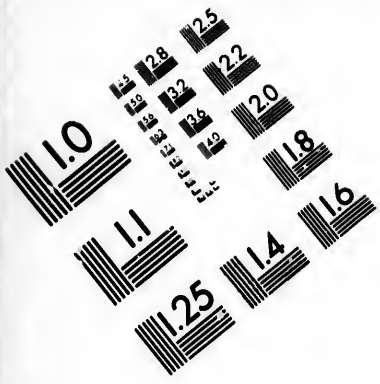

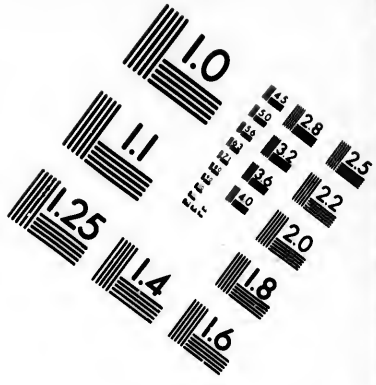

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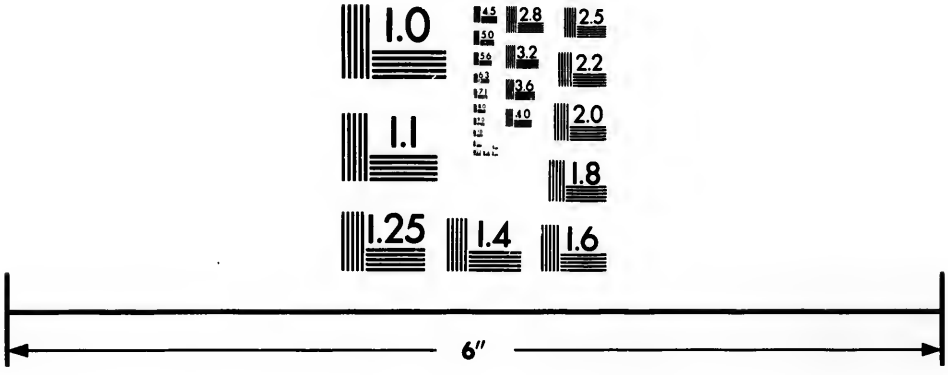

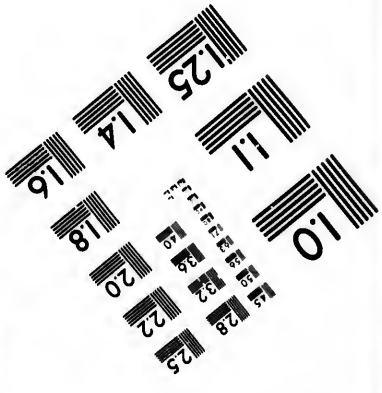

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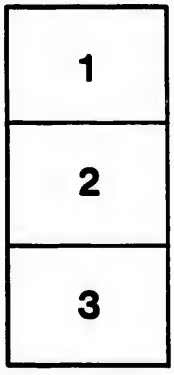

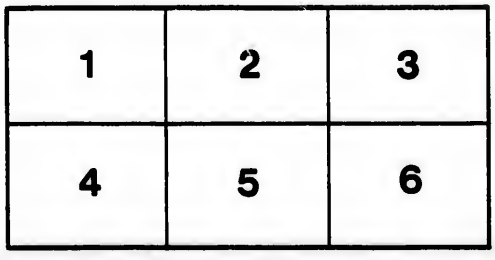

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ON THE RELATIONSHIP BETWEEN INFLAMMATION AND SUNDRY FORMS OF FIBROSIS.

BY

J. GEORGE ADAMI, M.A., M.D. (CAMB.),

Professor of Pathology, McGill University, Montreal.

BEING THE MIDDLETON GOLDSMITH LECTURES FOR THE YEAR 1896, DELIVERED BEFORE THE PATHOLOGICAL SOCIETY OF NEW YORK, AND REPRINTED FROM THE MEDICAL RECORD OF MARCH 14TH AND 21ST, AND APRIL 4TH AND 11TH.

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MIDDLETON-GOLDSMITH LECTURES[1]—ON THE RELATIONSHIP BETWEEN INFLAMMATION AND SUNDRY FORMS OF FIBROSIS.

By J. GEORGE ADAMI, M.A., M.D. Camb.,

PROFESSOR OF PATHOLOGY, M'GILL UNIVERSITY, MONTREAL.

Mr. President and Gentlemen: I cannot proceed to the delivery of these lectures without in the first place extolling the beneficence of him through whose regard for this society and generosity it has been made possible for you to institute this series of lectures—of him whom thus you are bound to keep in ever green remembrance. And in the second place I owe it not only to you but to myself to give utterance to my very sincere gratitude for the honor done me in inviting me to attempt to fill a position in which already the great pathologists of this continent have one after the other added new leaves to their laurels. For myself I cannot hope to vie with my illustrious predecessors. I can but exceed them in appreciation of the honor done to me, and through me to the city and university of my adoption. I feel acutely your kindness in thus inviting to deliver these lectures one who is a stranger among you, one who as yet can scarce feel himself other than a stranger to this continent. For my university it does not need that I should be specially empowered to announce to you how, striving toward higher things, that university appreciates and is encouraged by every act of recognition from the larger world.

It might, perhaps, sir, be expected by that larger

[1] Delivered before the New York Pathological Society.

world that I should here make due and telling reference to my presence among you at the present epoch. I am inclined to think that when the universality of science and our common brotherhood in it are so obvious to all of us, and the insistence thereupon is to us so much of a truism, it were almost an insult to your intelligence and good will did I say anything, however much I may personally appreciate your kind invitation at this especial juncture. The most I dare venture is to express the fervent wish that the same fellowship may bind together the nations which now unites all those striving after good works in all branches of science.

Throughout the days of this generation, and to an increasing extent in these latter days, there has been and there continues to be a lively discussion as to what is and what is not to be included in the scope of inflammation. And as of late among a narrow sect of surgeons or surgical pathologists there has been manifest the revival of what, were I a theologian, I should denominate a (not unqualified) heresy, but what, as a pathologist, I prefer to describe as, in my opinion, a serious misconception, I have thought it well, not only from the interest excited by the subject in our body but also from the recrudescence of this misconception, to select as the subject of these lectures this matter of inflammation and the relationship existing between it and fibrosis or fibrous hyperplasia in its various forms.

Even at the best this is a subject involved in difficulties. How involved I did not wholly realize until some months ago I was called upon by my friend, Prof. Clifford Allbutt, of Cambridge, England, to discuss the matter succinctly in the course of an article upon the "Pathology of Inflammation in General," and was forced to face the matter straightly. As I doubt not, most here present have found it is one thing to have general opinions, another to place them in

logical sequence upon paper. When I came to attempt the latter, and again to consult the accounts given in the leading articles and text-books, I discovered not only the inconsequential nature of many of my previous views but also that most of what had already been written read like the writing of scribes rather than of those having authority; and after having written the article or section of an article already referred to I cannot but feel that what is there stated merits the same reproach, and since the manuscript left my hands the more I have deliberated the more dissatisfied have I felt over my own writing. I am glad to have this opportunity to revise and advance my views upon the subject, and even before the article in question is published to amend it and carry to a more logical conclusion the treatment of the principles upon which the article is based. I cannot hope to solve all or any of the problems that a study of this relationship between inflammation and fibrous-tissue growth opens up; at most, suggesting rather than dictating, I may possibly help others toward solution and may indicate the lines along which future research would seem to promise satisfactory results.

We are accustomed to employ the termination "itis" with the prefix "chronic" in almost if not quite every case in which there is replacement of the cell elements proper of a tissue by new fibrous-tissue growth. That is to say, we assume all these conditions to be of like origin, to be manifestations of chronic inflammation, or as the attempt at repair following upon acute inflammation.

Fibroid areas in the heart muscle are all grouped together under the convenient term of chronic interstitial myocarditis. Fibrosis of the valves of the heart with its sequelæ we speak of as chronic endocarditis. Arteriosclerosis is indifferently spoken of as chronic arteritis or endarteritis. Whatever the form of fibroid change occurring in the kidney, it

comes under the heading of chronic interstitial nephritis. In the case of the liver it is true the conveniently non-committal name of cirrhosis is in English-speaking countries the term most usually employed to denote fibroid change, yet there are not wanting those who speak of chronic interstitial hepatitis.

I might similarly pass in order organ after organ of the body, with its chronic "-itis." Lax indeed is the employment of this common denomination of chronic inflammation, and its sole merit is its convenience in cloaking our ignorance of the exact causation of most of the conditions to which it is applied. In these lectures I wish to discuss how far and in what cases we are justified in the employment of the term, and to what extent the development of fibrous tissue in the more noble organs of the body is the result of inflammatory disturbance.

In such a discussion everything depends upon the definition of inflammation which is found acceptable, and the conclusions reached must stand or fall in the exact ratio in which the definition enunciated commends itself to other workers. Thus, first, it will be absolutely necessary for me to state clearly and distinctly what I understand by the term "inflammation."

Two courses, it seems to me, and only two are open to us with regard to our appreciation of the term. Either we can, with Thoma, agree that it is so unsatisfactory and that the discussions which have arisen as to its scope, or, more truly, as to the processes that are rightly to be included under the term, are so barren and profitless that we decide absolutely to expunge it from our vocabulary; or, on the other hand, we must determine to include in our idea of inflammation all processes having a like origin and tendency. There is no logical intermediate course unless it be to confine the term strictly to its primitive meaning and to determine that there can be inflammation only where there is "flaming," where there is redness and

heat. No one is prepared nowadays to take this course, for this necessitates physiological active congestion of a superficial organ being considered as inflammatory. Nor again are there many who, wedded to tradition and cardinally virtuous, with Celsus only see inflammation when rubor, calor, dolor, and tumor are present. For these cannot deny that identical processes may occur when one or two or more of these cardinal symptoms are wanting. Thus, nowadays, those who would define inflammation etymologically are non-existent, while the partisans of tradition are "minished and brought low," forming a small and an impossible remnant. Hence, to return to my previous statement, there are but two logical courses open to us. Can we accept the first alternative and banish the idea of inflammation? I trow not—the suggestion is too quixotic. It is not within the power of any workers in any one branch of our science, even if that branch be pathology, to expunge at will a term of universal employment, a term that has come down to us through the ages—a term which, however loosely and variously employed, does nevertheless for all cover a greater or less number of processes of common occurrence. We cannot in a widespread science suddenly create a "tabula rasa" and start anew. Just as were we to do away with the plutocracy and start equally endowed with worldly possessions, while in twenty years the old plutocratic families would perchance be non-existent as such, yet the amassing of money and possessions in the hands of a few would inevitably be manifested, so were we to banish "inflammation" from our vocabulary, in the same time or even less some other word would be surely in common employment to denote the same idea. It cannot be done, and as a consequence the adoption of the second alternative is our only practical course.

We have, that is to say, so to employ the term that it will embrace all processes having a like origin and

like import. Thus, then, starting from the generally accepted basis that the process is in its essence local and that the prime cause of all inflammations is injury to the tissues, if we are prepared to admit that one common or allied train of results follows upon all injuries, we must as our provisional definition state that inflammation is the series of changes constituting the local reaction to injury.

This is to all intents and purposes Burdon-Sanderson's definition and is that which for the last quarter of a century has been most generally accepted. For myself I cordially accept it as a good working definition; but at the same time I cannot but consider that the researches made since 1880 have materially added to our comprehension of the phenomena associated with the process and of their tendency, and permit us now to acknowledge the import as well as the origin of the process. Those researches have shown us that a very definite meaning is to be attached to the main vital processes which follow injury to a part. They have proved that the accumulation of leucocytes in the injured area is purposeful; that, whether by intra- or extra-cellular action, these cells are capable, up to a certain extent, of counteracting the irritant and of removing dead and effete material; they have satisfactorily proved that the inflammatory serum possesses both digestive and bactericidal powers greater than the serum of the circulating blood; they have demonstrated that the migration of the leucocytes into the inflammatory area is not a passive process, but an active one directly dependent upon the extent of the stimulus exerted upon these cells by chemical alterations in their environment; they have demonstrated that the amount of fluid exuded into any one region of the body varies *inter alia* directly according to the intensity of the irritant—the more intense the irritant the greater the extent to which it is diluted; while, further, the part played by the fixed cells in the im-

mediate neighborhood is equally evident and equally purposeful, tending manifestly to result in the cutting off of the damaged area from the surrounding healthy tissue and again to replace the tissue that has undergone destruction. Hence I am impelled to define inflammation as the local attempt at repair of injury, or, more fully, inasmuch as there is a certain small class of cases in which all the symptoms of inflammation are present as a consequence of nervous disturbance wholly unassociated with previous local injury,[1] as *the series of changes which constitute the local attempt at repair of actual or referred injury to a part.* So that needless objections be not raised, let me emphasize the fact that I do not regard inflammation as synonymous with repair. Attempt at repair and repair are two very different things, and no more to be confounded than attempted suicide and suicide, or, not to approach too closely to a very delicate subject, than the Emperor William's recent telegram to the Boers and actual war between two considerable European nations.

This, then, is the definition I am inclined to lay down. Save in the small matter of the wording, I do not claim any originality, for others in different lands have given forth definitions embracing the same idea. Thus Neumann, in Germany, defines inflammation as "the series of local phenomena which are developed in consequence of primary lesions of the tissues and which tend to heal these lesions."[2] Bland Sutton, in England, is somewhat more restricted. "It is," says he, "the method by which an organism attempts to

[1] The most striking example of this class is to be seen in the experiment which has been frequently repeated, among others by my colleague, Dr. James Stewart, of assuring a susceptible individual under hypnotic influence that the hand or other region has been burned or blistered, when within a very short period the part becomes reddened, swollen, and, it may be, the seat of marked serous effusion.

[2] Ziegler's "Beiträge," v., 1889, p. 347.

render inert noxious elements introduced from without or arising within it."[1] I doubt whether Sutton is right in speaking of it as a method and to me the larger view appeals, not simply of counteraction against the irritant but also of attempt to bring about a return of the region toward a functional condition—but the definition contains the same recognition of the purposive nature of the process. And lastly, here at home, Councilman acknowledges the same. In his most lucid article in Dennis' "System of Surgery" he defines inflammation as "the sum of the phenomena which take place in the tissue as the effect of an injury. The object of these various phenomena is to overcome or to diminish the effects of the injury."[2]

Whatever justice there might have been a few years ago in the objection that this view of inflammation is teleological, now, with the facts at our disposal, the objection is no longer valid. As well may the statement that the function of the heart is to propel the blood into the arteries be condemned as teleological, or objection be taken to the statement that digestion is the series of processes whereby matters received into the alimentary tract tend to be converted to the uses of the tissues of the body. We are ready enough to admit the deductions drawn from physiological experiments; we must equally accept the results of experimental pathology.

But the definition here enunciated is altogether too broad for many to accept, and ever since Hüter propounded the view that the term inflammation ought to be restricted to those conditions in which there is infection by micro-organisms, with pus formation, there have not been wanting adherents of the narrower view. And as what is to follow must largely stand or fall according to the acceptance of the definition herein set

[1] I here quote from Professor Senn, not having been able to discover the original passage.

[2] Dennis' "System," vol. i., 1895, p. 144.

forth, and inasmuch as this confounding of infection and pyogenesis with inflammation appears to be growing more and more popular upon this continent, I needs must for a short time discuss the propriety and soundness of the movement.

I do this, sir, with some hesitation, for I feel that I am reverting to very elementary pathology; nevertheless it is just because the matter is so elementary, so fundamental, so all-important for a right comprehension of all pathology, and because the distinction with which you have honored me affords an almost unique opportunity for calling attention to this matter, that I make bold to utilize this opportunity to urge a broad and logical consideration of the subject. Dr. Senn, professor of the principles of surgery in the Rush Medical College, Chicago, whose writings have obtained a wide circulation and whose influence in the North and West perhaps transcends that of any other surgeon, states in his "Principles of Surgery" that inflammation, in the widest and most comprehensive meaning of the word, should be made to embrace pathological conditions which are caused by the action of pathogenic microbes or their ptomaines upon the histological elements of the blood and fixed-tissue cells, and that "true inflammation is always caused by the presence of one or more kinds of pathogenic microbes," a statement which, it may be added in parenthesis, does not prevent him from employing figures from Hamilton and others to illustrate the stages of the process, although those figures represent the results obtained by the use of chemical and not bacterial irritants.

Dr. Roswell Park, professor of surgery in the University of Buffalo, in a straightforward address read before the American Surgical Association in May of last year [1] is inclined toward the same opinion, and, as he at the onset especially invites kindly criticism, I

[1] Medical Record, New York, i., 1895, p. 705.

may say that his challenge has perhaps more than anything else led me to take up the subject here. He urges first the revolutionary thesis that the combination of the four cardinal symptoms should not be regarded as indicating inflammation. We should dismiss from our minds the associated idea, and should refer to the redness and heat as hyperæmia, the swelling as exudation, the pain as the result of pressure. Only when these become developed or modified by the growth of micro-organisms in an injured area or by the action of their products should we venture to speak of inflammation. And the term should then comprise not only the local but also the general effects produced by the growth of the micro-organism. In fact, the existence of these general effects (as, for example, the rise of bodily temperature associated with the appearance of a small furuncle upon the nose) is given as a distinction between what Dr. Park regards as true inflammation and the non-inflammatory reactions of the tissues to non-microbic lesions.

While epitomizing Dr. Roswell Park's argument, I believe that I have accurately stated his main contentions.

Let us see what is the logical outcome of this idea. First and foremost the frequent association of redness, swelling, heat, and pain which may result from microbic invasions of the body is not in itself to be regarded as symptomatic of inflammation. The association is common to microbic and many other lesions. Only the extension of this series of symptoms in special directions under the continued influence of bacterial irritation is to be considered as inflammatory; or, to carry this view to its logical conclusion, the surgeon must no longer depend upon the presence of cardinal symptoms; he must only call a region inflamed when he has either personally or through a bacteriologist determined the existence of bacteria therein. There is no attempt made by Dr. Roswell

Park to limit inflammation to pyogenesis, and while this view of inflammation for surgical purposes, in the main, undoubtedly separates suppurative from other lesions, it is in the terms of this definition impossible to regard suppuration in itself as an inflammatory manifestation, simply because, as is well known, suppuration may be induced by caustics and severe chemical and physical irritants, apart from the action of bacteria. As above stated, the bacteriological is to become the sole sufficient test of inflammation. While it is true that the general adoption of this view would result in rendering it absolutely necessary that every general practitioner should continually practise himself in elementary bacteriology, or else should banish the term inflammation from his diagnostic vocabulary—a not undesirable consummation, it may be—I cannot but fear that the general practitioner will still continue to speak of the inflammation of scalded surfaces, of black eyes, and of fractured limbs; for he will still require some useful and generally accepted term to embrace the train of symptoms following upon every-day injuries. This attempt on the part of members of one branch of our profession to delimit our idea of inflammation largely for practical purposes must fail when put into practice.

Or let us examine the proposal from another side. "Without infection," says Dr. Roswell Park, "no genuine inflammation; with infection, inflammation and, what always goes with conflagration, more or less destruction. Congestion and exudation provoke little, ordinarily no constitutional symptoms; inflammation always does. . . . I would," he states later (after discussing hyperæmia, congestion, and "cirrhotic" changes) "in an entirely distinct chapter and in an unmistakably separate way, take up the matter of inflammation—*i.e.*, infection." To all intents and purposes Dr. Roswell Park would substitute a word which, I think most will agree, has wisely been re-

stricted to local disturbances for a word which has shown itself most useful as indicating the changes which may occur in the organism at large in consequence of microbic invasion. Up to the present time inflammation has been understood to indicate the local changes following upon an injury; fever and infection to indicate the more remote effects upon the organism at large. And I am forced to point out to Dr. Roswell Park that in "infection" he has a most useful word which will indicate everything that he wishes to include in his restricted idea of inflammation, and, that being so, there can be no valid reason why he should, with those "big, merciless hands" attributed by the late poet laureate to one of our surgical brethren, appropriate a word to which can be given a wider and at the same time a more exact use. The terms "wound infection," "local infection" and "general infection," and "infective inflammation," are in common and satisfactory employment and there can be little or no doubt as to their meaning. I beg Dr. Park to consider this before urging further the adoption of his proposals.

But while one is only too glad to have a word "infection" capable of covering the series of local and general effects induced by the presence and growth of micro-organisms within the body, its employment in nowise tells upon the fact that every change in the blood elements and tissues brought about by microbes and their products may be induced by irritants of another nature. While it is true that micro-organisms frequently lead to pus production and that suppurative inflammation is almost entirely induced by these agents, it is equally true, as was first clearly proved by Councilman, that sundry chemical substances can occasionally set up an identical process. And as Leber has shown, the purulent fluid produced by this latter means has definite powers of breaking up and digesting proteid matter; no clear distinction can be made

between the septic and the aseptic pus save that the one is of microbic origin, the other not. A broad idea of inflammation to include all like processes throughout the higher animals must take cognizance of these facts.

Nor again, may I add, is it possible to distinguish one series of micro-organisms as essentially pyogenic. To attempt this is to draw a line between human and comparative pathology. While it is true that certain forms in man are peculiarly liable to induce abscess formation, those same forms by no means necessarily exhibit the same liability in other animals, and even in man they do not always lead to pus formation; in short, suppuration is the expression, not of the presence of certain specific microbes, but of a definite grade of intensity of irritation, or, in other words, it is a phenomenon representing a certain ratio between the virulence of the irritant and the resisting powers of the organism. Increase the virulence of a micro-organism or diminish the resisting power of the organism, and in members of the same species similarly treated we may have every grade of acute inflammation, from local hyperæmia and slight diapedesis of leucocytes through local abscess formation, to spreading sero-purulent cellulitis and general septicæmic infection. Much has been done experimentally to prove the truth of this statement, while the recent work in the laboratories of this continent upon cases of typhoid and gonorrhœa has abundantly shown how micro-organisms which in ordinary are not pyogenic can be the prime causes of abscess formation. Indeed it may be said with some truth that the main bacteriological work of the past year has been in the direction of confirming this statement and in demonstrating in case after case this liability on the part of bacteria ordinarily non-pyogenic to lead to abscess formation.

If this be so and if bacteria can thus be the cause

of a series of reactive changes on the part of the tissues, advancing by imperceptible gradations from the simplest transient local inflammatory change up to the most profound generalized septicæmic disturbance, and if again, as all must admit, they can induce either profound local destruction of tissues or well-marked local tissue overgrowth, then surely it is impossible to to separate the lesions produced by micro-organisms from the parallel and identical series capable of being produced by other noxæ.

I trust, therefore, that I have made it clear that we are compelled to range together the series of changes induced locally in the tissues as the result of injury under the common heading of inflammation, and this irrespective of the nature of the irritant.

For pathologists in general, for those studying not merely gross anatomical lesions but finer also, for those dealing with lesions of internal organs as well as with lesions having an outward manifestation, for those whose pathology and study of medicine is not confined to man and who strive to base their knowledge of disease and its processes upon a study of the same throughout the animal kingdom, no other course is open and practical.

Following this train of thought it becomes evident that we must regard as of inflammatory origin all those changes in the tissues which we can prove to result from direct injury to those tissues, whatever the nature of the irritant, and which we can regard as tending toward repair. We can separate the various degenerations of the tissues, for these form a well-defined series of changes from the inflammatory lesions proper; we may regard them as associated with but not inherent in the inflammatory change.

Of these local attempts at repair the most durable and, when the process has come to an end or when, being of moderate intensity, it has continued for some little period, the most evident is the formation of

fibrous tissue. Now, in studying this formation and the broader subject of fibrosis[1] in general, the first point to be settled, one which will materially affect our whole comprehension and classification of the fibroses, is whether it is possible to distinguish between new connective-tissue formation which is directly the result of injury and that which is indirectly the result, and if we can determine this we can with greater freedom attack the question of the classification of the fibroses in general and can more surely state which of them are to be considered of inflammatory origin and constituting chronic "-itides," which non-inflammatory.

The first question is one of peculiar difficulty, and the problem presented for solution may perhaps be best approached by a consideration of two widely separated cases. A study of the various stages of the development of a tubercle demonstrates that in man and most mammals the first result of the lodgment and growth of the tubercle bacilli in the tissues is to stimulate tissue formation. Only at a later period, with continued action of the products of the germs and associated disturbed nutrition of the central area of the granuloma, does tissue destruction become manifest. There is perhaps no better demonstration than this, unless it be that afforded by lepra nodules, of injury leading directly to connective-tissue growth.

On the other hand, we may consider the processes which occur in the central nervous system following upon atrophy and destruction of ganglion cells or

[1] Here let me state that I have no liking for this mongrel term "fibrosis"; nevertheless, I know of none which can satisfactorily replace it. The terms "sclerosis" and "cirrhosis" indicate only the secondary consequences of fibroid overgrowth, and "fibrous hyperplasia" is a little clumsy, while "fibrosis" undoubtedly conveys clearly its meaning; and in its favor (although two blacks do not make one white) it may be urged that in common usage we have such other mongrel terms as "fibroma," "fibro-enchondroma," and so on.

upon separation of axis-cylinder processes from their trophic nerve cells. The results can best be seen when the injury affects secondarily all the members of an ascending or descending tract, and they are to be summed up as consisting of degeneration of the fibres forming the tract with replacement by fibrous tissue. Here there has been no irritant circulating in the lymph bathing the fibres and leading directly by its action to their destruction. The degeneration and atrophy has followed upon injury inflicted at a distance, an injury to another region of the body. If any irritant be present it is of intrinsic origin. All the same, we see that the atrophied fibres become replaced by connective tissue.

Are we to regard this "replacement" fibrosis as a form of chronic inflammation? Against so regarding it it can be argued that, as already stated, no specific irritant of external origin can be adduced as having acted upon the tract of degeneration, and that in case after case where the degeneration has been gradual none of the ordinary symptoms of inflammation are recognizable, neither the coarser conditions of hyperæmia and exudation nor those finer ones of determination of leucocytes (though this phenomenon is at times quite distinct), multiplication of capillaries and other microscopical evidences of removal of destroyed tissue, and active new growth. Almost imperceptibly the atrophied nerve fibres are replaced by connective tissue, and it may be that of all the accompaniments of ordinary inflammation the sole distinguishable is the "functio læsa."

But there is another aspect of the condition that we are forced to regard, and I may best approach this indirectly. What satisfactory distinction, it may with justice be asked, can be drawn between this more insidious replacement fibrosis and the grosser replacement occurring in the case of infarcts? In the latter the normal course of events is, that, infective agents

being absent, the necrosed area becomes surrounded by a zone of hyperæmia, the dead tissue undergoes disintegration and absorption and is replaced by new fibrous tissue. In such a case, it is true, we can recognize the distended peripheral vessels, the invasion by leucocytes, the formation of new vessels, all the main microscopical and most of the macroscopical signs of inflammation. But, as in our previous example, no extrinsic agent has set up the disturbances. It is difficult, indeed impossible, to arrive at any other conclusion than that the products of necrosis act as the irritant and that they must be regarded as the cause of the inflammation and subsequent fibrous-tissue development. It is competent for us to assume the existence of a cryptic inflammation in the former case, and to hold that a like cause, namely, tissue necrosis, has led to a like effect, namely, fibrosis. And indeed if we adhere to the definition of inflammation that I have laid down, both of these cases of replacement fibrosis so obviously represent the local attempts at repair following upon injury to the tissues, that unless we further define what is meant by injury we are forced to regard them as equally of inflammatory origin.

We see thus that two different types of fibrous-tissue development, one hyperplastic, the other, as I have termed it, replacement, may be of inflammatory origin, and the more one examines into the subject the more difficult is it found to recognize inflammatory fibroses by their histological characters. While it is true that in certain cases we have histological evidence of progressive inflammation—the presence of newly formed vessels, of an increased number of extravascular leucocytes and small round cells, and it may be of a certain amount of exudation—in cases of the same nature at a later date all these signs may be wanting, and again, in other allied cases, from the very onset both microscopical and macroscopical indications of inflam-

mation may be peculiarly rare. We cannot depend upon histological evidence alone. At the most we can classify the various forms according to the evidence in our possession as to their origin and tendencies.

The considerations I have brought forward up to this point would lead us to distinguish at least two main types of fibroid change associated with inflammation, one of which in default of a better name may be termed productive, the other replacement, fibrosis. In the former there is no causal relationship between the amount of new connective tissue resulting from the inflammatory action and the amount of tissue displaced; in the latter the amount of new fibrous tissue developed appears to be primarily governed by and proportioned to the extent of the destructive process, but both equally tend toward repair and arrest of injury.

This division will, I think, be found useful, and it will be seen that the leading forms of inflammatory fibroid change are to be grouped under one or other of these heads.

Under the first are to be included sundry localized fibroses of which the main forms are the focal areas of new connective-tissue growth induced by the presence of certain micro-organisms, that is to say, the more chronic or less acute forms of infective granulomata—the new growths (tubercles) induced by the tubercle bacilli, those (gummata) induced by the not surely determined organism of syphilis, the fibroid nodules caused by the presence of the leprosy bacilli, and, again, the more chronic type of actinomycotic and glanders lesions. Examples are not wanting of similar focal areas of fibroid growth induced by simple irritation. As such may, I think, be safely cited the earliest stage tof one form of cheloid. Although, as I shall point out later, cheloid growths must be included among the fibromata, nevertheless, in many cases of what is some-

times termed and regarded as spontaneous cheloid, localized connective-tissue growths can be excited by local irritation of the surface. This was well observed in a case which has recently been very fully studied by one of my students, Mr. R. H. Martin. In this, the mere scratching with a pin was sufficient to give rise to the new growth. I am myself fully prepared to regard sundry cases of focal growth as non-inflammatory—as due to stimulation rather than to injury. The difficulty is that there is no line separating the one from the other; there is no sharply defined boundary between simple hyperplasia and that which is obviously reparative.

Merging at times imperceptibly into the previous group there are the capsular fibroses, comprising those cases of connective-tissue development induced around an irritant, whether infective or not. Here the zone or capsule of tissue formation is a development of so much new material, laid down, it would seem, irrespective of previous tissue destruction in the immediate region of its appearance. Examples of this form will be immediately called to mind. Among the infective we have the thick capsules forming around obsolescent tuberculous masses, around chronic abscesses and phthisical cavities; among the simple irritative are to be classed the capsules developed around such foreign bodies as exercise little more than a mechanical irritation, whether those bodies be solitary and of large size, as, for example, impacted bullets, or minute and very numerous, as inhaled particles of coaly or silicious matter. Whether the capsules formed around and merging into the framework of benign tumors are to be classed as of simple irritative or of infective origin may possibly give rise to debate; provisionally I must refer them to the former class.

Another type of productive fibrosis, one that cannot satisfactorily be classed either as localized or

generalized, is that due to inflammation of serous surfaces, a form including the fibroid thickening of serous superficies and organized inflammatory adhesions.

Besides these, there exist also generalized productive fibroses of inflammatory origin, which again may either be of infective origin (induced by bacteria or their products) or the result of continued non-infective irritation. The chronic interstitial pneumonia following upon subacute pleurisy may be cited among the former; among the latter, in all probability, the generalized interstitial fibrosis of so-called chronic parenchymatous disease, of which a good example is afforded by the condition of productive parenchymatous nephritis. But, as I shall have later occasion to point out, some forms at least of interstitial fibrous overgrowth are rather to be counted among the replacement than among the productive forms.

The local and general forms may merge, the one into the other. Thus, a liver presenting gummata may exhibit also well-marked generalized interstitial fibroid overgrowth; a kidney the seat of chronic tuberculosis may show the same; or again, in the inhalation pneumonias the deposit of foreign particles along the lymph spaces of the lungs may be so extensive and the growth thereby excited be so great that the organs present the characters of a generalized interstitial inflammation. Nevertheless, the distinction between local and general is in the main useful and not pedantic.

To turn now to the replacement fibroses; among these we can distinguish certain well-defined types. All may in truth be termed cicatricial, but it may be well to restrict this designation to the ordinary surgical cicatrix, to the connective tissue developed after breach of continuity in a part. Speaking broadly, it may be said that every such breach of continuity results in the destruction of a certain number of cells,

and that in the absence of infective agents the new connective-tissue formation maintains a definite relationship to the amount of previous destruction, never exceeding it. Very closely allied is the development following upon the complete and sudden necrosis of all the elements of a tissue; of this, as previously hinted, a most satisfactory example is seen in the healing of a simple infarct.

If we, following what is not unusual nowadays, regard the blood as a tissue, the organization of thrombi must be placed under the same heading of fibrosis following tissue necrosis; if we are more conservative in our employment of the term "tissue," we must regard the gradual substitution of the coagulated and necrosed blood by fibrous tissue as a closely allied phenomenon, namely as a fibrosis occurring in and replacing a necrotic mass.

Associated with these we can recognize two other forms. I would not insist upon their separation, but there is a slight difference in their mode of origin. In the one the essential cause of the death of the cells is local, from impaired nutrition, in the other the nobler elements of the tissue undergo atrophy and death irrespective of local conditions. The two forms may be termed dystrophic and atrophic respectively.

Of the atrophic I have already furnished an example, namely, the sclerosis following degeneration of ascending or descending nerve tracts. Of the dystrophic the heart furnishes the most frequent examples, though I am inclined to regard much of the fibroid change seen in the senile kidney as of the same nature. As M. H. Martin[1] was, I think, the first to point out explicitly, and as Weber[2] has shown in a very careful research, where there is an "obliter-

[1] H. Martin: Revue de Médecine, May, 1881.

[2] A. Weber: "Contribution à l'Étude Anatomo-pathologique de l'Arterio-sclérose du Cœur," Paris, Steinheil, 1887.

ating endarteritis" of the coronary vessels with overgrowth of the intima and consequent diminution of the lumen, there must result a diminished nutrition of the area supplied by each affected artery or arteriole, and as these are of the nature of end arteries there is developed no satisfactory collateral nutrition. The result affords a very striking picture, more especially if the most frequent seat of the change be examined, namely, one of the papillary muscles of the left heart. In these the fibres run longitudinally and so also, entering at the base, do the nutrient arteries, and the condition is so common that I have never had difficulty in obtaining material for my class in morbid histology. In a typical fairly advanced case in transverse section of the muscle, the arterioles with thickened intima are seen cut transversely; around each is a zone of fairly healthy fibres also cut transversely. Passing outward from the artery these give place to fibres that present atrophy and pigmental degeneration with intermingling of new connective tissue, while the outer zone of supply of the arteriole is represented by a ring of clear, transparent fibrous tissue with relatively few nuclei and here and there the last remnant of a degenerated muscle fibre. This, I may remark, is but one form of cardiac sclerosis. It would be difficult to find a more demonstrative case of this dystrophic replacement fibrosis.

But while thus we are able to recognize examples of the uncomplicated occurrence of one or other form of inflammatory fibrosis, and while I hold that it is useful to us both as students of medical science and as practical physicians and surgeons to seek to analyze the nature and character of every morbid change, it has to be admitted, if we look honestly at things as they are, that case after case presenting itself to our notice cannot possibly be docketed and pigeonholed under one heading. Time and again we come across what can only be classified as mixed forms of the

conditions already indicated, not to mention mixture of these with fibroid conditions which I have still to take into consideration. I can only urge that it is well to strive to cultivate our garden and not to allow our ideas of chronic inflammation to continue a riotous and tangled growth. Only by such cultivation can we hope to gain good fruit.

It is when we come to study the chronic inflammations affecting glandular organs that our great difficulty begins in comprehending the essential nature and causation of connective-tissue growth. Let us take the commonest case, namely, that of continued parenchymatous inflammation. Here the first obvious disturbance in the tissue is an affection of the glandular cells. With this there is an accompanying congestion of the interstitial vessels, and this gives place eventually to a condition in which the collections of gland cells are separated from each other by increased connective tissue, while coincidently the gland cells themselves show signs of atrophy. Two conditions might produce this picture: either the atrophy of the gland cells might be primary and the increased fibrous tissue an indication of replacement fibrosis; or, on the other hand, the picture might indicate, as is usually held, a productive interstitial fibrosis with the malnutrition and atrophy of the gland cells as a secondary consequence of irritation, impaired nutrition, and pressure exerted by the new-formed tissue combined. It is only by a very full and cautious observation that it is possible to arrive at a decision in any given case as to which form of fibrosis is represented and often, indeed, one is induced to take the middle course and consider both in operation.

If, for example, we study the various forms of cirrhosis of the liver, both experimentally and by histological examination of various cases, this difficulty is very forcibly borne home to us. We can occasionally, it is true, make out with certainty the existence of a

productive fibrosis; thus we frequently meet with what appears to be the earliest stage of ordinary so-called alcoholic cirrhosis, in which we observe small masses of small-celled infiltration along the portal sheaths. The condition looks definitely productive; it appears to be an inflammation around the interlobular branches of the portal vein, and the cells in the immediate neighborhood of these accumulations show no very decided signs of degeneration and atrophy. We can, again, as is occasionally the case in early stages of biliary obstruction, find the bile ducts enlarged and dilated and surrounded each with new connective tissue, so that the picture given is that of a productive inflammation immediately around these ducts. We can also, more frequently than is usually recognized, make out signs of fibrous-tissue overgrowth around the branches of the hepatic artery; out of eighty-eight post-mortems performed during last year, I found this periarteritis to be well marked in six cases; but in advanced cases of ordinary cirrhosis of the atrophic type it seems to me more than doubtful whether malnutrition of the cells does not become an important factor and their atrophy be not followed by replacement fibrosis, rather than be the result of pressure and encroachment of the newly developed connective tissue.

In this connection it is interesting to note how the majority of observers who have attempted experimentally to induce cirrhosis of the liver have noticed changes of a degenerative character in the hepatic cells as a first effect of irritation rather than productive inflammation in the interstitial substance. This, of course, is what might be expected, the nobler cells of the tissue being the more sensitive. I merely draw attention to it because it is so common to regard hepatic cirrhosis as primarily an interstitial disturbance. I do not wish to give the impression that this may not be so in certain cases; very frequently,

I feel as sured, it is not. I need but remind you how strongly the recent studies by Flexner[1] uphold this view.

Here I may briefly refer to certain studies which have occupied me during the last two years upon the causation and nature of a very remarkable disease affecting the cattle in a limited region of Nova Scotia, the so-called Pictou cattle disease. I do not wish here to publish a detailed and circumstantial account of my observations, for to do so would not be just to Professor Welch, to whom I have promised my completed paper upon the subject. I may, however, repeat what is stated in my reports to the Dominion government, namely, that the disease is of an infectious nature and due to a minute bacillus, characterized, as are so many of the pathogenic micro-organisms of lower animals, by an intense polar staining, so that frequently it has the appearance of a diplococcus rather than of a bacillus.

The disease is apparently of slow onset; the affected cattle eventually suffer from an abundant dark-colored diarrhœa, present a moderate amount of ascites, fail to give milk, and then the end is ushered in either by a condition of violent excitement or by progressive muscular weakness.

At the post-mortem the most characteristic features are the ascites, a remarkable submucous œdema of portions of the intestine (I have seen similar submucous œdema in cirrhosis of the liver in man), enlargement of the abdominal lymphatic glands, and a very extensive cirrhosis of the liver. It is in the lymph glands and the hepatic cells that the bacilli are present in greatest abundance.

The cirrhosis is generalized and of the pericellular type, and if the livers from a large number of cases be examined the earliest stages would appear to be those of swelling and vacuolation of the hepatic cells

[1] Flexner: Medical News (Phila.), ii., 1894, p. 116.

with great irregularity in the size of the nuclei. There may be great congestion of the hepatic (venous) capillaries, but this is unaccompanied by any notable small-celled infiltration. Following upon this stage of swelling, the hepatic cells undergo atrophy, sundry lobules and portions of the liver showing the process at a more advanced stage than do other portions. And this process may be so extensive that over large areas of the organ only isolated liver cells or clumps of three or four degenerating cells are to be recognized. With this the organ is not diminished, indeed the edges often tend to be slightly rounded and full; there is replacement of the degenerating cells and lobules by a delicate somewhat œdematous connective tissue. A characteristic of this new tissue is the relative absence of the ordinary signs of productive inflammation in the shape of small round cells. Of these there are a few, but very few; more frequent are small irregular cells, evidently degenerated liver cells and others of the "spider-cell" variety, with fairly numerous delicate processes.

In short, the impression gained by studying numerous sections obtained from many animals dying in different stages is that there is here a primary irritation or overstimulation of the hepatic cells by the bacilli, followed by an atrophy of the same and coincident replacement fibrosis. I will not say that this replacement fibrosis is the only form of connective-tissue hyperplasia present in these cases; there are occasional indications of productive change. But it is, I feel assured, the main form present.

This generalized pericellular cirrhosis is, of course, not strictly comparable with the more usual forms of hepatic cirrhosis met with in the human being. Its interest lies in this, that occasionally, more especially in children, we observe a curiously similar condition of the liver without any clear evidence of syphilis, and in children also the victims of congenital syphi-

lis, even as to a less extent in adults presenting tertiary syphilis, we are apt to meet with a more or less extensive pericellular cirrhosis. In such cases it may well be that the cirrhosis is of like origin, due, that is to say, to the direct irritation of the hepatic cells by pathogenic bacteria or their products, to the atrophy of these cells and their replacement by delicate connective tissue.

Thus far, therefore, we have been able to recognize the following forms of fibrosis of inflammatory origin:

A. "Productive" fibroses.
   (1) Localized { focal. / capsular.
   (2) Serous and adhesive { local. / general.
   (3) Interstitial,
B. "Replacement" fibroses.
   (1) Cicatricial.
   (2) (Post)-necrotic,
   (3) (Post)-atrophic.
   (4) (Post)-dystrophic.
C. Mixed fibroses.

But this classification does not nearly include all the examples of connective-tissue overgrowth and sclerosis occurring in the organs of the body.

One further group of cases may at first sight appear to be sharply defined, namely, the group of the true fibroid neoplasms, the fibromata proper. Nevertheless, a study of the forms usually included in this group reveals the fact that there has been in the past not a little confusion as to what constitutes a fibroma, and an attempt to classify the various forms cannot but lead to the conclusion that the line separating inflammatory new formation from fibroid neoplasms can be drawn only with a cautious hand.

As I have pointed out, one result of irritation may be overgrowth of connective tissue. Ordinarily this appears to be not greatly in excess of the needs of the injured area, nevertheless at times it exhibits itself

greatly in excess of these needs. When infective agencies interfere with the normal course of cicatrization of a wound and the healing becomes delayed, when, in short, superadded to the normal tendency for fibrous tissue to be developed so as to repair a wound there is a stimulus to connective-tissue proliferation from the presence of bacteria and their products, then it would appear that fibrous tissue may be developed in excess of the requirements of the part. This "false" cheloid, it is clear, originates primarily after inflammation, and we may have every gradation from what may be regarded without second thought as redundant cicatricial tissue up to what, from its continued and very extensive growth, it is difficult to regard as other than a frank neoplasm. Another form I have already referred to, namely, the "spontaneous" cheloid developing where there has been no breach of continuity of the tissues. On this continent among the colored population (and the negro appears to be peculiarly prone to be affected) cases have been recorded in which the new formation has attained enormous proportions.

As an example of so-called spontaneous cheloid let me here briefly describe the case already referred to, studied by Mr. R. Martin, for it throws light upon sundry important features in this class of tumors. The patient was a French Canadian girl, aged twenty, who had always been healthy until about four years ago, when she noticed a very small growth which looked like a little pimple on her left shoulder. This gradually enlarged and in about a year began to be painful, causing sharp, stinging pains. At the end of two years it was two inches long and three-quarters of an inch wide, and was then removed by the knife. About three weeks after the operation it recurred and became as large as before. An operation four months later was again followed by a recurrence. Three or four months later it was removed "by means of a

plaster." It has never returned, but there remains a very large cicatrix, larger in fact than the original tumor. The patient was free from any further growths until about a year ago, when another small pimple appeared on the outer side of the right arm just above the elbow, which gradually grew larger until in April, 1895, it was one inch long, about a third of an inch wide, and elevated above the skin. The edges where it passed into the surrounding skin were irregular and claw-like. On further examination another similar tumor was found on the back, and when the skin was made tense in several places, principally on the outer side of the right arm, clusters of flat, small round cicatricial spots were noted, of a white and glistening appearance. Each cluster contained about four or five spots. Upon relaxing the skin these clusters were unnoticeable. In July the clusters had all disappeared and there remained only the tumor on the back, which was also diminishing in size. At this time needle scratches were made on the left arm. When seen again in September, 1895, little nodular lines of cicatricial aspect were to be observed corresponding to the previous slight scratches caused by the needle. It may be added that microscopical examination of the tumor removed from the arm in April presented all the characters of true cheloid.

Here, then, we have a case apparently of spontaneous cheloid, in which nevertheless the subsequent history, results of operation, and of experimental slight cutaneous disturbance show that the fibroid hyperplasia was to be induced by injury, so that presumably the primary growth had a similar origin, not improbably, as in certain recorded cases, from an acne pustule. The case affords an example of what might very easily in its earlier stages have been classified as spontaneous cheloid.

In fact, from this case and from a study of the literature of cheloid, I am led with Jonathan Hutchinson

to doubt whether the conception of a spontaneous cheloid is possible or consonant with facts.

Thus, it can be shown that in those exhibiting a tendency to the disease—those in whom cheloid masses already exist—a minimal irritation as, for example, the scratch of a pin, may induce the subsequent appearance of a mass of subcutaneous fibrous tissue in the region. Where this is the case it is difficult to deny that the condition originates as a productive inflammatory fibrosis, and the fact that at times some if not all of the multiple nodules undergo absorption and disappear (as happened in Mr. Martin's case to which I have already referred) is against regarding the condition as typically fibromatous. It is equally difficult, in fact impossible, to maintain that a mass of new tissue, which occasionally attains to the weight of a pound or more, projecting from the head or trunk is an example of inflammatory fibrosis. It is difficult to see where the line is to be drawn, unless, as I have recently urged in an address before the Medico-Chirurgical Society at Montreal,[1] we recognize that in inflammation the new-tissue formation ceases with the removal or cessation of the irritant, whereas in neoplasms the cells, having once commenced to proliferate rapidly (whether as the result of chronic inflammation of moderate intensity or from other cause or causes), gain a habit of growth and continue to proliferate independently of any due stimulus. Assuredly, in these multiple cheloids as in the cicatricial forms growth of the tissue is continued after the irritant has ceased to be in evidence, and consequently I am bound from their course to classify them as among the fibromata—as fibromata of inflammatory origin.

I am not prepared to do the same with another form, the so-called "lamellar fibromata," whereof the most frequent examples are to be encountered as

[1] "The Habit of Growth," Montreal Medical Journal, February, 1896.

dense, sharply defined, whitish nodules and small plaques upon the surface of the spleen. So far as I have been able to follow their development, these appear to be examples of pure and simple inflammatory growth. I can see in them no evidence of continued growth independent of injury or irritation.

Besides these two forms we have the group of typical fibromata, isolated, sharply defined neoplasms of in general slow growth. While among the cheloids we can postulate an inflammatory origin, in these we cannot as yet venture to assign a satisfactory causation. Nor is the time quite ripe to make a positive statement concerning the massive interstitial tissue occurring in sundry mixed tumors, in fibrolipomata, fibromyxomata, scirrhous cancer, etc. Studying these and comparing the outer border with the more internal parts, I gain the impression that in many cases we have, as in cheloid, to deal with a productive inflammatory fibrosis which merges insensibly into neoplastic incontinent growth. This is my impression, and I dare make no more definite statement.

Thus we can divide the forms contained under the title of fibroma into:

A. Pure or true fibroma.
   (1) Of inflammatory origin (most if not all examples of cheloid).
   (2) Of undetermined causation (typical hard and soft fibromata).

B. Mixed fibroma, benign, cancerous, and sarcomatous (admixture of fibroid overgrowth with overgrowth of other tissues).

C. False fibroma (due to simple productive inflammation, *e.g.*, "lamellar" fibromata).

LECTURE II.

In my last lecture, having laid down my definition of inflammation—namely, that it is the series of changes constituting the local attempt at repair of injury or referred injury to a part—I proceeded to discuss the forms of fibrous hyperplasia which in the terms of this definition might well be held to be of inflammatory origin, and showed or attempted to show that such forms might be divided into the two main classes of productive and replacement fibrosis. Following upon this, I discussed the group of localized neoplastic fibrous hyperplasias, and pointed out that two groups might be recognized: the neoplasms of inflammatory origin and those of as yet undetermined causation—the true fibromata.

A consideration of neoplastic growth leads almost insensibly to the inquiry whether it is requisite that injury should precede new connective-tissue formation. The answer must, I think, be an unhesitating No.

In the nobler tissues of the body we know full well that increased work leads to hypertrophy or, more correctly, to hyperplasia; that is to say, a physiological stimulus leads to multiplication of the cell elements. What are the exact steps whereby this is brought about must perhaps always remain a matter of supposition, the most that we can say being that the call for increased work is followed by increased blood flow to the part with presumably increased nutrition, and that the increased work necessitates greater activity and increased metabolism in the individual cells. In connection with the basal connective tissue of the body it is difficult to grasp the idea of active work; to attempt to formulate such an idea may perhaps justly lay me open to the charge of dealing in transcendental pathology, and yet, as I shall proceed to show, a consid-

eration of several forms of fibrous-tissue hyperplasia in connection with the different organs and diverse in character, forms in which it is difficult to decide any clear inflammatory origin, leads to the conclusion that there is a certain bond of union between them, that in them the existence of an increased strain upon the tissue is to be recognized, and that if we could group them together as being of the nature of "functional" hyperplasias or hyperplasias of increased function, we should advance materially in our grasp and comprehension of the same.

I had at one time thought that increased nutrition would be sufficient to explain these cases, and indeed I have been inclined to press this point until quite recently. It is certainly true (as is best shown by the cases of dystrophic sclerosis already mentioned) that a nutrition insufficient for the nobler elements of an organ suffices often for the active growth of connective tissue. This fact that a nutrition ample and suitable for one tissue does not suffice for another has long attracted attention, while the converse, or rather the corollary, was proved more than a century ago by John Hunter in his classical experiment of grafting the scantily-nourished cock's spur upon the cock's comb, and in this richly vascular and well-nourished area obtaining a remarkable, if temporary, hypertrophy of the grafted organ. Under certain conditions, then, active increase of nutrition of a part may lead to hyperplasia of its cells. Where the specific cells of a tissue undergo atrophy it may well be that there results a definite increase in the amount of nutritive fluid at the disposal of the baser interstitial cells, and that this has to be taken into consideration as well as any more direct stimulus to proliferation afforded by the products of tissue degeneration.

If this be so we are met with the likelihood that in conditions tending to altered nutrition of a part—leading to the tissues becoming bathed with lymph, either

in excess of the needs of the specific and nobler cells of that tissue or of a quality not suited for the uses of those cells—there may be induced an overgrowth of connective tissue, a fibrosis, to be ascribed primarily to nutritional disturbances; or, in other words, it becomes likely that there may be nutritional fibroses as distinguished from inflammatory. Plausible as this seems, a fuller study of those cases which at first appear to be examples of simple nutritional fibrous overgrowth leads to the conviction that there is some further factor also at work. Or otherwise, increased nutrition, even if long-continued, does not inevitably lead to increased connective-tissue overgrowth, and therefore when we find this factor most in evidence in the production of any form of fibrosis we are bound to assume that there must be some additional directive factor. What I mean will best be shown by a study of the cases I am about to bring before you.

Take in the first place chronic obstruction to the flow of lymph. Where such obtains—whether by pressure of tumors upon the main lymph channels of a part, by blocking of the same, or by diseased states of the lymph glands—it is a matter of frequent observation that in the absence of satisfactory collateral tracts the part becomes swollen and gradually the fluid swelling gives place to a generalized, if not very extreme, connective-tissue overgrowth. In such cases the circulation of the blood through the affected area is maintained, there are no positive signs of inflammation evident either macroscopically or microscopically. We cannot recognize in the condition an attempt at repair. The primary injury has been at a distance from the region of fibrosis. Nevertheless, it may be argued that the stagnating lymph acts in these cases as an irritant to the connective-tissue cells and that the condition must be regarded as a productive inflammatory fibrosis.

While this view deserves full consideration, its ac-

ceptance must lead us almost inevitably to a point at which we become bound to regard as of inflammatory origin every condition of fibroid overgrowth, whatever be the stimulus. Some limit, I think, must be given to our conception of what is included in the process. It will be seen that thus far every example given by me until the present case has been strictly within the limits of the definition laid down, namely, it has been reparative in its tendency and has been due to evident injury to the part which becomes the seat of the fibroid change. We must, I take it, decline to consider a lesion as an inflammatory fibrosis in the development of which these two conditions cannot be clearly recognized.

Failing inflammatory origin, can we regard the example given above as being brought about by perverted nutrition pure and simple? I am inclined to think that we cannot. We should expect perverted nutrition to tell first upon other and higher tissues, but in many of these cases we find singularly little evidence of primary degeneration of nobler tissues (the muscles and skin of an affected extremity, for example). Where the circulation of healthy blood persists through such a region there must occur constant interchange between blood and lymph, and the blood must carry away the products of tissue change to a considerable extent. In deed we know that it is capable of vicariously removing much of the lymphatic fluid. With our present knowledge, all that it is absolutely safe to say is that we are here dealing with a quantitative disturbance in the lymph of the region, coupled with a mechanical disturbance, namely, increased extravascular and interstitial pressure; or, to put it otherwise, the cells of the connective tissue are subjected to an altered tension. The qualitative disturbance is of doubtful extent.

With these cases of obstructed lymph flow in a part certain examples of elephantiasis Arabum would appear to be classed—provisionally. So little has been

accomplished in establishing the real nature of this disease, or more truly of this group of diseases, that the most I dare venture to say is that disturbed outflow of lymph from the affected region seems to be in operation in some cases (elephantiasis lymphangiectatica), while others present indications of venous disturbance (elephantiasis telangiectodes); others again (the neuromatous and lipomatous forms) can only safely be described as hypertrophic conditions approaching peculiarly close to generalized neoplastic formation.

Without discussing further the intimate nature of the fibrous hyperplasia in these cases at the present time, let me pass on to consider another class of cases. Increased bathing of the tissue with lymph and increased lymph tension may also result from active and from passive hyperæmia. From either of these causes there may be passage outward of lymph from the blood-vessels in amount exceeding the efferent capacity of the lymphatics. Here again mere increased amount of lymph does not seem to lead necessarily to fibrosis. Some other factor or factors must be invoked. Thus in the liver, while extreme congestion leads especially to dilatation of the vessels with pressure atrophy of the specific cells, and though presumably there is here increased exudation, we get little evidence of fibrosis; long-continued moderate congestion induces, on the other hand, a very evident fibrosis, most marked, it is true, in the walls of and immediately around the intralobular branches of the hepatic vein, but seen also in the interstitial substance of the neighborhood. The peculiar arrangement of the new fibrous tissue shows that it cannot be regarded simply as an example of replacement fibrosis. The history in these cases points to the long-continued action of two factors—increased effusion of a not greatly altered lymph and long-continued (and probably varying) pressure affecting especially the central parts of the lobule.

The relative rarity and the slight extent of the fibrous hyperplasia accompanying well-marked passive congestion is in itself an indication that the quality of the effused lymph plays a part in the development of the hyperplasia. Neither increased amount of lymph of poor quality in a part nor increased interstitial tension alone, it would seem, is capable of inducing overgrowth.

From this brief and hasty consideration of fibroid changes associated with the lymphatic and venous systems which are not to be regarded as of inflammatory origin, I will now pass on to discuss in somewhat greater detail what appear to me to be allied conditions affecting the heart and arterial system.

In ordinary practice apart from malformations, neoplasms, and the direct effects of trauma, the pathological changes of the heart valves are divided into the two broad classes of acute and chronic endocarditis, and although the non-committal name of arterio-sclerosis is in frequent use and although its employment appears to indicate a doubt as to the exact etiology of the condition, it must, I think, be admitted that such arterio-sclerotic changes are regarded as inflammatory in character, while sporadically the attempt is made to explain them by suggesting or presupposing the existence of some irritant substance in the blood which by direct action upon the vessel walls leads to injury and to reaction in the shape of connective-tissue overgrowth. I see, for example, that in a recent number of the *British Medical Journal* the apostle of uric acid, Dr. Haig, suggests that a cause for sclerosis of the heart valves is to be found in the irritant action of his beloved uric-acid crystals.[1]

The existence of inflammation as a cause of sclerosis is more frequently to be determined in connection

[1] Alexander Haig: "Arthritis and Endocarditis Due to Drugs which Diminish the Solvent Power of the Blood for Uric Acid," *British Medical Journal*, December 28, 1895.

with the heart valves than with the arterial intima. Thus, it is well recognized that acute valvular disease may be followed by chronic thickening of one or more segments, that similar thickening may follow rupture of a segment, and that a valvule which has from any cause become injured, whether from simple roughening of its surface or more usually from the development upon it of vegetations, may by friction induce inflammatory disturbances in the parts with which it comes into contact.

In general these forms present an irregular or varicose type of fibrosis, but it is often difficult, if not impossible, to distinguish from them sundry cases of chronic generalized thickening in which through degeneration localized disturbances have occurred in the thickened valves with, it may be, ulceration, deposit of fibrin, and subsequent organization. There are, that is to say, doubtful cases in which it is practically impossible to declare whether we are dealing with processes following upon localized valve lesions or with the sequelæ of a generalized lesion.

Apart from these undoubtedly the most common form of valve lesion met with in the post-mortem theatre is a generalized thickening. Perhaps generalized is not a wholly correct designation, for in the slightest forms it manifests itself more especially along the edges of the mitral segments, and in the aortic valvules it is below the line of apposition, and again at the insertion of each segment, that the fibrosis is most marked. So common is the condition that in general we disregard it and, accepting it as almost physiological, make no note thereof. But in the examination of a series of hearts we may pass almost imperceptibly from one case to another until we reach conditions of extreme mitral stenosis, with such extensive generalized thickening of the whole valve and consequent shortening of the new connective tissue laid down that the mitral veil becomes converted into a

circular plate, or more generally into a short blunt funnel with button-hole passage. And we come across case after case of this category which shows no sign of localized valvular disturbance either old or recent. The condition affects the whole of the valve and affects also the chordæ tendineæ, which are thickened and shortened.

While in acute endocarditis and in the nodose or verrucose sclerosis following upon such we find clear evidence of vascularization of the valves, and sections show fairly frequent vessels, this is not the case in the generalized thickening here referred to. The essential characteristic as revealed in sections is the rarity of the vessels; the fibrous tissue is laid down in layers parallel to the surface, and the most recent, the most cellular layers are those nearest to the endothelium—while the deepest layers, those most remote from the surface, show a peculiar tendency to degenerative changes. This tendency to hyaline swelling, fatty degeneration, and other evidences of necrobiosis —in short, to atheroma—is in itself a demonstration of lack of due vascularization and of malnutrition. Indeed, although I know that Luschka and others have described vessels throughout the extent of the mitral valve segments, my own injections of healthy hearts of several species have led me to the more generally accepted conclusion that the outer two-thirds of the mitral are almost, of the aortic valves are quite non-vascular, and to the further conclusion that healthy valvules gain their nutrition in the main from the blood circulating within the heart. It is, I hold, by passage or circulation of the plasma through the stomata of the lining endothelial cells into the lymph spaces between the layers of connective tissue forming the supporting frame of each normal valvule that the main nutrition of the non-vascular areas of the valves is effected. While a layer of the vascular myocardium is contained in the proximal third or so of the seg-

ments, the outer two-thirds is scarce anything but a fold of the endocardium.

That the endocardium of the heart in general gains its nourishment from the blood within the chambers and that the nourishing plasma may even extend for some little distance beyond, is very prettily shown in some cases of advanced sclerosis of the papillary mus-

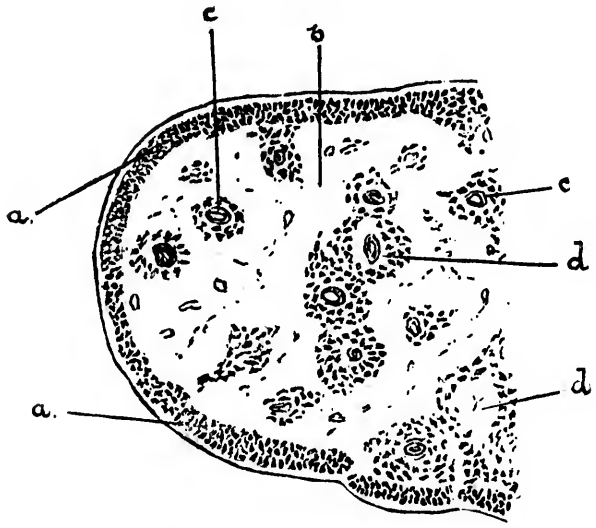

FIG. 1.—Transverse section of a papillary muscle exhibiting dystrophic sclerosis to show zone of intact muscle fibres immediately beneath the endocardium. *a*, Layer of intact muscle fibres beneath endocardium; *b*, sclerosed areas—replacement of atrophied muscle tissue by fibrous tissue. In this are venules and occasional atrophied muscle fibres; *c*, arterioles cut transversely, exhibiting thickened and sclerosed coats, and surrounded by intact muscle fibres; *d*, periarterial sclerosis.

cles, which present complete fibroid metamorphosis of the central area of the pillars with a zone of healthy fibres all around the periphery immediately beneath the endocardium. These healthy fibres present no accompanying arteries; all the arterioles coursing up the papillary muscle may exhibit advanced proliferating endarteritis. The only and the obvious explanation why these peripheral fibres remain is that they

have gained their nourishment through the endocardium.

Wherever we find well-marked vascularization of the outer two-thirds of the mitral valve, for example, we may feel assured that there has been inflammation present. The vascularization is strictly comparable to that obtaining in the cornea and other non-vascular areas, and indicates a development secondary to acute disturbance of the organ. In the generalized thickening to which I have referred one is struck by the peculiar rarity or almost complete absence of vessels and by the fact that the hypertrophic fibroid tissue is laid down after the plan of the normal connective layers of the region. And while obviously the new growth is continuing and the newest tissue is situated immediately beneath the endothelium, we do not there recog nize any characteristic presence of small round cells. The appearances in this region are those of an orderly hypertrophy.

Two hypotheses may be adduced to explain this state of affairs: Either that the sclerosis is of inflammatory origin, the result of an irritant mild in character, causing little reaction but acting continuously over a long period, or that it is non-inflammatory and comparable to the fibroses already referred to in connection with the lymphatic system.

It is, I must frankly confess, impossible to adduce sufficient proof to entirely refute the former hypothesis —there may be chronic intoxications, auto-intoxications, or otherwise, due to substances which manifest a special tendency to act upon the endocardium; but such substances have not yet been isolated. Increased pressure upon the valves may directly damage them and the fibrosis may be the indication of a reaction to chronic injury, but the thickening would appear to be progressive and to continue until a condition is reached out of all proportion to the injury. We find, therefore, no absolute and sufficient reason for regarding the con-

dition as of inflammatory origin. Nevertheless, the mere fact that we at present are ignorant of any immediate cause for the production of this lesion is not sufficient ground for flatly denying the existence of such cause, and even the fact that the microscopic appearances are not those of ordinary inflammation is not proof positive that the process which has led to the lesion has not been essentially of an inflammatory nature.

I cannot, that is to say, hold it proved or disproved that generalized sclerosis of the cardiac valves is in all cases of inflammatory nature. And the matter being thus an open one, it may be well to hold it possible that the second alternative may be correct and to seek for evidence in support of it.

Now, it is interesting to note that just those conditions in which there is a liability for the production of generalized thickening of the heart valves are clinically conditions in which there is found heightened arterial tension, conditions which also bring about arterio-sclerosis. It is just in these conditions that we might expect to have, with increased pressure, increased nutrition of the endocardium and of the intima—increased passage of plasma from the intracardiac blood through the endothelium, or perhaps, more correctly, between the endothelial cells. And I cannot but consider that this increased nutrition coupled with increased strain may afford a satisfactory explanation for this condition of so-called chronic endocarditis. Such a proof as one would desire of the correctness of this opinion is difficult if not impossible to devise, for the condition is the production not of a few hours but, not to exaggerate, of many weeks. Experiments upon the subject are almost if not quite outside the range of experimental pathology. Yet certain considerations appear to support the view. Roy and I,[1] for example, found that by con-

[1] Roy and Adami: "On Failure of the Heart from Overstrain," *British Medical Journal*, December 15, 1888.

stricting the first part of the aorta in the dog and in the rabbit and thereby raising the blood pressure within the heart, we were able in the course of a few minutes to bring about the production of numerous small pearly vesicles along the edges of apposition of the mitral and aortic valves, and we could only account for this development by assuming that with the increased blood pressure the plasma of the blood had been driven into the substance of the valve, and that the pearly vesicles of lymph (or plasma) appeared where they did because at these regions the difference between the pressure on one side of the valve segments and on the other was most in evidence. We obtained, so we held, clear proof that with increased blood pressure increased fluid penetrates the valve substance. It is important to note that similar pearly elevations are generally regarded as the first indication of valve disease.

But, as I have already pointed out, it is unsafe to regard increased nutrition alone as a cause of connective-tissue hypertrophy, and if we cast round to find what other factor there may be I am inclined to consider that it may briefly be entitled increased strain or tension acting upon the individual connective-tissue cells.

The idea may at first appear transcendental; we are not accustomed to think of the connective-tissue framework of the organism as being strained or, to carry this view to its logical conclusion, performing work. We only regard the nobler tissues as workers—the muscle fibres, the nerve cells and the specific cells of the glands. Nevertheless, we acknowledge freely that increased work thrown upon one of the connective tissues —namely, bone—does lead to its hypertrophy. It is a matter of common observation that not only are the bones of those accustomed to active exercise larger and heavier than the bones of the sedentary, but also that where any muscles are strongly developed there bony ridges and bony overgrowths are most developed at their origins and insertions.

The factors leading to this overgrowth may be summed up under the comprehensive title of increased work. And in connection with connective tissue where there is any force in action tending to draw apart and pull upon the constituents of the tissue—whether the force acts from without or (as in cases of increased effusion of lymph) from within the tissue—where, in short, there is a strain upon the components of the tissue—there, if we regard the work of the connective tissues, as is most plausible, as being to bind together and support other tissues, undoubtedly that work is increased and, granting that at the same time the nutrition remains good, we have a condition favorable to increased growth. *A fortiori* we might expect such hypertrophy where simultaneously the amount of nutrition is increased.

I suggest this very tentatively, for I have a horror of far-fetched pathology and an accompanying belief that the fuller our knowledge of a subject the simpler and more straightforward do we find the laws governing the associated phenomena, and it is only because the idea is straightforward and is in harmony with our knowledge of occurrences in connection with other tissues that I venture to formulate it. My aim in these lectures is throughout not to dictate but to suggest and call attention to the many diverse conditions which may bear a part in the production of increased fibrous tissue. At most I will here urge that it is possible that increased functional activity of the connective tissues results under favorable conditions in increased growth of the same.

Passing now to the arteries, we find that just as the muscular walls and pericardium of the heart are nourished by the coronary vessels, so the media and adventitia of the arteries are nourished by the vasa vasorum, whereas in health the intima appears to be non-vascular. Indeed, where it is well developed, the internal elastic lamina appears to constitute a boun-

dary line between the vascular and non-vascular areas of the arteries. We are forced, I hold, to regard the intima as nourished from the blood circulating within the arteries.

The diseases to which the arterial walls are subject are closely comparable with those of the heart. There can, for example, be undoubted inflammation; we may even have collections of pus cells separating the intima from the media, although this is very rare and is always secondary to a purulent mesarteritis, the pus cells wandering into the intima from the vessels of the media. Even in cases of septic embolism or thrombosis, necrosis is the first noticeable change in the intima, and the invasion of leucocytes appears to be associated with the later inflammation of the media and adventitia. Rather more frequent is an acute productive inflammation, seen especially in the first portion of the aorta. This appears to be secondary to similar verrucose, subacute, and ulcerous inflammation of the aortic valvules. It is characterized by the development of almost papillomatous or warty processes projecting into the lumen of the aorta, and these are richly cellular and also vascularized from the vasa vasorum. They are often covered by a layer of coagulum.

But these obviously inflammatory conditions are relatively rare. The most common form of arterial disease in the larger arteries is that termed by Virchow endarteritis chronica nodosa sive deformans, the arterio-sclerosis of Lobstein, or atheroma. I need not here enter into statistics concerning its frequency, or take up your time by details concerning the forms that it may assume. I will accept Dr. Councilman's classification,[1] simply modifying his terminology to indicate my doubts as to the endarteritic or inflammatory na-

[1] Councilman: "On the Relations between Arterial Disease and Tissue Changes." Trans. Association American Physicians, vi., 1891, p. 179.

ture of the conditions. With him, therefore, I would distinguish (*a*) a nodular arterio-sclerosis, (*b*) senile arterio-sclerosis, and (*c*) diffuse arterio-sclerosis; and would with him acknowledge that these three forms merge one into the other. For our purpose, as throwing light upon the nature of the condition, the nodular form, the true endarteritis nodosa of Virchow, is that to which I would more especially call your attention.

The process begins by the development of semi-transparent, almost gelatinous, plaques here and there upon the walls of the aorta and larger vessels, most often in the neighborhood of and around the orifice of some side branch. Where the process is older the plaques are found firm, dense, and of almost cartilaginous hardness, and with this stage the deeper regions of the plaques exhibit manifest degenerative changes, passing on to the deposit of calcareous salts in the necrobiotic substance.

If we examine these plaques we are struck by the following peculiarities: (1) The endothelium over the plaque is continuous and apparently unaffected; (2) the new tissue is laid down regularly in layers parallel to the endothelium; (3) the connective tissue of the intima in the immediate neighborhood of the plaque passes imperceptibly into the hypertrophied connective tissue forming the plaque; there is no boundary line to be made out; (4) the oldest layers of the plaque are evidently those nearest to the elastic lamina, the most recent are beneath the endothelium and farthest away from the vasa vasorum of the media; and (5) the plaque is devoid of vessels save and except in those cases in which there is an evident attempt at the removal of the necrosed atheromatous material, and vessels penetrate into the atheromatous mass from the media in a manner comparable with their passage into a thrombus. Such passage, it will be recognized, is of purely secondary nature—the fibrous tissue has de-

veloped and undergone degeneration before it takes place.

The picture presented is not one usually associated with inflammation. The picture is rather what we should expect to find in an orderly connective-tissue hypertrophy, while the degeneration appearing in the deeper layers is what might be expected to occur in a non-vascular area in which layer after layer of con-

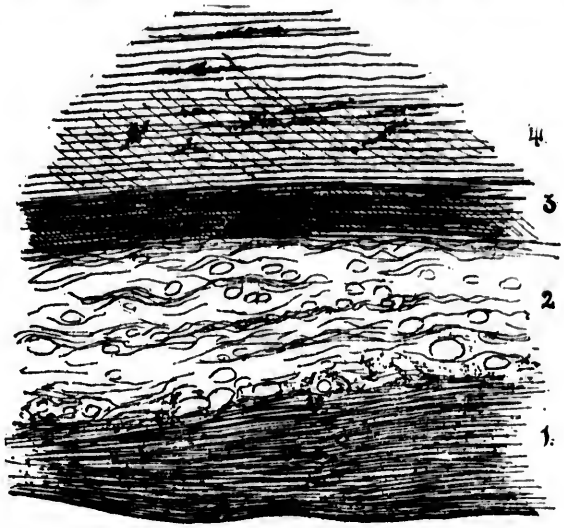

FIG. 2.—Section of the Aorta from a Case of Nodose Arterio-sclerosis. 1, Thick layer of hyperplastic connective tissue lying immediately beneath the endothelium; 2, hyaline and fatty degeneration of the lower layers of the intima; 3, internal layers of the media, staining poorly and having a hyaloid appearance; 4, outer layers of the media—cellular infiltration around the vasa vasorum.[1]

nective tissue cut off these deeper parts from their ordinary source of nutrition. Indeed, the sharp definition of the necrosed and calcareous tissue at the internal elastic lamina is often very remarkable and

[1] For this specimen and that from which Fig. 3 has been made I am indebted to Dr. G. H. Mathewson, who is studying the cases of arterio-sclerosis occurring at the Royal Victoria Hospital, Montreal.

would appear not only to afford a proof of the correctness of the view that the intima is nourished from the interior of the artery, but also would suggest that the internal elastic lamina performs a very definite function in separating two vascular areas.

This, however, is not the whole picture. Constantly accompanying and indeed preceding the changes in the intima, there is to be recognized an injury or degeneration of the outer coats, whether of specific, inflammatory causation (as in cases recorded by Thoma and Peabody), or whether due to more obscure alterations in nutrition associated with disturbances of the vasa vasorum. In many cases these small vessels are congested and present either an infiltration of small round cells in their immediate neighborhood or the development of surrounding fibrous tissue. The muscle fibres of the media frequently exhibit hyaline and other degenerative changes, and there may be some replacement fibrosis, or again evidences of more extensive failure of nutrition and of necrobiosis in the shape of small areas of calcareous deposit. That is to say, the media is very definitely affected and, as Thoma's experiments have fully proved, each plaque of overgrowth of the intima corresponds to a localized giving way of the arterial wall, to a localized slight bulging of the same; for by injecting affected arteries with paraffin under a pressure of one hundred and sixty millimetres of mercury, Thoma obtained a smooth cylindrical mould showing no signs of depressions corresponding to any projecting plaques; the hypertrophied intima fills and obliterates the slight bulgings or pouches of the outer coats. However produced, there can be no question that we have here to deal with a compensatory hypertrophy of the intima.

In the diffuse form also Thoma has demonstrated that the growth of connective tissue in the intima has a similar compensatory nature.

Is this process to be denominated an inflammation? Thoma and his pupils have shown that a thickening of the intima which they regard as strictly analogous is to be met with in the arteries of amputated limbs, in the portion of the aorta between the ductus Botalli and the offset of the umbilical arteries immediately following upon birth, in the uterine arteries after menstruation has set in, and still more clearly after childbirth; so to a less extent in the splenic arteries. All these latter cases must surely be classed among physiological rather than pathological reactions. Surely it is impossible to class a normal constant change, such as the overgrowth of the aortic intima following upon birth, as an inflammation. Nevertheless Thoma refers—or referred—to all these as conditions of compensatory endarteritis. But if he is right—and I do not see that he is not—in grouping all these cases, physiological and pathological, into one common class and ascribing to all a common causation, then not one ought strictly to be regarded as of inflammatory origin.

Thoma would explain his compensatory endarteritis according to the following law, namely, that the condition is to be ascribed to a slowing of the blood current. If this slowing be not arrested by a contraction of the media and consequent narrowing of the artery, leading to more rapid flow, then there occurs a new growth in the intima which leads to the same end—causing the lumen to become narrowed and the current to be restored to its normal rate.

He thus holds, and in this we must agree with him, that the primary lesion in arterio-sclerosis is a defect, a giving way, of the media, due to loss of elasticity however produced—and the only factor that he judges capable of explaining both the physiological and the pathological cases of connective-tissue overgrowth in the intima, and which is common to all cases, is relative slowing of the blood current. It is difficult to

follow his explanation of the mechanism whereby such slowing induces the hyperplasia of the fibrous tissue. Even if this slowing leads, as he indicates, to functional disturbance of the vasa vasorum, I cannot see how these vessels influence the nutrition of the intima. As I have said, I cannot find evidence that in healthy arteries or in the earlier stages of arterio-sclerosis any branches of these vessels pass into the intima. The process within the "bandelette" (as French histologists term the internal elastic lamina) appears to be at first sharply cut off from that occurring outside the same, and to be of a different nature—the new growth does not appear to develop from the neighborhood of

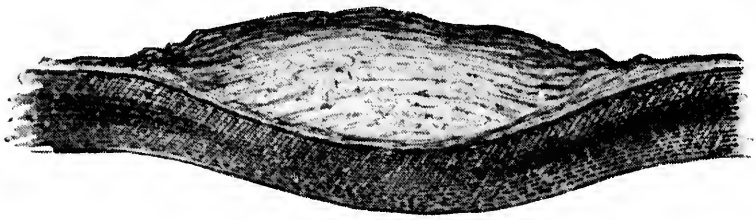

FIG. 3.—Section of the Aorta from a Case of Nodose Arterio-sclerosis, to show the bulging and thinning of the media, prepared by Dr. Mathewson; magnified 8 diameters. The section shows also the hyaline degeneration of the deeper layers of the overgrown intima, and the persistence of a fine layer of less altered intima tissue immediately beneath the media. The media in this case showed evidences of calcareous degeneration in patches, with some hyaline change.

the "bandelette" and in the proximity of branches of the vasa vasorum entering the intima, did they exist (save, as I have already stated, secondarily to degenerative changes), but occurs at a region farthest away from such branches. At most a thin and in general hyaline degenerated layer may frequently be found lying between the calcified atheromatous mass in the overgrown intima and the internal elastic lamina. This would indicate that a small amount of nutrition is derived from the media. On the other hand, the examination of numerous sections would indicate that after the degeneration of the lower layers of the intima

and the deposit there of a dense calcareous mass, growth still occurs actively and new layers become formed immediately beneath the endothelium. Were the main nutrition from the vasa vasorum of the media

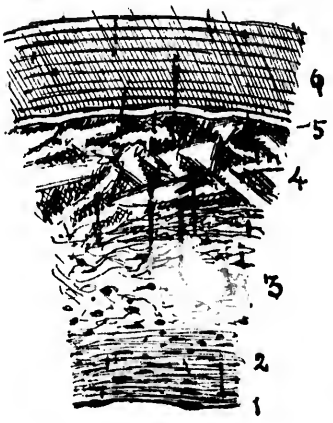

FIG. 4.—Section of an Artery of Medium Size, from the collection at McGill University. [This had been employed as a test specimen for the class and its label removed so that its exact origin cannot be stated.] 1, Intact endothelium; 2, layers of fibrous hyperplasia; 3, hyaline degeneration of the fibrous tissue; 4, layer of calcareous degeneration lying in immediate proximity to 5, the internal elastic lamina, somewhat swollen; 6, media presenting no distinct evidences of disease.

FIG. 5.—Section of Coronary Artery from a Case of general Arteriosclerosis, to show the persistence of a layer of but slightly altered connective tissue between the internal elastic lamina and the layer of calcareous degeneration. In this artery there had evidently been, as indicated at 4, two successive periods of sclerotic thickening of the intima, corresponding to a giving way of the media in two places.

this would not be possible, and malnutrition in consequence of disturbances in these vessels would lead to the production of wedges of degeneration extending toward the lumen, rather than to plaques of degenera-

tion lying deep down in the thickened intima close to the internal elastic lamina.

Thus I cannot but conclude that disturbances in the vasa vasorum are incapable of immediately originating the changes that occur in the intima. There may be fibroid, hyaline, and necrotic changes in all the coats of an artery, but the sequence of changes in the intima does not maintain a strict dependence upon and direct association with the sequence in the media and adventitia.

Alterations in the vasa vasorum failing to explain the new growth, I am compelled to fall back upon altered tension as a factor to be adduced in partial explanation of these cases of increased growth. With Thoma we may possibly also call in the agency of the sensory and trophic nerves as governing the growth, but here we enter further upon speculative ground. They may play—they probably play—an active part, but we have no direct evidence that they do.

The most that we can safely urge is that with relative expansion of an artery or portion of an artery there must be an altered tension acting upon the cells of the intima of the affected region—that accepting the view that the intima is nourished from within the lumen, anything which will lead to increased passage of the blood plasma into the subendothelial layers of the intima may at the same time lead to an increased strain upon the connective-tissue cells of the intima, and so to increased proliferation of the same.

If this be so, we may have another ground than the histological appearance for regarding the condition as non-inflammatory; we have to deal with a stimulus rather than injury to the cells of the intima, and may see in the fibrous hyperplasia a response to a physiological stimulus rather than a reaction to injury. In any case with our present knowledge, limited as it is, I would urge that the non-committal term of arteriosclerosis is preferable to that of chronic endarteritis.

Than this latter the term chronic arteritis is more acceptable, for in connection with the artery as a whole as distinguished from the intima there is in the giving way and thinning of the media evidence of injury, and in the intima as well as in the media, and it may be in the adventitia also, evidence of repair—of the

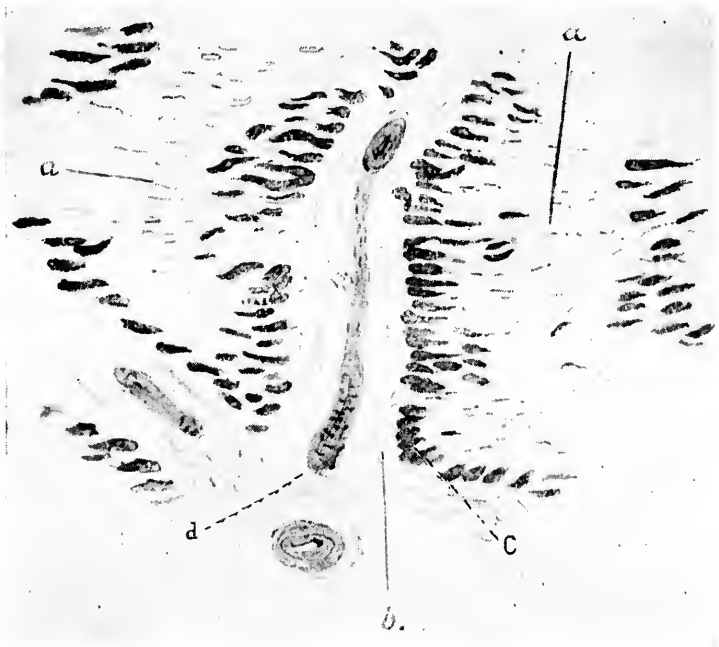

FIG. 6.—From a Section of the left Ventricle of a Patient dying from aortic stenosis with general arterio-sclerosis, to show mixed dystrophic (*a*) and periarterial fibrosis (*d*).

artery as a whole, not of the intima; an arteritis, not an endarteritis.

The distinction I admit is fine drawn, yet I am compelled to acknowledge that it exists. I cannot acknowledge a physiological inflammation, and if, as Thoma points out, the initial process is identical in physiological overgrowth of the intima and that occur-

ring in arterio-sclerosis, then the latter process must be regarded as functional. Were some irritant discovered capable of directly inducing the hyperplasia of the intima, the case might present a different facies. That such an irritant exists is, it seems to me, highly improbable. The peculiar contrast between the pulmonary and the systemic arteries in their liability to arterio-sclerotic changes is strongly suggestive of the action of differences in the circulation as explaining the contrast and not of the action of any irritative component of the blood.

I do but suggest this, and suggest it most tentatively. I shall feel rewarded if the suggestion leads to increased study into the phenomena underlying some of the commonest and most important forms of connective-tissue overgrowth. We are so woefully ignorant of the causation of such common conditions as chronic valve disease and arterio-sclerosis that I feel that, even if the views here enunciated originate strong and successful opposition, the stimulus they may have given to further investigation will be an ample reward.

The whole matter, as it appears to me, resolves itself into this: "Can we regard fibrous connective tissue as following the same laws as the higher tissues and so as undergoing hypertrophy in consequence of increased work or increased strain brought to bear upon it?" If we can, then it would seem that we can divide off an important series of fibroses from the huge class of inflammatory fibroses. If we cannot, then we must continue to regard all fibroses save the neoplastic as chronic "itides."

Provisionally, therefore, I would divide the various forms of fibrosis as shown in the diagram, namely:

A. Of inflammatory origin:

1. Replacement.
2. Productive.

3. Combined productive and replacement.
4. Neoplastic.

B. Neoplastic, of undetermined causation:

1. True fibromata.

C. Of functional origin:

1. Lymphatic.
2. Venous.
3. Arterial.

There are very many individual cases of fibroid change that I have not discussed in these two lectures. To have done so would have consumed too much time and would have carried us still farther into conjectural regions. But the cases that I have brought before you represent, I believe, the main types of fibrosis; and those not here taken into consideration will, I believe, fall into one or other of the main classes here indicated.

In conclusion I beg, Mr. President, to thank you and all the members for your great courtesy in enduring so patiently the long discourse that I have inflicted upon you, and once again to thank you for the honor you have conferred upon me in inviting me to deliver these lectures.