accumulations as the "yolk nucleus" of the ovum (see Fig. 322), or the "archoplasm" of sperm and other cells, described by the cytologists. The obvious conclusion is that the nucleolar matter is not directly converted into the specific granules; that, on the contrary, there is an interaction between the nucleolar granules and certain specific cytoplasmic or paraplasmic substances, and that thus *it is the interaction between nuclear and cell body substance that gives origin to the specific secretions.* Here it may be noted that prevalent opinion among pathologists at the present time is with Farmer, Walker and Moore[3] and Greenough[4] to regard the Plimmer's and "pigeon-eye" bodies seen in cancer cells, and with Ewing[5] and Guarnieri, Councilman and Calkins to regard the vaccine and small-pox bodies, not as parasites but as modifications of this archoplastic matter of nucleolar origin. A very clear statement of this point of view profusely illustrated has been given by Borrel.[6]

[1] R. Hertwig, Arch. f. Protistenkunde, 3: 1902; Sitzungsber. d. Gesellsch. f Morphol. u. Physiol., 18: 1902: 77; and Festschr. f. Ernst Haeckel, 1904: 301: see also Gerassimow, Beihefte z. Botan. Centralbl., 18: 1904, and Goldschmidt, Biol. Centralbl., 24: 1904, and Arch. f Protistenk., 5: 1904.

[2] Verhandl. d. physiol. Gesellsch. z. Berlin, 1896-97, and 1899-1900.

[3] Proc. Roy. Soc., B. 76: 1907.

[4] Journ. of Med. Research, N. S., 8: 1905: 137.

[5] Ibid., 8: 1905: 233.

[6] Bullet. de l'Inst. Pasteur, 5: 1907: 497

APPENDIX D.

THE ACCESSORY CHROMOSOME AND ITS BEARING UPON SEX AND HERMAPHRODITISM.

THE evidence is steadily accumulating in favor of McClung's hypothesis (p. 258), that sex is determined by the presence of an accessory chromosome, either in the spermatozoon or the ovum. In close upon sixty species of insects, Professor E. B. Wilson,[1] the foremost upholder of this hypothesis, has now determined the existence of two numerically equal classes of spermatozoa, differing constantly in the number of their chromosomes, the difference involving the members of one, or, in a few cases, two or three pairs. In insects that produce a series of parthenogenetic generations (Aphides and Phylloxerans), and in which the fertilized eggs produce females only, while the parthenogenetic ova produce both males and females, Professor T. H. Morgan[2] has shown that the production of the one sex only is associated with the fact that the spermatozoon with the fewer chromosomes is so small and contains so little cytoplasm that it degenerates without attaining full development; there is thus only one order of active spermatozoa, and all the fertilized eggs become females. As regards the males and females produced parthenogenetically—without fertilization—Morgan has made the remarkable discovery that the *somatic* or tissue cells of the male individuals in the species studied contain only five chromosomes, whereas those of the female contain six. At some period, therefore, in the life cycle of the parthenogenetic eggs one chromosome disappears in those eggs that become males. There are thus conditions under which the ovum, and not the spermatozoon, determines sex.

So far, these researches have been carried on mainly with insects, and it is not unnatural that there has been doubt as to whether we might not be dealing with a particular case, obtaining in this order only. Now that Correns has demonstrated that the like is true as regards the pollen and ova of dioecious plants, *i. e.*, of the ordinary flowering plants, it would seem obvious that we deal with a phenomenon of wide occurrence —so that we become justified in suggesting that hermaphroditism is based upon aberration in the distribution of the chromosomes in either ovum or spermatozoon, or (in lateral hermaphroditism) in the first blastomeres.

[1] Proc. Soc. for Exp. Biol. and Med., 5: 1908: 55. [2] Ibid., p. 56.

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