HAEMOCYTES AND HAEMIC INFECTIONS

FREDERICK W. E. BURNHAM

HAEMOCYTES

AND

HÆMIC INFECTIONS

A Hand-Book for Students and Practitioners

By

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WITH

Two Hundred and Twenty-six Microphotograms by the Author

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To
PIET,
in appreciation of her loyalty and
affection, this volume is gratefully
dedicated.

INTRODUCTION.

This volume is offered to the student and general reader, with the feeling, that a beginning only is made with the subjects of which it treats. Hæmocytes and hæmic infections, embraced in the subject of Hæmatology, is one of which the greater part is yet to be told.

In the compilation of this volume, it has been the author's desire to present a certain amount of information, in a readable and acceptable form; no pretension is made to a complete treatise.

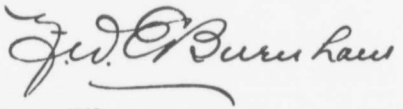
Attention has been directed to the relation, which the pathological changes bear to the physical signs.

The nomenclature adopted is one which may be readily understood and remembered.

In presenting the illustrations contained herein, the author feels that many of the difficulties, attending satisfactory microphotographic reproductions, have been overcome. The microphotograms have been taken at a magnification, which would clearly set forth the morphological characters of cells and parasites, as seen in the blood, in various phases of disease.

In the preparation of the text, every effort has been made to give investigators credit for original observations, and discoveries. It is probable that, in some instances, credit for original research is not given to those entitled to it. If such be the case, and it should happen that this volume is of sufficient merit to warrant future editions, this oversight will be generously corrected.

The microscopical material received from friends and correspondents in all parts of the world, has been of invaluable assistance, and is gratefully acknowledged.



WINNIPEG, January, 1913.

CONTENTS

NORMAL CHROMOCYTES.

In the circulating blood of healthy adults, the so-called red corpuscles are recognised easily, as circular, biconcave discs, from 6 μ to 9 μ in diameter, and about 1 μ in thickness. In infancy, larger and smaller forms are found, even in health, but in the adult the predominant characteristic is the persistent uniformity of size and shape. A departure from this uniformity is considered morbid.

In health, the variations which occur in the size of the red corpuscles are comprised within very narrow limits. Variations from 7.5 μ, the ordinary diameter of the red corpuscles, seldom exceed 1 μ above or below this, and are comparatively seldom seen. In infancy, the diameter ranges from 3 μ to 10 μ. To these aberrant forms the terms microcytes and megalocytes are applied.

No satisfactory explanation has been afforded, of how the red corpuscle acquires its biconcave form. It is certain that this special characteristic of the full grown corpuscle is no accident, but evidence of a developmental tendency.

Various as may be their source of origin, in early fœtal life, modern physiologists regard the red corpuscles, during the period of growth and adult life, as being developed from nucleated cells, termed erythroblasts, which are found in the red marrow of bones. Erythroblasts multiply by karyokinesis, and gradually become transformed, with disappearance of the nucleus, into erythrocytes, or red blood corpuscles. The red corpuscles, thus evolved from the erythroblasts, have arrived, so far as we know, at the highest stage of their development.

Gibson has described, very fully, the changes that take place in the development of red blood corpuscles from marrow cells. He describes a thin ring, containing hæmoglobin, at the periphery of the cell; this gradually increases, so as to fill the whole space between the cell envelope and the nucleus, and, as the hæmoglobin-tinted, perinuclear substance increases in amount, the nucleus appears to become smaller, and to retreat towards the centre of the cell,—the cell as a whole at the same time becoming smaller. He believes that the nucleus is the active agent, in attracting hæmoglobin

to the cell, and that, when its function is fulfilled,—that is, when the cell is fully charged with hæmoglobin, being of no further service, it disappears.

Ehrlich believed that the normoblast is converted into the red blood corpuscle, by extrusion of the nucleus. This theory of blood formation, by extrusion of the nucleus, has been generally abandoned.

The transformation of the nucleated cell, into the ordinary red blood corpuscle, is brought about by the disappearance of the nucleus, by karyolysis.

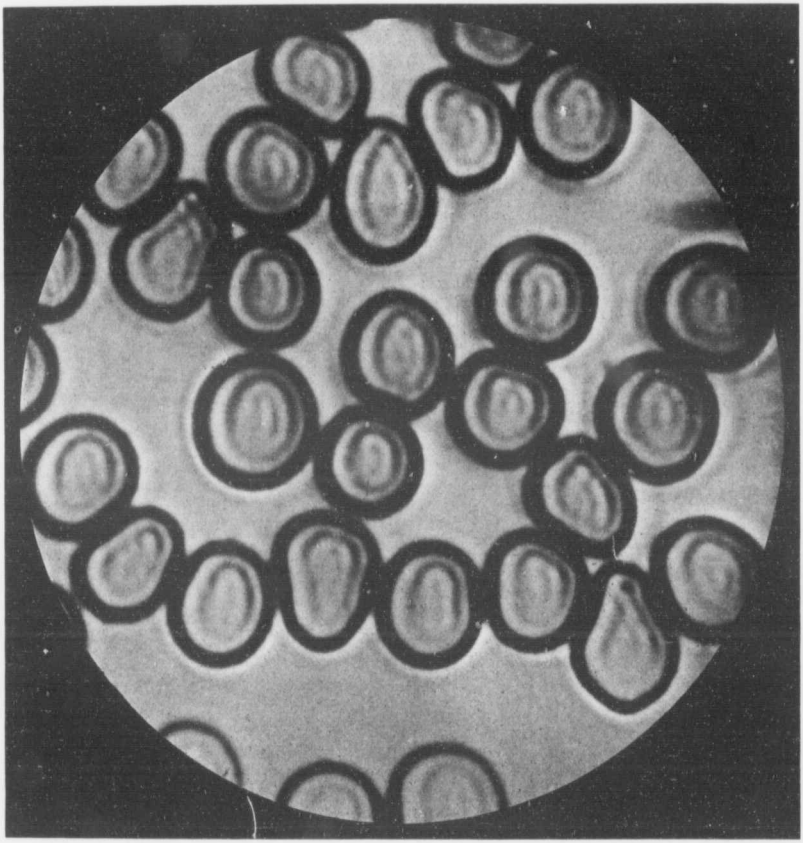
The life duration of chromocytes.

The question of the normal life duration of red blood corpuscles is of prime practical importance, in its relation to the important question of transfusion of blood in man.

Worm-Muller (Christiania, 1875) found, after transfusion of blood in dogs, that, two or three days later, the number of corpuscles closely corresponded with that previously present, plus those injected. This condition, however, did not continue long. In a few days, the corpuscles began to diminish in number, and, in a few weeks at most, they had fallen again to their original number. The greater the quantity of blood transfused, the longer did this process of destruction and removal take; for whilst, after the transfusion of 20 to 30 per cent. of blood, the whole of the injected corpuscles were removed in the course of a few days, after the injection of 60 to 80 per cent., their destruction was not complete, for a period of 2 to 3 weeks. According to these observations, therefore, the longest possible life duration of corpuscles, after transfusion in dogs, would be about 2 or 3 weeks.

With this estimate Quincke's observations agree. The life duration of the red corpuscles, in dogs, he also estimates to be about 2 to 3 weeks. Quincke's method of investigation was the same, namely, the intravenous transfusion of blood; but, instead of enumerating the corpuscles, he estimated the hæmoglobin percentage of the blood. This method of investigation is open to considerable fallacy, since the hæmoglobin percentage does not necessarily correspond with the number of corpuscles.

The method, employed by Hunter (London), to determine the life duration of red corpuscles, differed from those previously mentioned. The blood, instead of being transfused directly into



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Normal red corpuscles.

the circulation, through a vein, was introduced indirectly through the peritoneal cavity, the absorption from which is rapid and continuous. This method of procedure causes no distention of the vascular system, such as would be present, after intravenous transfusion of large quantities of blood. After the injection of defibrinated blood, Hunter found the amount of absorption was fairly proportional to the amount of blood injected, and its rapidity fairly uniform, throughout the whole period of absorption. In these experiments, the time taken for the complete removal of the excess of corpuscles, in the case of entire blood, varied from 5 to 26 days. The life duration of the injected corpuscles was found to be, on an average, 3 weeks. In the case of defibrinated blood, the time varied from 4 to 21 days; on an average, 17½ days.

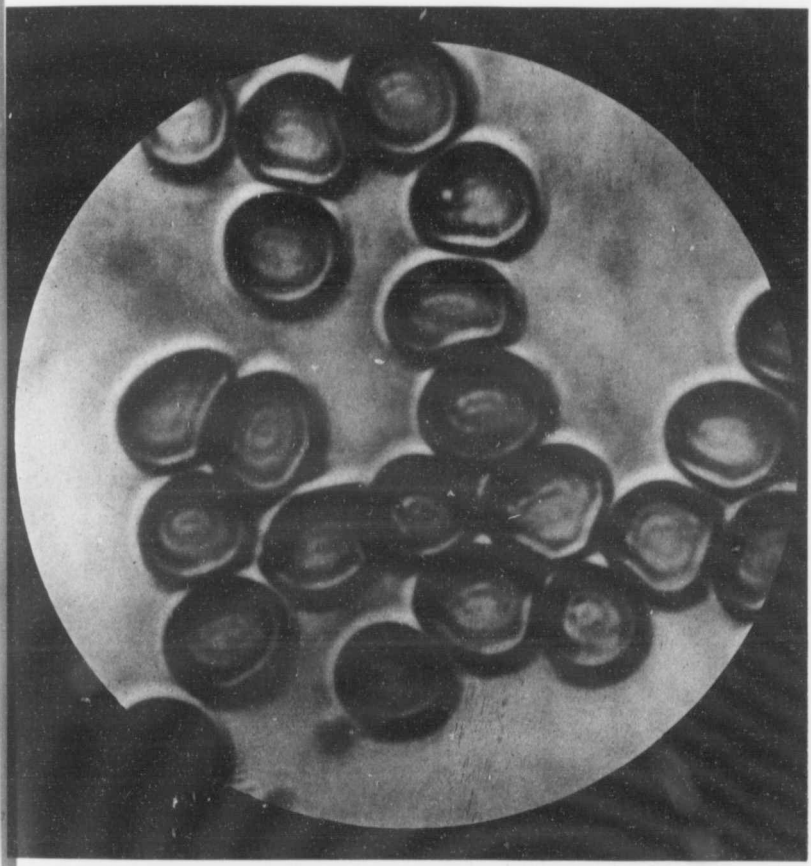
Hunter therefore concludes, from these experiments, that the longest duration of life of the red blood corpuscles, after transfusion in rabbits, is about three to four weeks.

Regeneration of blood.

After hæmorrhage, the generation of red blood corpuscles goes on very actively. Von Ott found, by depleting dogs, that the time required for the restoration of the red corpuscles, would be about 3 weeks. Lyon similarly found that, after severe loss of blood, in man, the time required for the return to the normal varied from 19 to 31 days, with an average of 25 days. The time required for the corpuscles to be completely restored, counting from the period of lowest fall, was on an average 20 days.

The effect of change of temperature.

Friedlænder reports that, after prolonged exposure to cold, there was diminution of the red blood corpuscles, increase of white corpuscles, and lowering of specific gravity. There was no alteration in the density of the serum. After short exposure to cold, the red corpuscles were increased, as well as the white; and the specific gravity was raised; serum density was unaltered. The effect of warmth was to increase both red and white corpuscles, especially the latter, and to raise the specific gravity of the blood, and the density of the serum. Friedlænder considered that perspiration probably played some part in producing the changes observed.



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Normal red corpuscles.

Ziegler reports the following constant changes in the blood of overheated animals, in Werhowsky's experiments.—(1) Emaciation. (2) Progressive diminution of amount of hæmoglobin, in the blood, by as much as 30 per cent., in a long experiment. (3) Diminution of the total number of red corpuscles, but often not in the same proportion as the hæmoglobin. (4) The only change in the red corpuscles is an increase of the small forms. (5) The white blood cells; there is an increase of the large single nucleated cells and of the polynuclear pseudo-eosinophile cells, and a diminution of the small single nucleated leucocytes.

The blood in malignant disease.

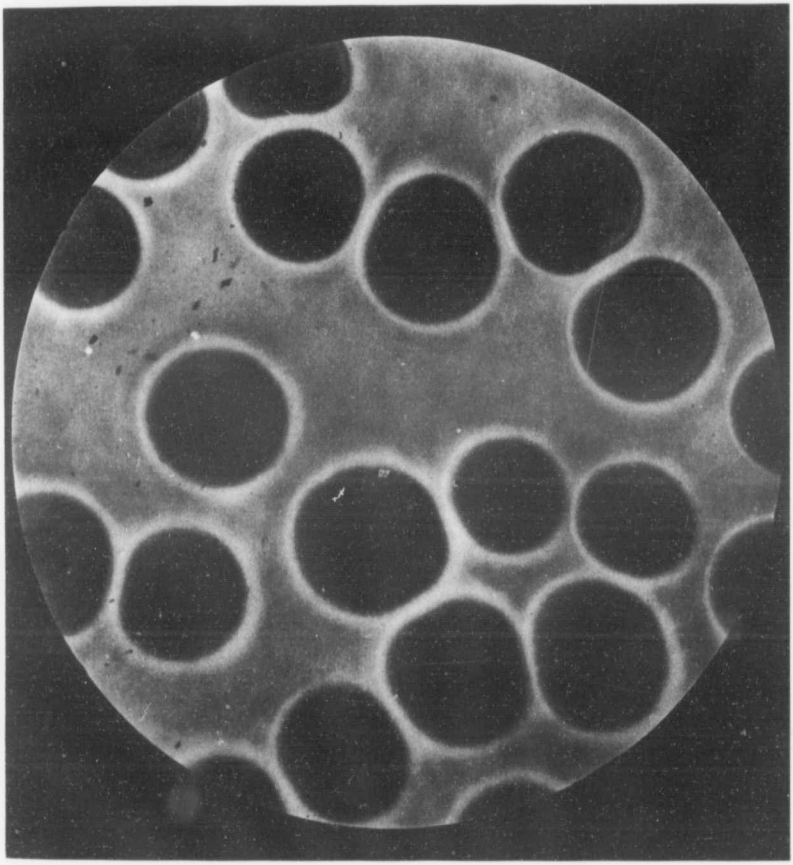
Although certain changes are more or less constant, it would appear that there is no specific type of blood, associated with malignant disease. Speaking generally, the changes observed are a diminution of the hæmoglobin, and in the number of corpuscles; alterations in the shape and size of red corpuscles, and in some cases the presence of erythroblasts; absolute and relative increase in the white corpuscles. The blood changes, in malignant disease, would appear to depend more on the seat of the tumor, than on its nature. In an enormous sarcoma, originating in the abdominal parietes, in which one would expect serious blood changes of a secondary nature, the author found the blood quite normal.

The blood in diabetes.

The blood in diabetes frequently shows, not only no diminution in the number of red corpuscles, and in the percentage of hæmoglobin, but distinct increase. By Leichtenstern and others, this has been explained, as being due to concentration of blood, resulting from polyuria.

The number of chromocytes in the blood.

In health, the number of red corpuscles in the blood varies, within narrow limits. By general consent, the standard is fixed at 5,000,000 per cubic millimetre, for the adult male, and 4,500,000 for the adult female.



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Hyperchromemia.

Oligocythæmia.

The condition of the blood, in which the red cells are reduced in number, is termed oligocythæmia. This reduction may be temporary, as after hæmorrhage, or it may be persistent. In extreme cases of anæmia, the number of red cells may be reduced to one-tenth of the normal, or even less. Hulmerfauth has shown that, after simple loss of blood, the minimum number of corpuscles was reached in from 1 to 5 days, according to the extent of the loss; and the time taken for the return to the normal, from 14 to 23 days. Lyon similarly found that the time required for the return to the normal varied from 19 to 31 days, the minimum number of corpuscles, after blood loss, being reached in from 2 to 6 days, average 4 days.

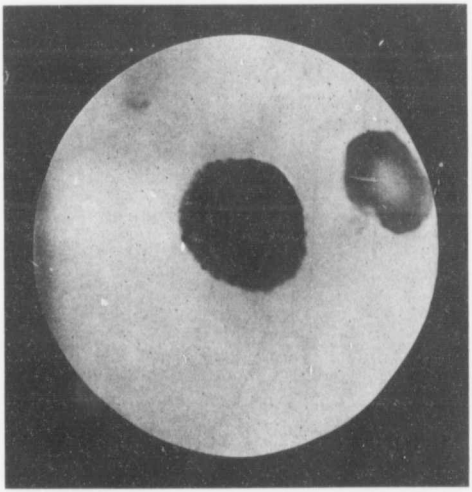
The effect of a great loss of blood is to create a condition of oligocythæmia, and to lessen, for the time being, the oxidative processes going on in the body, and correspondingly diminish the activity of the various organs. There is every reason to believe, that this lessened activity will apply to the processes of blood destruction, and, to a less extent, to the processes of cell formation (Hunter).

Polycythæmia.

Cheron has observed that massage, dry friction, and electricity, will, within ten minutes, greatly increase the number of corpuscles, in one case of anæmia raising it from 2,430,000 to 4,080,000 per c. mm. He attributes the rise to the concentration of the blood, from increased transudation of fluid, which results from augmentation of the blood pressure.

The general result of exercise is a rise in corpuscles, which, after a variable period, subside, but remain above the initial percentage, while the exercise lasts. Dislodgment of resting corpuscles has been advanced, in explanation of the increased proportion of chromocytes to plasma, during muscular activity.

All observers are agreed as to the presence of an increased number of hæmocytes, in the blood of the inhabitants of mountainous regions,—an increase which rapidly passes away, on their return to lower altitudes. On his visit to Davos Platz (5,200 ft.), Oliver found that the corpuscles began to rise, within 24 hours, and attained their maximum percentage, within the first week. The average increase, from the fourth to the fourteenth day, was ten per cent. and



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Small lymphocyte with protoplasmic granulation.

the maximum rise fourteen per cent. The hæmoglobin increased to a less extent than the corpuscles.

The polycythæmia of high altitudes is due to rapid blood formation, incited by lessened supply of oxygen from reduced pressure, and the need of more oxygen carriers, to supply the tissue requirements.

Pathological polycythæmia.

In splenomegalic polycythæmia, blood counts of 12,000,000 per c. mm. have been reported.

This pathological condition is due to an actual increase in the number of red corpuscles, a true plethora, and is not merely a concentration of the blood.

Theoretically, polycythæmia may be due to an over-production, or a diminished destruction, of red blood corpuscles. No evidence has yet been produced, to indicate that diminished destruction plays any part in this condition. The cause of this over-activity of the erythroblastic function is not clear.

The blood is very dark purple in colour, and flows sluggishly from a puncture; the viscosity is greater than normal, and the coagulation time markedly shortened.

The cases present the symptom-complex of cyanosis, polycythæmia, and splenomegaly.

The splenic enlargement, though a constant feature in all cases, is never extreme. It is apparent long before the appearance of the cyanosis.

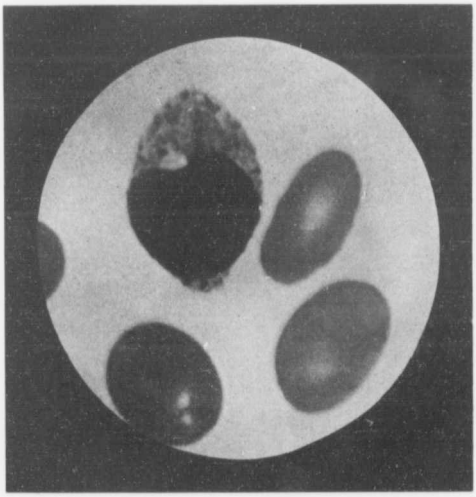
The red corpuscles range from 8,000,000 to 12,000,000 per c. mm. and the hæmoglobin varies between 110 and 200.

There is an increased erythroblastic activity in the bone marrow, with consequent polycythæmia, causing an increase in the specific gravity, and the viscosity of the blood; increased blood pressure, dilatation of the small blood vessels and venous stasis result.

The disease, which is generally fatal, usually lasts from four to ten years, with periods of remission.

The hæmoglobin content of chromocytes.

The percentage of hæmoglobin, contained in the blood, is determined clinically by colorimetric analysis. Normal corpuscles, 100 per cent, should contain hæmoglobin, which reads as near as



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Small lymphocyte with protoplasmic granulation.

possible 100 per cent., so that, when the latter is divided by the former, the unit obtained will represent the normal mean value of the corpuscle in hæmoglobin.

$$\frac{\text{Hæmoglobin percentage}}{\text{Corpuscle percentage}} = \text{Colour index.}$$

The quotient thus obtained has been designated "the worth," "the blood decimal," "the hæmoglobin index," and "the colour index."

Supposing the red corpuscle count to have been 2,000,000, which is 40 per cent. of the normal, and the hæmoglobin 50 per cent., the colour index is determined by dividing 50 by 40 which gives a hæmoglobin index of 1.25.

In health the hæmoglobin percentage varies from 90 to 105.

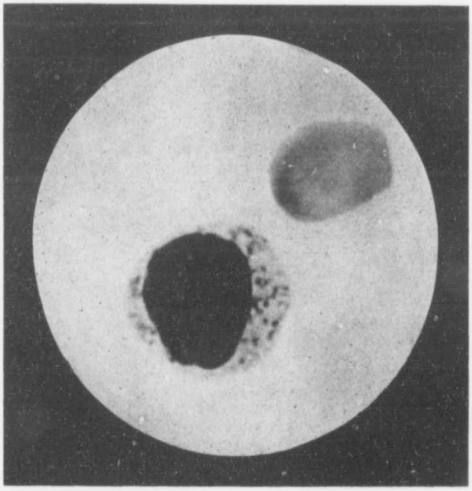
Hyperchromemia.

Instances have been observed in which, with a normal percentage of red corpuscles, the colour index considerably exceeded the normal limits. Such a case was examined by the author to discover the cause of a florid, at times almost cyanotic, facial coloration, in an apparently healthy woman. A blood examination revealed a normal corpuscle percentage, with a colour index of 1.25. No reason is offered, in explanation of this unusual condition.

Blood platelets.

In spite of all the work that has been done on the subject, the origin and nature of the blood platelets is still unknown. The significance of this element of the blood is in dispute; by Hayem, who considered them young red cells, they were named hæmatoblasts. Some have considered them among the normal histological elements of the blood; others thought them degeneration products of leucocytes, or chromocytes. Some observers, who have studied the effects of destructive agents on the blood corpuscles, have been struck by the resemblance of certain fragmented corpuscles to the platelets, and believe that the latter originate from the red cells.

According to Wright, the blood-platelets arise by the pinching off of the ends of slender processes of mononuclear giant cells, and they first appear in the embryonic blood, after the giant cells have been produced in the blood-forming organs.



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Small lymphocyte with protoplasmic granulation.

The platelets are circular, or oval elements, about 2 or 3 μ in diameter, with well defined margins, and consist of a homogeneous, or granular protoplasm. No nuclear matter is discernible.

In normal blood, the number of platelets per c. mm. is found to be about 775,000. The maximum, in 19 individuals, was found by Kemp and Calhoun to be 961,500, and the minimum 730,000. The ratio of the platelets to the red blood corpuscles is fairly constant.

The staining affinities of the platelets are not constant. Their micro-chemical reactions resemble, to some extent, those of red corpuscles, and also those of the nuclei of leucocytes, but are identical with neither.

Their histological structure, and function, are still a subject of discussion.

The platelets have long been known to have some bearing on coagulation, and are the only elements, whose disintegration is to be seen in the coagulation of normal blood. In the coagulation of blood, as observed with the microscope, the fibrin strands are seen to start from groups of the platelets.

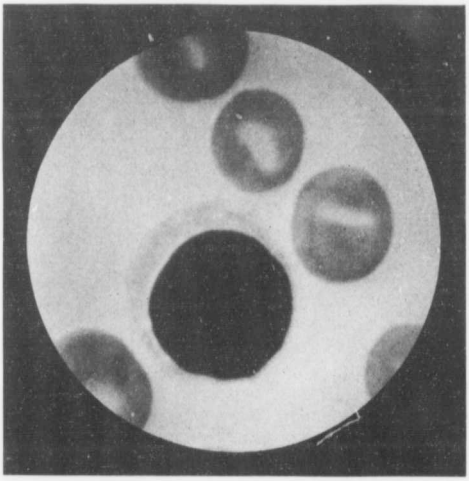
In a case of purpura hæmorrhagica, Hilber compared the number of platelets with the coagulation time, and found there was an apparent relation between the two. When the platelets numbered 40,000, the coagulation time was 9 minutes. Later when the platelets increased to 64,000 the coagulation time was 7 minutes and still later when the platelets had risen to 81,000, the coagulation time was shortened to 4 minutes.

LEUCOCYTES.

Leucocytes may be divided according to the presence (1), or absence (2), of granulations in the protoplasm.

1. The leucocytes, in which the protoplasm is non-granular, include all those which go by the name of lymphocytes; and may be further subdivided according to their size.

(a). *Small lymphocytes.*—The small lymphocyte is a rounded cell, about the size of a red corpuscle, with a large, strongly basophile, homogeneous, rounded nucleus, occupying nearly the entire cell, and surrounded by a thin envelope of protoplasm. They consti-



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Transitional lymphocyte.

tute about 23 per cent. of the total number of leucocytes, in normal blood. The small lymphocyte has its origin in lymphatic glands. It is practically immobile, and never phagocytic.

(b). *Transitional lymphocyte.*—This term is given to a cell, which is intermediate, in size, between the small and large lymphocytes, and differs from them in the irregularities, and indentations, of the nucleus. They are usually grouped under the head of small or large lymphocytes, as the case may be. It is probable that the transitional cell is a stage in the development of the small lymphocyte, into the larger cells, while in the circulation. All cells of this type are over 8 μ, and under 13 μ, in diameter.

(c). *Large lymphocytes.*—These are cells, of which the transitional are forerunners, and differ from the preceding forms, only in the increase of perinuclear protoplasm. The protoplasm is clear, faintly basophile, and faintly reticular, with occasional nodal thickening, resembling granules. The large lymphocytes, in size, generally range from 13 μ to 17 μ in diameter. As regards size, every gradation, between the two forms, is met with, and the division is purely arbitrary.

The nucleus of the large lymphocyte is round, or oval, in outline, and in many cases is indented more or less deeply. Phear (London) points out that the notch is more often present, than at first sight appears; for it is only conspicuous, when in profile, *i. e.*, when the position is such, that the notch is situated laterally. If, from the position of the cell, the notch lies, not at one side, but above or below, the visible outline of the nucleus is not broken by the notch.

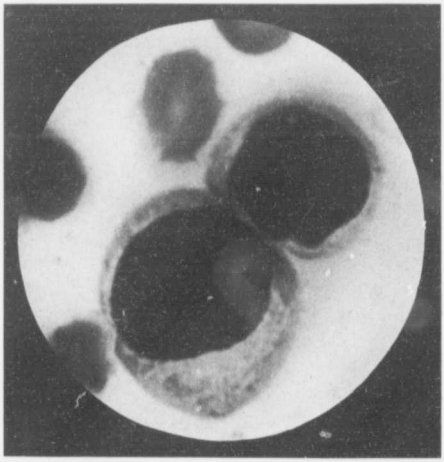
The large lymphocytes, together with the transitional forms, make up about 3 per cent. of the normal number of leucocytes.

The small lymphocyte is the only cell, to which the large one has obviously clear relations; no transitional forms are found between the large lymphocyte, and any other kind of leucocyte, found in normal blood.

The large lymphocyte possesses much protoplasm, and is actively amœboid, and feebly phagocytic.

Granular leucocytes.

Granular leucocytes make up about 75 per cent. of the leucocytes of normal circulating blood. They are amœboid, and, mostly, actively phagocytic. The further subdivision of granular leuco-



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Large lymphocytes.

cytes depends on the differentiation, which various aniline dyes bring about, in the protoplasmic granules. The micro-chemical reaction of leucocytes is of supreme importance, in the recognition of the different varieties of leucocytes, and of leucocytosis in its various forms.

Sheridan Delepine divided aniline dyes into two classes: (a) acid, of which acid fuchsin may be taken as a type, and (b) basic, of which basic fuchsin is an example. The first class stains the most differentiated, and the second the least differentiated portions of cells. In a film of blood, subjected to the acid stain, the chromocytes are most deeply stained, the leucocytes but faintly stained, while the nuclei are not stained at all. The reverse is true, if a basic stain is used; the nuclei are stained most deeply, the cytoplasm of the leucocytes to a less extent, and the red blood corpuscles least of all.

The nucleus of the leucocyte, like the nucleus of every other cell, with which we are familiar, is invariably basophile, while the granules, which are found in the normal circulating blood of mammalia, are neutrophile or oxyphile.

Classified according to their behaviour toward acid, basic, and neutral aniline dyes, Ehrlich distinguishes five kinds of granulations, which he designates α, β, γ, δ, and ε.

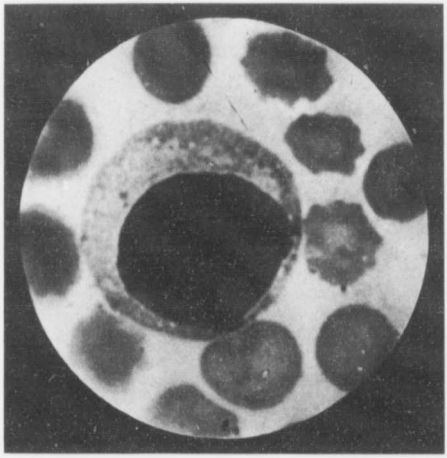
According as the leucocyte contains oxyphile, neutrophile, or basophile granulations, we recognise the following types in the normal circulating blood:—

The neutrophile leucocyte.

This, the most common form of leucocyte, present in normal human blood, constitutes from 70 to 72 per cent. of the total number of leucocytes present. The protoplasm does not stain with methylene blue, and shows no structure beyond a fine granulation. The granules are minute, numerous, and evenly diffused throughout the protoplasm.

The nucleus is irregular in shape, often semicircular, or lobed. Ordinarily, there is no break in the continuity of the parts of the nucleus, which are united by narrow or fine threads.

The polymorphism of the nucleus of the neutrophile is a subject, over which there has been considerable discussion, among hæmatologists. The writer prefers to view the cell as polymor-



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Large lymphocyte.

phonuclear, rather than polynuclear. The nucleus stains deeply, but not evenly, with methylene blue.

The granules of these cells take up the neutral aniline dyes, and, by reason of their micro-chemical reaction, have been termed neutrophile. Kanthack and Hardy state, that this is not strictly correct, for the granules will stain with eosin, which is an acid stain. Hence, they prefer to call them finely granular eosinophile, or oxyphile cells.

The polymorphonuclear neutrophile leucocytes measure from 11 μ to 15 μ, averaging 13.5 μ.

Of considerable interest is Arneth's work on the variability of the nuclei of the polymorphonuclear leucocytes. The central idea of his work is, that the young cell has but a single nucleus, while the older forms are polynuclear. In infections, the older or polynuclear forms are destroyed first, and, with the increased production, there appears in the blood a larger number of younger forms, so that an estimation of the varieties of nuclei will give an idea of the severity of the infection, and the strength of the resistance.

Black (Hereford) has noted, after tuberculin treatment, an increase in the number of neutrophile leucocytes with fragmented nuclei. Before treatment, polymorphonuclear leucocytes with one nucleus were estimated to be 33 per cent., after treatment, 9 per cent.; those with two nuclei, 40 per cent.,—after treatment, 32 per cent.; those with three nuclei, 16 per cent.,—after treatment, 42 per cent.; and those with four nuclei and over, 11 per cent.,—after treatment, 16 per cent.

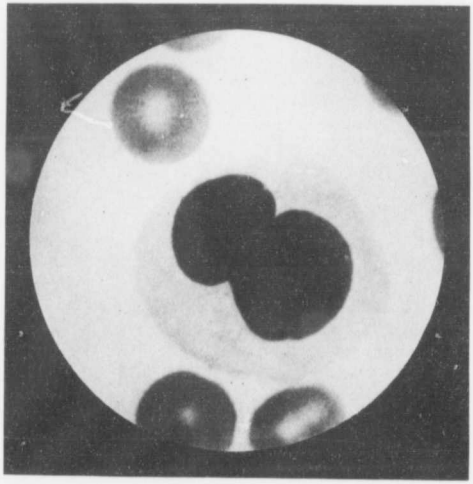
The eosinophile leucocyte.

The eosinophile leucocytes present many points of interest; morphologically, they are of great antiquity, for they are found in most animals possessed of a vascular system.

The granules, which are large, measuring up to 1 μ in diameter, appear as round, glistening objects, of a uniformly dark green colour. When treated with a mixture of acid, basic, and neutral aniline dyes, the granules take up the acid stain, and the name eosinophile is derived from the fact that, of the acid stains, eosin is the one most frequently employed.

The nucleus stains feebly with basic dyes, and is often placed excentrically. It is frequently divided into two or more parts; a connecting strand, between the parts, can sometimes be made out.

The oxyphilic, or eosinophilic leucocyte, is 9.5 μ to 10.5 μ in



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Large lymphocyte.

diameter; their numerical proportion is 2 to 4 per cent., in normal blood.

Kanthack and Hardy have shown that, in animals, these cells are especially numerous, in the fluid of the cœlomic spaces; also, that they are found in the spleen, and the bone marrow, and in the connective tissue, their habitat being in the interstitial tissues, while the neutrophile cells are confined almost entirely to the blood. Some authorities consider that they originate in the bone marrow, but the observations of the authorities, quoted above, tend to show that the interstitial spaces play an important part in their history.

Many views, as to the origin of eosinophiles, have been put forward. Some believe, that the coarsely granular leucocytes are derived from the finely granular; others, that they are transformed connective tissue cells; others, that they are formed in the bronchial and intestinal mucosa. Another view is, that the eosinophile granules are formed from acidophile substances, ingested by leucocytes. Metschnikoff has noticed spirilla of cholera, taken up by leucocytes of the guinea pig, become altered, so as to take the acid stain. Mesnil states that anthrax bacilli are taken up and transformed into eosinophile granules by the lizard. Opie is of the opinion, that the origin of the eosinophile, from the eosinophile myelocyte, in the bone marrow, represents an analogous phenomenon, to the origin of the polymorphonuclear neutrophile leucocyte, from the neutrophile myelocyte.

Ehrlich regards the eosinophiles as secretory cells, and assumes that they constantly discharge their granules into the blood.

The eosinophile is easy of recognition, for the granulations present in the cell are conspicuous, by virtue of their size, and sharp contour. The protoplasm connecting the granulations is very delicate.

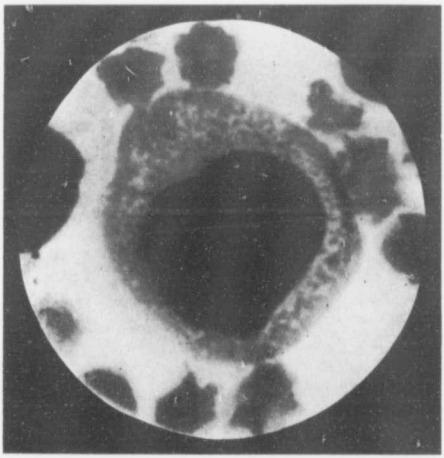
The eosinophile is very actively amœboid, but never phagocytic.

The basophile leucocyte.

The basophile leucocyte, or mast cell, is characterised by having large and small granules, in the cytoplasm, which have a special affinity for basic aniline colours.

In normal blood, they rarely exceed 0.5 per cent. of the total number of leucocytes.

The nucleus is lobulated, placed excentrically, and stains with difficulty.



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Large lymphocyte.

The cell is about 8 μ in diameter.

The basophile leucocytes are found chiefly in the connective tissue, in the neighborhood of blood vessels.

LEUCOPENIA.

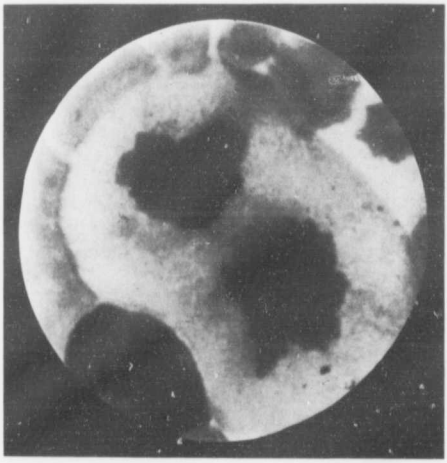
Hypoleucocytosis and leucopenia are synonymous terms, which signify a diminution of the total number of leucocytes, in the circulating blood: the condition is observed in comparatively few diseases.

The fall in the total number of leucocytes may be due to the following circumstances:

1. Accumulation of leucocytes in various organs.
2. Emigration of leucocytes into the tissues.
3. Leucocytolysis in severe septicæmic conditions.
4. Interference with leucocyte formation, in bone marrow, as result of the action of toxic substances.
5. Negative chemotaxis.

The leucocytes in pneumonia.

It had been noted that, in cases of pneumonia ending in recovery, the blood generally contains a greatly increased number of leucocytes, while, in fatal cases, the leucocytes are diminished far below the normal number. Tchistovitch made the following interesting observations, on the cellular elements of the blood in pneumonia, to elucidate the relation between the virulence of the *Diplococcus pneumoniæ*, and the changes in the number of leucocytes, in the blood of animals inoculated with this microbe. Cultures were obtained, by inoculating a rabbit with pneumonic sputum, and, on its death, inoculating tubes of bouillon with heart blood, in which diplococci abound. These broth cultures are at first extremely virulent, but, on being kept at 38° C., lose their virulence, from day to day. A series of cultures, of different virulence, were thus obtained, and inoculated into rabbits, of which the leucocytes had been carefully estimated, for some days previously. After inoculation, the leucocytes were again counted, at stated intervals, until either



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Mitosis in large lymphocyte.

the recovery, or the death, of the animal. The following results were obtained: 1. Attenuated cultures caused, in every case, an increase in the number of leucocytes, which lasted one or two days, and disappeared with the recovery of the animal. 2. With virulent cultures, after a few hours even, there was marked diminution of the leucocytes, which became more evident till death took place. 3. The course of the disease was dependent on the virulence of the culture, and on the resistance of the animal. A culture, strong enough to kill a young rabbit, failed to cause the death of an older one, and produced diminished leucocytosis in the former, increased leucocytosis in the latter.

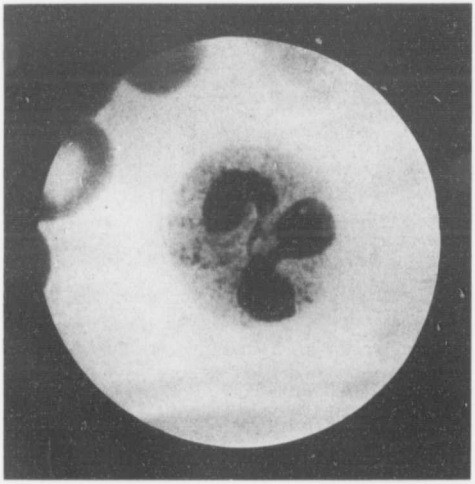
It would seem to be certain, that a benign course is closely connected with increased leucocytosis, a fatal course being marked by leucopenia. Thus, examination of the blood, in pneumonia, may be important from the point of view of prognosis.

Leucopenia in typhoid fever.

Gennari gives the results of the examination of the blood of 106 cases, presenting very early symptoms of typhoid fever. The serum reaction for the typhoid, and paratyphoid bacillus, was taken, and the blood count for the white corpuscles observed. It was found that leucopenia may exist as early as the second day of the disease (in 4 cases out of 9), whilst the Widal reaction was present in only 2, out of 9. A similar relation, between the two phenomena, was found to exist in later stages, so that Gennari concludes that leucopenia is more frequently to be met with, in the early stages of the disease, than any other sign (including the Widal test). Thus, out of 66 cases, 47 had less than 5,000 leucocytes per c. mm., whilst only 23 reacted to the Widal test. Hyperleucocytosis was never present in any of the 106 cases, or, if so, was due to some complication. According to Gennari, no prognostic import can be drawn from the presence of leucopenia, as it occurs in mild, and in severe cases.

Leucopenia in malaria.

Billings found a striking diminution in the number of leucocytes, during the febrile stage of malaria. The maximum number of leucocytes was found, 2 or 3 hours after a chill. From this time,



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Polymorphonuclear neutrophile leucocyte.

there was a progressive diminution, until the minimum was reached, at the end of a paroxysm. The number of leucocytes then rises somewhat, and, during the interval, occupies a position midway between the maximum and minimum.

It is probable that, in most cases of leucopenia, a combination of circumstances is responsible, for example, in the fall of leucocytes, in pneumonia, without a true crisis.

Another interesting fact has been noted, namely, that, in various infective conditions, when the leucocyte number falls, there appear in the blood some of the finely granular myelocytes, which are so numerous in the blood of myelemia. Muir (Edinburgh) looks upon this sign as a bad omen.

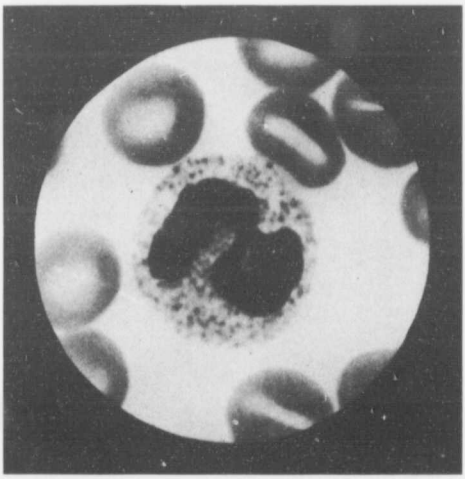
Hypoleucocytosis is a fairly constant feature of pernicious anæmia, and is found in some cases of chlorosis, and in anæmia with splenic enlargement.

Leucopenia in x-ray workers.

Jagic, Schwarz, and Liebenrack examined the blood, in those exposed more or less, in their work, to small but frequent doses of Roentgen rays, over a long period of time. Most of the cases were men who had worked for years with x-rays, always, except in the earliest years, with protective apparatus; most of them were in normal health, or complained only of slight general weakness. There was, in all cases, a slight but definite diminution in the total number of leucocytes in the blood. The number was either below the normal, or near the lower limit of normal variation. The diminution was chiefly in the polymorphonuclear leucocytes. The eosinophile leucocytes were, in some cases, altogether absent. The lymphocytes were in every case increased.

Leucopenia in hæmophilia.

A percentage of polymorphonuclears, as low as 35 per cent. has been reported by Wright, in hæmophilia. This observer has found low percentage of polymorphonuclears, generally in bleeder families, and is of the opinion that an unduly low percentage of polymorphonuclears, and an unduly small sum total of leucocytes, stand in some causal relation with the hæmophilic diathesis.



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Polymorphonuclear neutrophile leucocyte.

LYMPHOCYTOSIS.

Lymphocytosis is a relative, or absolute increase, of the lymphocytes in the peripheral blood. While polynucleosis is of great diagnostic importance, lymphocytosis is of slight clinical interest.

The condition is supposed to be due to an increased flow of lymph, washing the cells out of the lymphatic tissue, in a simple mechanical fashion.

Lymphocytosis in infancy.

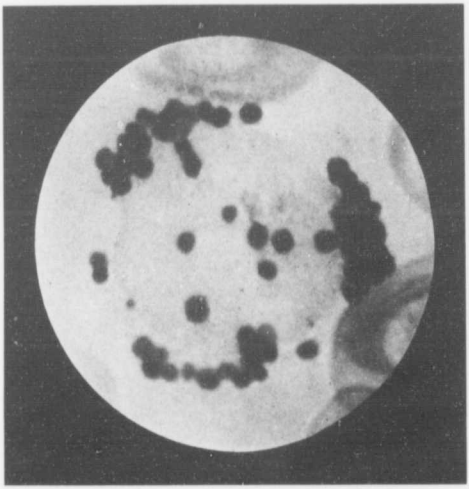
During the first week after birth, there is a polynucleosis of about 20,000, which rapidly diminishes, so that, at the end of the week, the polymorphonuclears number about 5,000. A second rise now occurs, due to increase in lymphocytes, which persists until the sixth month. After the sixth month, the total number of lymphocytes slowly declines, and, with it, the total number of leucocytes, until about the sixth year, when the adult proportion is reached. The lymphocytes show a gradual rise, from the beginning of the second week, reaching its culmination about the sixth month. They then fall, and, at the end of the third year, about equal the polymorphonuclears, but do not reach the stationary until the sixth year, which number persists. The increase in polymorphonuclears is a phenomenon connected with birth.

The characteristic features, of the infantile type of blood, is a high absolute lymphocytosis, and a relatively low percentage of hæmoglobin.

Lymphocytosis in malaria.

A marked increase, in the large lymphocytes, in the afebrile stage of malaria, has been noted. Christophers and Stephens found percentages, varying from 15 to 30 per cent., and considered that one of 15, or over, was of great diagnostic value. Türck made a careful estimation of the leucocytes, in cases of malaria, and found that the large lymphocytes were decidedly increased, in every stage of the disease, excepting the cold stage.

Daniels (London) places the proportion of large lymphocytes at 25 to 30 per cent., as a common finding, and looks upon a percentage of 15, as distinctly a low one, for this condition.



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Eosinophile leucocyte in blood of frog (Bufo regularis).

Discrepancies in lymphocyte counts are due, no doubt, to difficulty in separating the non-granular leucocytes into distinct groups. Different observers have different ideas as to what constitutes a small, or large lymphocyte, or a large mononuclear cell. In the classification of the non-granular leucocytes, which the writer has chosen to adopt, the confusing term "large mononuclear" has been discarded. There appears to be no sharp morphological differences, in larger lymphocytes, which, in his opinion, would justify their separation into distinct types.

EOSINOPHILIA.

Eosinophilia, or, in other words, eosinophile hyperleucocytosis, is an absolute increase of eosinophiles in the blood.

The infectious diseases generally are associated with a reduction in the number of eosinophiles in the blood,—for example, typhoid fever and pneumonia, though this hypo-eosinophilia is, in favourable cases, succeeded by hyper-eosinophilia, during convalescence, a fact which is considered of importance in prognosis: in scarlet fever, however, there is hyper-eosinophilia, during the active stages of the disease.

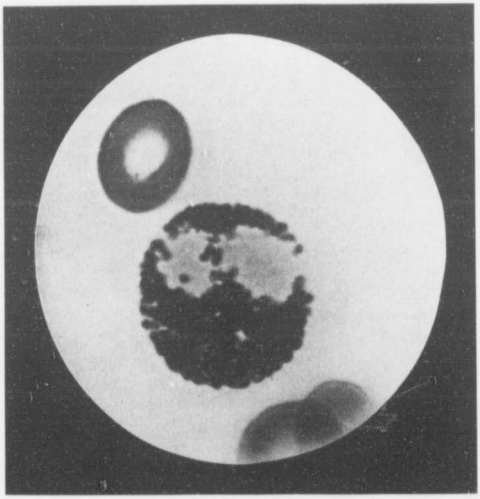
While a relatively high proportion of eosinophiles is found in asthma, the main interest in eosinophilia centres in its association with parasiticism, and skin diseases.

Eosinophilia in skin disease.

In the examination of the blood, in a woman suffering from pemphigus, Drysdale (London) reports the extraordinary percentage of 69.7 eosinophiles. A blood count showed corpuscles 3,704,000 and leucocytes 27,000. A differential count gave,—

Large lymphocytes	1.2 per cent.
Small lymphocytes	10.1 per cent.
Neutrophiles	19.0 per cent.
Eosinophiles	69.7 per cent.

The increase in the number of eosinophiles does not often reach 10 per cent. and rarely exceeds 20 per cent., of the total



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Eosinophile leucocyte.

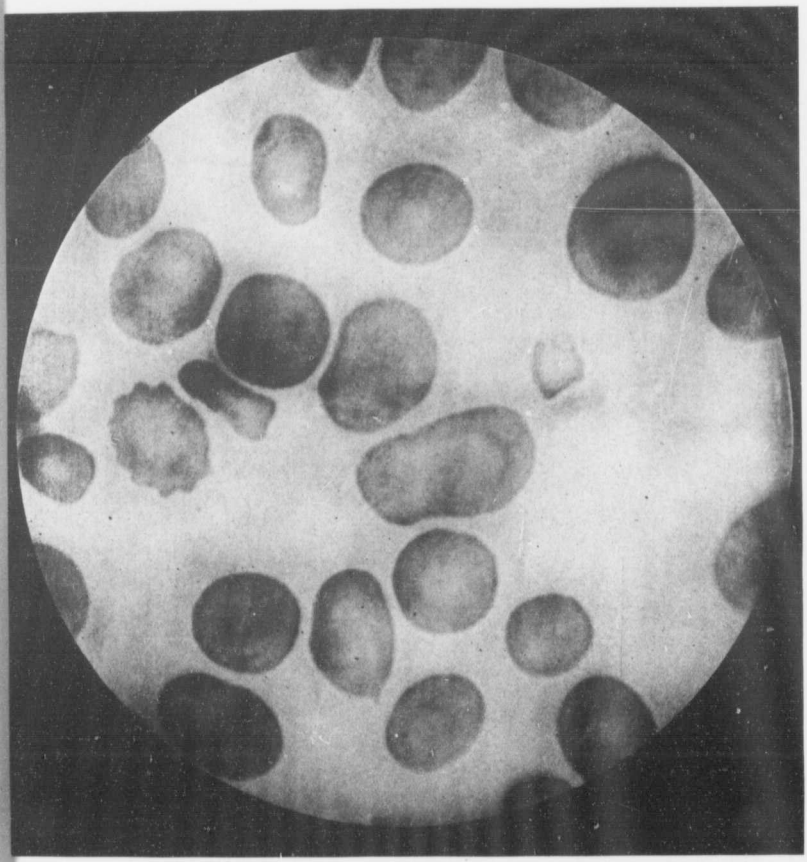
leucocyte count. Zappert, in nearly 400 observations, most of them in cases where an increase might be expected, only 3 times found percentages exceeding 20 per cent., twice in cases of pemphigus (33 and 29 per cent.) and once in a case of ankylostomiasis (27%).

The suggestion is made, that these cells are not eosinophiles, in the sense of bearing *α*—granules of Ehrlich, but are neutrophile leucocytes, with their granules in an altered condition. The nuclei of the cells resemble more nearly those of neutrophile leucocytes, than those of the normal eosinophile, and the granules are not so regular in size, so that the cells are clearly not typical.

Hoffman has observed eosinophilia, in one case of mercurial dermatitis, reach 49 per cent.

Eosinophilia in ankylostomiasis.

Ch. Honoré has made very thorough observations on the blood of patients suffering from ankylostomiasis, with the object of discovering whether the form of the leucocytosis, met with, will help in the diagnosis both of the disease, and of recovery from the disease. The patients were miners working in the Cockerill mines at Seraing. As a result of his examinations, he found that the number of eosinophile cells in the blood was increased in every case, that leucocytosis was nearly always present, and that abnormal cells, such as myelocytes, and polynuclear cells with basophile granules, were present in small numbers. The proportion of eosinophiles varied greatly in the different cases, being sometimes as low as 5.8 per cent. and as high as 52 per cent. Where two or three blood examinations were made of the same patient, the number of eosinophiles present was sometimes found to be the same at each examination, sometimes to have diminished from one time to the next, and sometimes to have increased. The most obvious explanation of these variations is, that the number of eosinophiles varies with the number of parasites present, but the facts observed did not bear out such an explanation. Where the blood count was made just before an anthelmintic was taken, the number of eosinophiles certainly did not vary with the number of parasites subsequently expelled, in the stool; thus, in one case, where forty-five parasites were expelled, the eosinophiles were present in a proportion of 26 per cent., and in another in which only six parasites were expelled, the eosinophiles were 28 per cent. of the whole number of white corpuscles. Such discrepancies may, of course, be due in part to the uncertain action of anthelmintics, and



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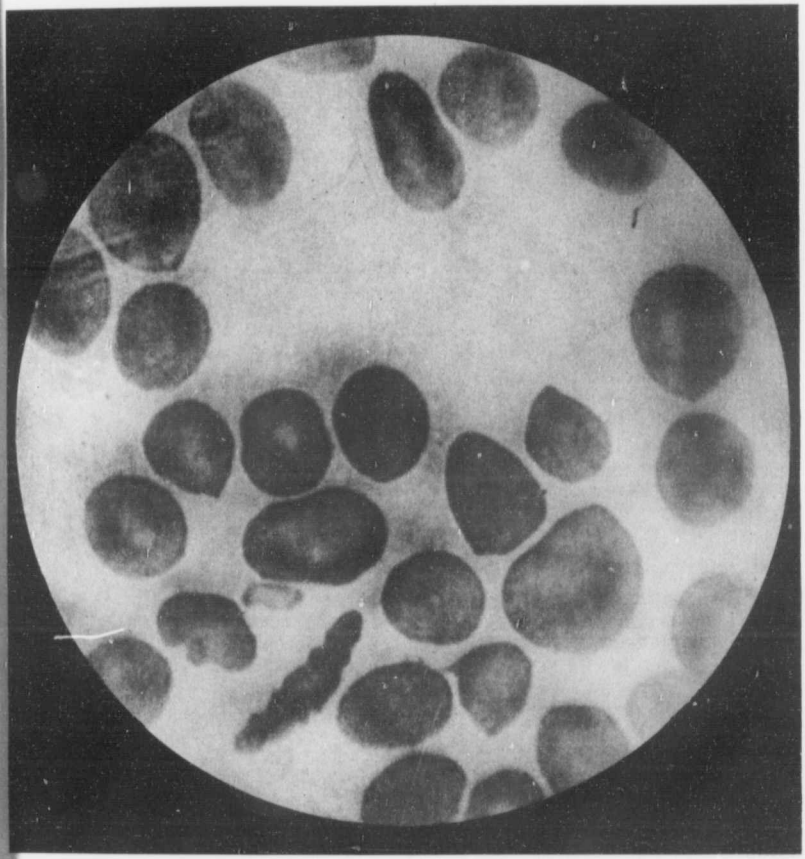
Chlorosis.

absolute proof as to the number of parasites present at any given time could not be obtained, because there was no hospital in which the miners could be kept under constant observation, out of reach of fresh infection, but instead they returned to the mines a day or two after taking the anthelmintic. In one case a patient, whose stools constantly contained the ova of the parasite, took an anthelmintic twice without passing on either occasion an *Ankylostomum duodenale*. Between the times of taking, the patient worked in the mine within reach of fresh infection. It may, therefore, be concluded that the number of parasites increased rather than diminished, during the whole period. At the three blood counts, the number of eosinophiles showed a steady but very slow rise, the figures being 10.7 per cent. in March, 11.8 per cent. in April, and 12.2 per cent. in June. This increase may have been due, either to increase in the number of parasites, or to the increased length of time during which the patient had suffered from ankylostomiasis. The patients were not under inspection with enough continuity, for it to be possible to determine, how soon after infection the number of eosinophiles began to increase, nor how soon after recovery the blood returned to a normal condition. Honoré's experiments on animals also failed to give information bearing on these points. In one case he infected two dogs with *Tænia serrata*, and in another case he injected into a vein of a rabbit a filtered product obtained from treating ankylostoma reduced to a powder with a solution of sodium chloride. In no case did he succeed in obtaining experimentally any increase in the number of eosinophiles in the blood. There did not appear to be in any of his patients any relation between the degree of leucocytosis as a whole, and the degree of increase of eosinophile cells, nor any relation between the proportion of mononuclear to polynuclear leucocytes, and the increase in eosinophiles. An increase in the number of eosinophiles is met with, not only in ankylostomiasis, but in certain skin diseases, in infection by other parasites, as, for instance, by the *Tænia serrata*, and as a temporary phenomenon in convalescence from certain infectious fevers. Nevertheless, such an increase may be a very useful diagnostic point. At the present time, the diagnosis of ankylostomiasis rests upon the presence of ova in the stools, and, except with careful and repeated examination of the stools, these may be overlooked. An increase of eosinophiles can be readily detected, in many cases without staining or fixing the preparations, and may settle the diagnosis before ova have been discovered.



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Chlorosis.

Eosinophilia in trichinosis.

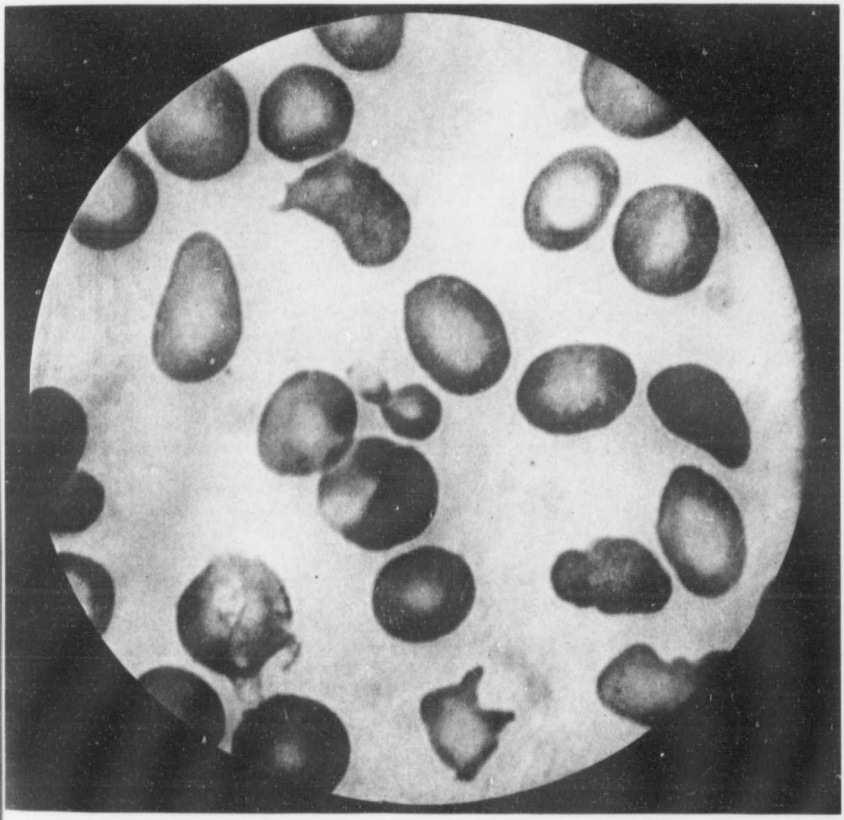
It is not surprising, that small epidemics of trichina infection are reported in man, inasmuch as the disease is of frequent occurrence in hogs, of which it has been estimated that about 2 per cent. are infected. Sporadic cases of trichina infection are no doubt frequently mistaken for typhoid fever, rheumatism, ptomaine poisoning, cholera morbus, etc. The disease usually results from the eating of pork, or sausage, which has not been exposed to a sufficient temperature to kill all of the parasites.

Eosinophilia is present in practically every case of trichina infection. In no other condition do the eosinophiles reach such high percentage, and so constantly, as in trichinosis. The eosinophilia of trichina infection varies from 10 to 60 per cent. Albert and Norris report an eosinophilia of 72 per cent., in one case. They state that eosinophilia makes its appearance, with the beginning of the acute muscular symptoms, which represents about the seventh to twelfth day after infection. It is at its highest, at the height of the acute muscular symptoms, which is ordinarily during the second or third week after infection. After this time, it gradually disappears, so that, at the end of the second or third month, there is usually no increase in the number of these cells.

In Gaisboek's cases, the number of eosinophiles quickly diminished from the first height, only to again increase, and finally gradually diminish, as convalescence set in. The first rapid fall was coincident with an increase in the severity of the symptoms, and is to be explained, either as the result of the severe damage to all the organs, including the blood forming organs, or of the onset of a new illness, probably through a mixed infection. Gaisboek believes, that trichinosis may be diagnosed, simply from the examination of the blood.

Kerr reports two cases of trichinosis, with excessive eosinophilia. In one case, the eosinophiles ranged from 31 to 68 per cent., during five weeks; in the second case, they were from 18 to 86 per cent. In each case, there was a leucocytosis of 25,000.

As the result of an investigation on trichinosis, with especial reference to the increase of eosinophile cells, in the blood and muscle, and to their origin and diagnostic importance, T. R. Brown claims to have demonstrated: (1) In a case of acute trichinosis, an extensive leucocytosis, with great absolute and relative increase in



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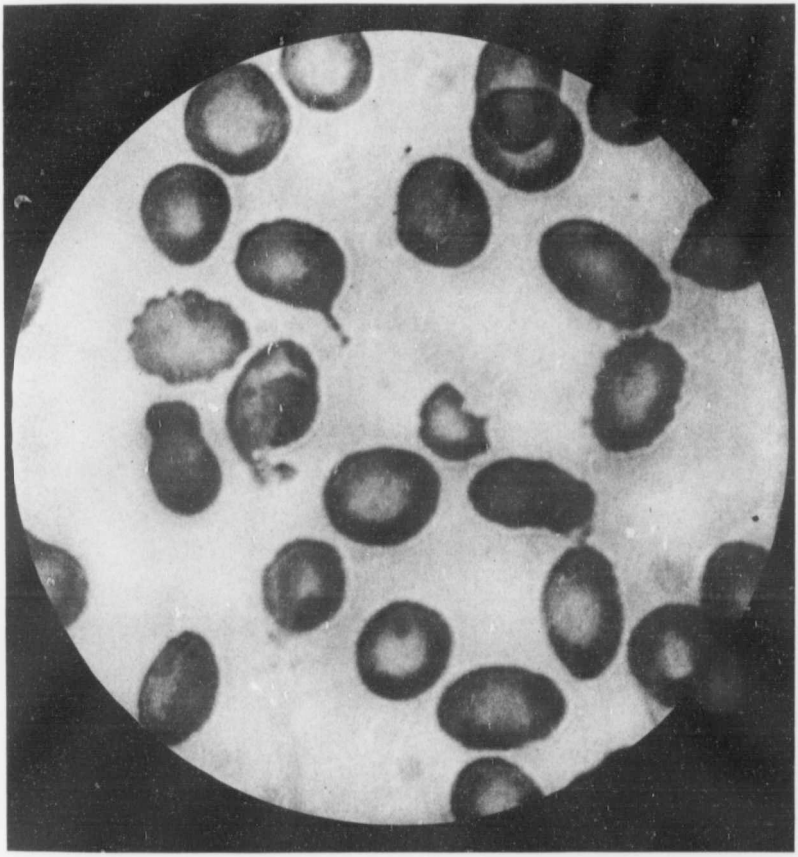
Chlorosis.

the number of eosinophilic cells in the blood, associated with a coincident decrease in the quantity of neutrophilic elements. (2) From the examination of the specimens of muscle removed during life, besides the peculiar degenerations of the muscle, a longitudinal splitting of some of the fibres, a remarkable transverse splitting of others, a great proliferation of nuclei, about many of which vacuoles are seen, and large numbers of polymorphonuclear eosinophilic cells, which were especially prevalent in the more degenerated areas. (3) In a second case after death, besides similar changes in the muscle, large numbers of eosinophiles throughout the infested portion. (4) In two other cases during life, a great increase of the eosinophilic cells in the blood, with a coincident increase of the polymorphonuclear neutrophiles, associated with leucocytosis, though of less extent than in the first case. (5) In pieces of muscle removed, in these last two cases, changes in most respects similar to those cited in the first case, but of less degree. (6) The similar character of the nuclei of the eosinophiles and the neutrophiles, both in the blood and in the muscle, and the presence in the first case of certain cells which might be regarded as forms transitional between neutrophiles and eosinophiles, suggesting the possibility that the increase in the latter elements may in these instances take place in the muscle by direct transition from the neutrophiles. From these observations, Brown thinks it fair to conclude: (1) That there is a marked increase in the percentage of eosinophilic cells in the blood in trichinosis. (2) That this increase may be used as a diagnostic sign in this disease. (3) That this disease in its sporadic form is more common than has hitherto been supposed. (4) That a systematic examination of the blood should be undertaken, in cases with indefinite intestinal, muscular, or articular symptoms, in the hope that in some at least of the hitherto doubtful cases a diagnosis may be reached.

Eosinophilia in filariasis.

Gulland reports a case of filariasis, with eosinophilia, and he noted that the increase of eosinophiles was most marked in the evening, when the blood contained numerous embryos. The percentage of eosinophiles varied from 3 per cent., in the morning, to 12 per cent. in the evening. The evening leucocytosis was slightly increased over the morning count.



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Chlorosis.

Eosinophilia in ascarides.

The great diagnostic value of the routine examination of the blood, is illustrated by a case simulating meningitis, which is reported by Mazzuoli. The case was a child, aged 9 years, who first showed signs of illness, about a month before, becoming strange and excitable, with loss of colour and appetite. After a month's indefinite malaise, the child was seized with general tremor, cold sweats, loss of consciousness, and chronic generalised convulsions. The pupils were small, reacted slightly to light, and were rotated upwards. Opisthotonos was present; very marked dermography, boat-shaped abdomen, and Kernig's sign, were also observed. The pulse was 58, temperature 37.6° C. and respiration 16. There was no vomiting. The chief fact, about the blood, was the presence of marked eosinophilia (95% eosinophiles). On examining the fæces, large numbers of ascarides eggs were detected. Anthelmintic treatment was practised, and about fifty *Ascarides lumbricoides* evacuated. After this, the child got rapidly well, and eventually the eosinophiles came down to 2 per cent.

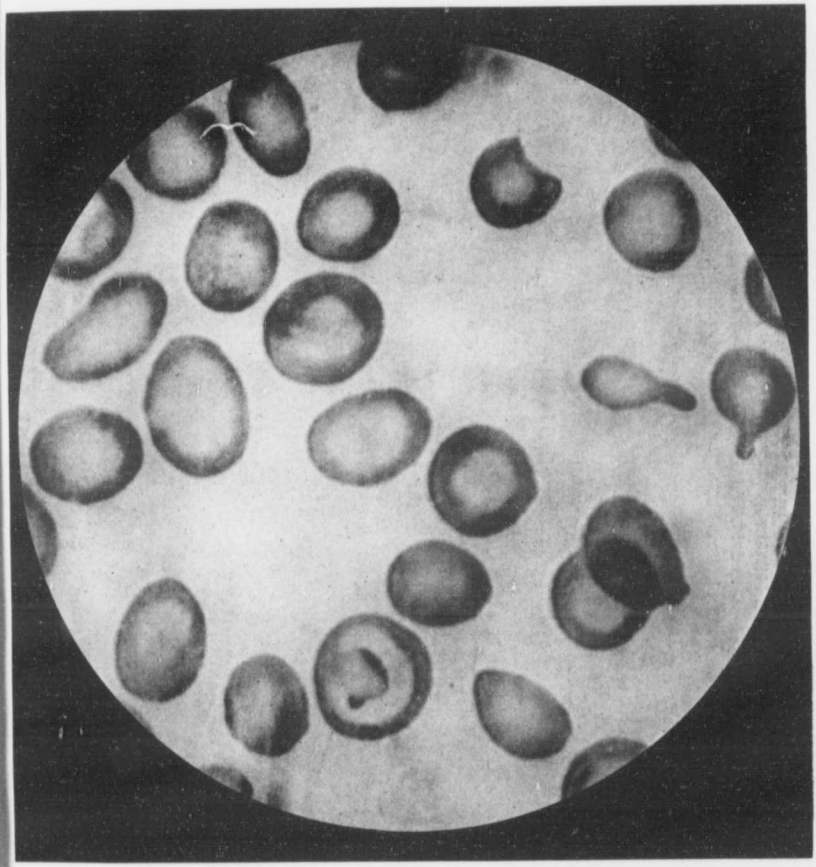
Eosinophilia in hydatid infection.

It appears that hydatid cyst of the liver is the only abdominal tumor, in which eosinophiles are found to be increased. In a case reported by Seligman and Dudgeon, the blood examination showed neutrophiles 22 per cent., and eosinophiles 57 per cent. After enucleation of the cyst, the eosinophiles rapidly dropped to normal.

LEUCOCYTOSIS.

An increase in the number of polymorphonuclear neutrophile leucocytes, is the expression of nature's efforts to counteract noxæ of various kinds. Chemical substances are the means, by which this increased addition of leucocytes to the blood is brought about, and it can be produced, where there is no inflammatory change.

Leucocytosis, as a definite pathological entity, came into existence, in a communication by Wilks, in 1878, to the Pathological Society of London, in which he reported "a remarkable discovery



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Chlorosis.

made last year, in University College Hospital, in a case under the care of Jenner, where the presence of a large excess of leucocytes, in the blood, coincided with the formation of an abscess, disappearing after the abscess was opened."

While our chief interest in leucocytosis is centered in the relation of the condition to pathological causes, an increased addition of leucocytes to the blood is found under certain physiological conditions.

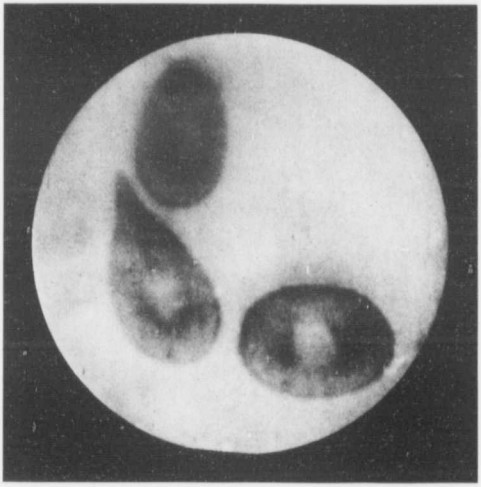
Leucocytosis of digestion.

During the process of digestion, the number of leucocytes is considerably increased, but the numbers given vary. Cabot states that, two and a half hours after a meal, the leucocytes may vary from 1,000 to 7,000 in excess of the normal.

Gardall and Paton have carried out a research into the source of the added cells. In a previous investigation they had found, that the removal of the spleen did not affect the leucocytosis of dogs and rabbits. This organ, therefore, does not play any important part in the supply of leucocytes to the circulation. No excess of leucocytes was found in the mesenteric veins, over the number in the arteries, during digestion, which would exclude the intestinal wall, as a source of the increased number of cells supplied to the blood. An examination of chyle, from the thoracic duct, led to the conclusion, that neither do the mesenteric glands furnish the cells. Experiments upon the bone marrow led to positive results. During proteid digestion, blood, coming from the marrow, constantly contained more leucocytes than either venous, arterial, or capillary blood, and, in six experiments, the average excess was 37 per cent. Hence they concluded, that the bone marrow is probably the sole source, and certainly the only important source, of leucocytes.

Leucocytosis of infancy.

The physiological influence of age, on leucocytosis, is marked in the early months of life. At birth, the number of leucocytes averages 18,000, sinks to 12,000 at the sixth month, and reaches the normal about the sixth year. The normal percentage of polymorphonuclears, in infancy, is from 25 to 40 per cent.



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Poikilocytes.
Poikilocytic phase of pernicious anæmia.

Leucocytosis of pregnancy.

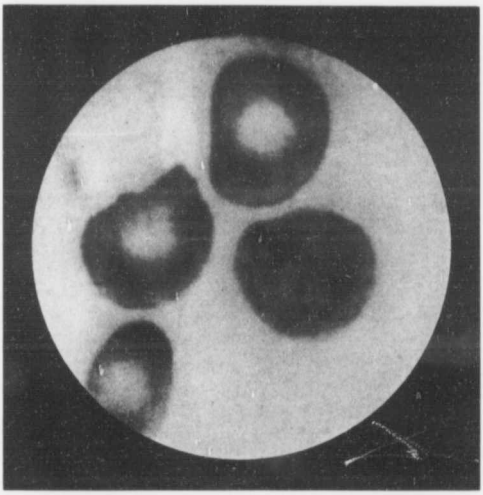
Marked leucocytosis accompanies the later months of pregnancy. For the greater part of the term of pregnancy, the figures representing the number of leucocytes are high, yet quite within the physiological limits. Sudden well marked increase of polymorphonuclears is found immediately after labour, and has probably commenced during labour. The polymorphonuclear increase rapidly sinks to normal, in the few days following labour. Given found the leucocytosis about equally common in primiparæ and multiparæ, also in full time, and premature labour.

Commencing a few days after labour, and becoming very evident in the second and third week, of a normal puerperium, the lymphocytes show a well marked increase. This post-partum lymphocytosis is coincident with the involution of the uterus.

Leucocytosis of cold.

Winternitz has described investigations made upon 56 cases, either in health, or with slight ailments, and particularly anæmia. In a general application of cold to the body in varying ways, the red cells showed considerable increase, as well as the white cells. The hæmoglobin was also present in larger quantity. This increase does not take place immediately, and often an hour was found to intervene. It was often recognised two hours afterwards, but usually, by this time, it had commenced to decline. The leucocytes are less constant in their behaviour. The increase in the blood cells can hardly be due to increased production, but rather to circulatory changes. Winternitz thinks the effect, as regards metabolism, is virtually the same, as if the cells were actually increased. He has shown that more oxygen is taken up, and more carbon dioxide given off, as the result of the application of cold. Winternitz refers to the beneficial effects obtained in anæmia, from hydrotherapeutic measures, and suggests that by methodical repetition the changes should become permanent.

Ciuffini concludes, that the variations in the counts of the red and white cells, that appear to be caused by either hot or cold baths, are inconstant, and that they depend upon peripheral disturbances of the circulation, for the most part, rather than upon any special action exerted on the blood forming organs.



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Pernicious anæmia.

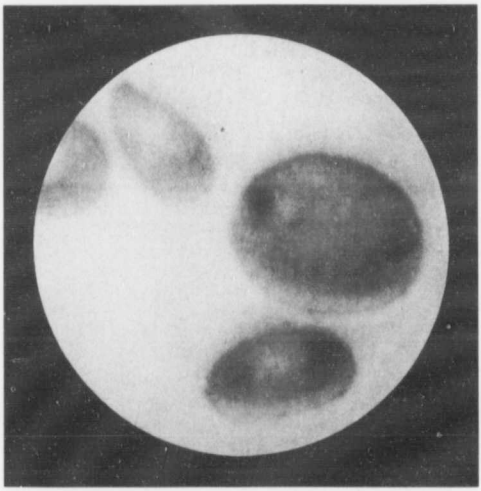
Leucocytosis of sleep.

Fulpius points out, that sleep must be added as another physiological factor, which produces a marked variation of the leucocyte equilibrium. Fulpius has come to the conclusion, that the time, at which the blood count is made, is responsible for the discordant reading of the blood, in tuberculous cases. If the blood of an individual, asleep, or just awake, is examined, it is found that the lymphocytes, which were normally 25 per cent., rise to 40 per cent., or more, while the neutrophiles diminish, in proportion as do the eosinophiles, and basophiles. Two or three hours later, when the patient has begun to move about, the normal ratio is established. The results obtained go to show that, contrary to the usual opinion, the leucocyte equilibrium is not constant physiologically.

Experimental leucocytosis.

De Sandro, experimenting on dogs, with reference to the effect of quinine, in small and repeated doses, on the blood, found the amount of hæmoglobin increased, from the third and fourth days up to the seventh, and remained at that level, during the course of the treatment. *Pari passu* with the increase in hæmoglobin, there was a corresponding, but slightly smaller increase, in the number of red corpuscles. The leucocytes increased to double, and sometimes treble, the initial number. The polymorphonuclears were increased (10 to 13 per cent.), with a relative diminution in the number of lymphocytes. On the whole, small doses of quinine appeared to improve the state of the blood, by raising the hæmoglobin index, by increasing the number of red cells, and by inducing a certain degree of leucocytosis; in larger doses, a contrary effect is produced.

Among the drugs, which are known by experiment to promote the increase in leucocytes, are pilocarpin, camphor, and nuclein. In cases of pneumonia, running its course, without increase in leucocytes, Horbaczewski advocates the use of such agents as are known to promote leucocytosis. Becker also proposes the production of a leucocytosis by means of drugs. He advises pilocarpin, sodium cinnamate, and nucleinic acid. He advises the use of the last named remedy, in a 5 per cent. solution, 5 to 20 minims being given at a dose. It must be given hypodermically as it is decomposed by the gastric juice. One dose is usually sufficient, and improvement is said to begin, in six to twelve hours.



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Pernicious anæmia.
Megalocyte and poikilocytes.
Megalocytic phase.

The general result of the injection of quinine, salicin, camphor, and pilocarpin, is to cause a diminution in the number of leucocytes, per cubic millimeter. The degree and duration of the diminution varies with the drug employed. Coincidently with the diminution in the total number of leucocytes, there is a distinct increase in the proportion of the non-granular to the granular varieties. Following the diminution, an increase in the polymorphonuclears is observed. This increase is a more evident phenomenon than the preceding diminution, and is of much longer duration. The changes in the numbers, and relative proportions, of the leucocytes, are analogous to those which occur after the introduction, into the circulation, of bacteria and their toxins.

Under the influence of repeated doses of pilocarpin, Wilkinson (Liverpool) found that the granules of the polymorphonuclears become gradually less distinct, and eventually the protoplasm appears perfectly homogeneous, and takes up the stain very feebly. This change was found, in one instance, to be very pronounced, in so short a time as fifteen minutes, after the first dose of the drug. The reaction of the nucleus, to nuclear stains, diminished to a corresponding degree. The eosinophiles show no change whatever, and stand out in marked contrast to those of the other variety.

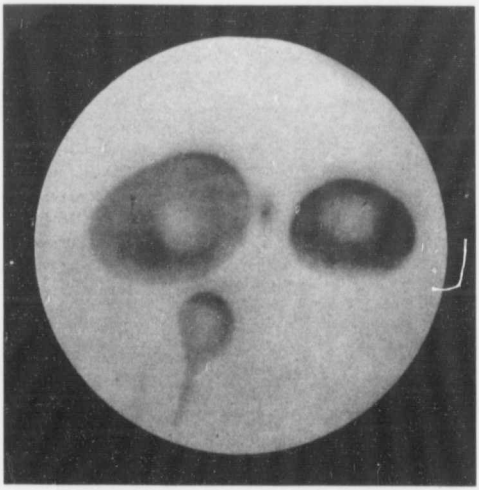
Pathological leucocytosis.

The pathological condition of hyperleucocytosis is present when the number of leucocytes exceeds 10,000 per c. mm.

Among the changes induced by bacterial products, acting as chemotactic substances, we find (a) locally, an enormous number of finely granular leucocytes; (b) in the blood, a great increase in the same cells; and (c), in the marrow, a great increase in the cells, from which these leucocytes are derived.

Chemotaxis.—Each infection develops a special resistance, and it is in the development of this special resistance, that immunity consists. The increased number of leucocytes, in the circulating blood, plays an important part in the mechanism, which the organism possesses, of protecting itself against infection. Leucocytes are attracted, or repelled, by a variety of substances, of chemical and bacterial origin. This phenomenon of positive and negative chemical attraction, in the former, resulting in the afflux of leucocytes to the invaded regions, is denoted chemotaxis.

The phagocytic leucocytes are powerfully attracted by many



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Poikilocytes.

Poikilocytic phase of pernicious anæmia.

micro-organisms, and their toxins, and as powerfully repelled by others, and their toxins. In other words, leucocytes have a positive chemotaxis for certain bacteria, and a negative chemotaxis for others.

The chemotactic substance may be present in inflammation, or suppuration, in such quantity, as not to excite a general leucocytosis.

Granted the presence of a chemotactic substance, the leucocyte reaction is determined by (a) the resistance of the patient and (b) the intensity of the infection.

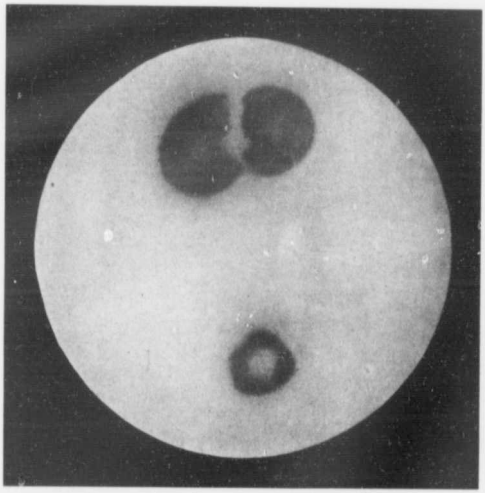
A high leucocytosis will result, where the patient is in a high state of resistance, and the infection severe, while a patient in a low state of resistance will, under the same circumstances, exhibit but a feeble leucocytosis.

Again, the toxæmia may be so intense, that the reaction of the patient is overwhelmed.

Leucocytosis in typhoid fever.

Observations on the changes, both in number and character, of the leucocytes, in typhoid fever, are reported by Courmont and Barbaroux, in which they state, that there does not seem to be a fixed formula for the leucocyte condition in typhoid. Many different changes may be observed, so that, in cases practically similar, the leucocyte curve may be quite different. They report two cases, showing the greatest divergence in the behaviour of the leucocytes; in one, there was leucopenia, with decrease in the percentage of neutrophile cells; in the other, there was hyperleucocytosis, with increase in the neutrophile percentage. In one, the leucocyte curve rose during convalescence; in the other, it fell. In some fatal cases, hyperleucocytosis was present; while, in others of a mild character, the white cells were decreased. In the greatest number of cases, however, hypoleucocytosis was the rule. This may be temporary or constant. It is shorter in mild cases; more prolonged in severe.

Courmont and Barbaroux are uncertain as to the exact period the decrease in leucocytes may be observed; their earliest case was on the seventh day. They also noted that frequently there is a rise in the leucocytic curve and the number of polynuclear cells towards the end of pyrexia, or when the temperature begins to drop. As regards the polynuclear cells, as a rule they follow the leucocytic curve, but by no means constantly so. In the greater part of average cases, the percentage of polynuclear cells keeps high, notwithstanding that



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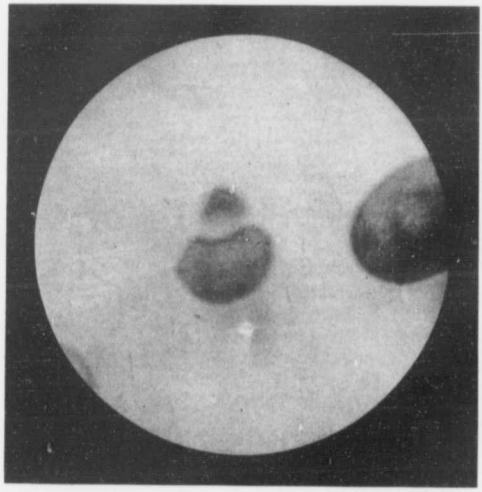
Pernicious anæmia.
Formation of microcytes by schistocytosis.

the total number of leucocytes diminishes. The writers, therefore, formulate the statement that hypoleucocytosis is due to decrease in the lymphocytes. The total number of polynuclear cells falls proportionately much less, and their percentage is generally increased. In certain severe cases, however, the percentage of polynuclear cells is never raised above the normal, so much so that one might almost be tempted to give this fact some importance in prognosis, were it not that this same condition is now and then observed in mild cases. One of the most constant observations is the considerable decrease of the leucocytes, especially polynuclear, during convalescence. It is not possible so far to define the relation of this with the gravity of the cases, nor to say how this phenomena is related to relapse. In cases of typhoid fever, the leucocyte curve regains fairly rapidly its normal condition, though now and then the process is much prolonged. It is more especially the lymphocytes and mononuclear cells that first reach the normal. There may even be a temporary hyperleucocytosis, as a kind of reaction.

Leucocytosis in typhus fever.

An extended series of observations on this subject is recorded by Love (Glasgow).

Details are given of 26 cases, comprising 9 which proved fatal, and 17 which recovered. The average leucocytosis of the total number of cases was found to be 24,000 per c. mm., whilst the maximum estimate, in the fresh blood made in the different cases, varied between 8,000 and 54,000. In the greater number of the fatal cases, leucocytosis was present, though it usually manifested itself in a marked degree only after the appearance of the rash. As a general rule, in these cases, the leucocytosis increased to a maximum, at or just before the crisis, and declined afterwards, if death did not supervene immediately. In none of the fatal cases were eosinophile corpuscles found at any time. The number of red cells, in all the fatal cases, was higher than is usual in normal blood. In the cases which recovered, there was a gradual increase in the number of leucocytes, from the beginning of the disease onwards, more marked after the appearance of the rash, until the maximum was reached by a rapid rise either a day or two before, or coincidently with, the crisis. After the crisis a sudden fall occurred, and the leucocytosis gradually declined during convalescence, until the normal was reached. With the supervention of inflammatory phe-



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Pernicious anæmia.
Formation of microcytes by schistocytosis.

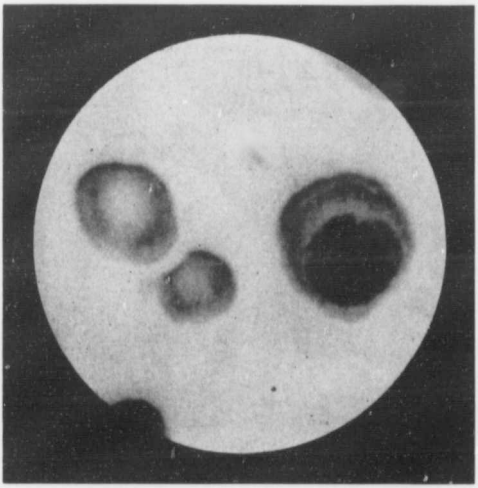
nomena during convalescence, the leucocytosis in some cases exhibited a secondary rise, which, however, never became even approximately as high as the rise which occurred at the crisis. As contrasted with the fatal cases, there was never a complete absence of eosinophile cells in the non-fatal cases. These cells were not constant as regards the time of their appearance; in some cases they were found only after the crisis, but in the majority they were marked from the first count onwards. In all the cases, both fatal and non-fatal, the leucocytosis was mainly due to an increase in the polymorphonuclear leucocytes; these cells frequently numbered from 80 to 90 per cent. of all the white cells present, and in one or two instances amounted to 93 per cent. In the non-fatal cases, there was also a limited increase of the large mononuclear cells, which generally became more pronounced after the crisis, and disappeared after the early period of convalescence.

Leucocytosis in diphtheria.

Researches on the blood of 26 patients, suffering from diphtheria, were made by Antonio Mariottini (Naples); their age varied from 5½ months to 8 years; 24 of them had the fibrinous form, and 2 only had the phlegmonous, and they all recovered, although several were very seriously ill. The observations were always made in the evening at the same hour, and always from three to four hours after the injections, when these were being given. In all the cases, leucocytosis was present in greater or less degree, and without relation to the temperature and age of the patient; neither was it possible to discover a constant relation between the intensity of the morbid process and the leucocytosis. The leucocytosis, however, increased with the increase of the malady, and only began to decrease after the complete absorption of the exudate. The injection of anti-diphtheritic serum caused an increase in the leucocytosis. The observation of the progressive diminution of the leucocytosis, along with clinical phenomena, may be used in making a favourable prognosis.

Leucocytosis in scarlet fever.

Tileston and Locke find, 1. That the blood of scarlet fever, in children, differs from that in adults, only in proportion to the differences in normal blood at different ages. 2. That a slight secondary



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Pernicious anæmia.
Normoblast and microcytes.

anæmia is the rule, in all but the very mild cases, and varies directly with the severity and duration of the disease: the fall in hæmoglobin is from 5 to 25 per cent., in the corpuscles from 100,000 to 700,000 per c. mm., both returning to normal, after a period of several weeks. 3. A hyperleucocytosis invariably accompanies the disease, and runs a characteristic course, rising abruptly on the second to eighth day to 18,000 and even to 40,000, and falling rapidly for a few days, then more gradually, to reach the normal in convalescence. 4. During the period of invasion and eruption, the polymorphonuclear leucocytes are both relatively and absolutely increased, but decrease gradually with the fall in leucocytosis, until convalescence, when they become relatively, though never absolutely, below normal. The mononuclears take an exactly opposite course, and, with the onset, the eosinophiles disappear entirely, or are greatly reduced, to rise above normal, when defervescence begins, this eosinophilia persisting until late convalescence. 5. Complications, with a few exceptions, exert no influence upon the course of the blood. If severe, they may increase the anæmia, and in a few instances (nephritis and diphtheria), even produce a rise in leucocytosis.

Sevestre (St. Bartholomew's Hospital) has reached similar conclusions. He publishes the following summary:

1. There is a leucocytosis in scarlet fever which reaches its maximum in the first few days of the disease, but the return to normal is gradual.

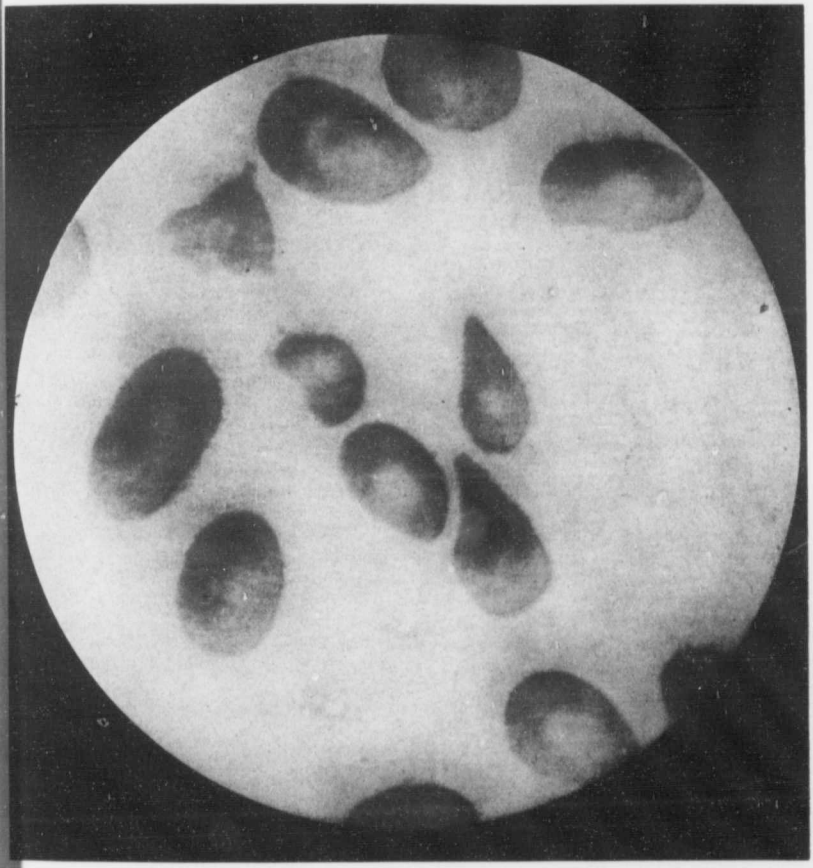
2. The actual time of onset of the leucocytosis is uncertain: it is found to be present on the first day of the disease, and it continues throughout the period of desquamation.

3. No absolute relationship can be traced between the curve of the temperature and that of the leucocytes, but they tend to run a similar course.

4. A closer relationship has been found to exist between the leucocytosis and the rash: the former varies with the severity of the latter, and with the fading of the same the leucocytes show a marked diminution in number.

5. Complications, such as otorrhœa, rhinorrhœa, adenitis, tend to increase the number of white cells.

6. In nine cases, the percentage of the various forms of white cells to the total number of white cells present was estimated. It was found that the percentage of the finely granular eosinophilous cells was greatly increased during the first few days of the disease;



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Pernicious anæmia.
Poikilocytes.

but, within the next few days, the percentage falls below the normal, and continues so for some considerable time. The large uninuclear cells and lymphocytes are diminished in number in the early part of the disease: after a short time, the percentage of both forms gradually increases, the large uninuclear cells remaining about normal, but the lymphocytes increase, and this increase exists for some time.

In the majority of cases, the percentage of the coarsely granular eosinophilous cells was found to be diminished during the whole period of the disease. In no cases were they found to be absent.

7. A slight leucocytosis usually accompanied a mild infection.

A high leucocytosis indicates a pronounced reaction against a severe infection, and is not a sign of an unfavourable prognosis.

In severe cases, it was found that the percentage of the finely granular eosinophilous cells was always high.

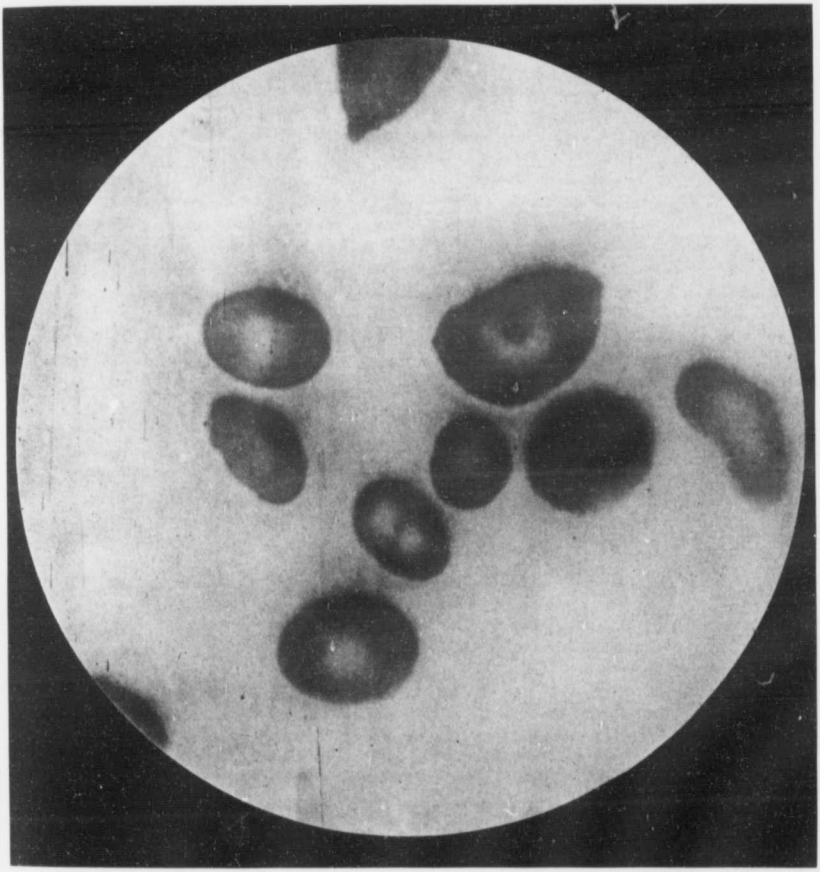
Inflammatory leucocytosis.

Leucocyte counting is of great diagnostic importance, to one who values correctly its possibilities and limitations. There is great difference of opinion, as to the value of the leucocyte count, in the inflammations which come under the care of the surgeon. This uncertainty is due to the fact, that a moderate increase of leucocytes is of little diagnostic value, and that pus cannot be excluded, even when there is no leucocytosis.

In the first two days of appendicitis, Federmann found the count below 20,000, in the simple cases, and higher in the severer cases. Marked symptoms with a low count, in the early stage of appendicitis, indicates severe intoxication, and is an unfavourable sign. A high count on the third to fifth day indicates pus. A falling count, with increased severity of symptoms, is a bad sign. A count of over 20,000, after the first week, indicates encapsulated pus.

French found, in his own case, and those collected from the literature, that the lowest leucocyte count which has always indicated pus is 32,000.

Hewitt expresses his opinion on the value of leucocyte count, in acute surgical diseases, as follows: (1) The total count is an index of the patient's resistance to the infecting organism; (2) the relative polymorphonuclear count is an index of the degree, or the severity, of the infection; (3) a percentage of polymorphonuclear



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Pernicious anæmia.
Poikilocytes and normoblast with pycnotic nucleus.

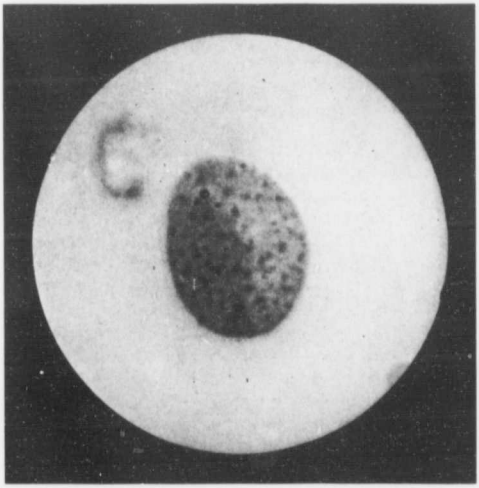
cells, from 75 to 80, means that infection is probable; if from 80 to 85, infection is usually found, and this regardless of the total leucocyte number.

Da Costa has collected a series of observations on the blood in appendicitis, and the result of his investigations is summarised as follows: (1) Moderate leucocytosis may occur, both in the absence, and in the presence, of an abscess, and its consequences. It accompanies about 35 per cent. of non-purulent, and 90 per cent. of purulent cases. (2) Leucocyte counts, ranging between 10,000 and 17,000, cannot be depended upon to reflect the nature of the local lesion, since this degree of increase may be found, both in mild catarrhal, and in purulent cases. Counts of 20,000, or more, almost invariably indicate the presence of pus, gangrene, or general peritonitis, one or all. (3) Leucocytosis may be absent both in trivial, catarrhal, and in fulminant cases, as well as in forms of circumscribed abscess. (4) In operative cases, thorough evacuation of the abscess is followed, within a few days, by a decline to normal, in the number of leucocytes, provided that the recovery of the patient is uneventful. Persistence of the leucocytosis, after the third or fourth day following the operation, may usually be attributed either to undrained pus pockets, to general peritonitis, or to both of these factors.

In a general way, the significance of inflammatory leucocytosis is as follows: (a) If the total leucocyte count, and polymorphonuclear count, rise together, it is an indication that both the infection, and the bodily resistance are on the increase. (b) If they both fall together, it indicates the subsidence of the infection. (c) If the total leucocyte count falls, and the polymorphonuclear percentage remains high, or rises, it indicates a spreading infection poorly resisted.

Leucocytosis in appendicitis.

Curschmann has found, in 60 cases of appendicitis, that the number of white cells, in the blood, is a reliable indicator of the presence of pus. If the exudation is serous, the physiological number is increased but little, if at all. If, however, there is a tendency to suppuration, or an abscess is already present, the number of leucocytes in the c. mm. rises to 20,000 or even 25,000. This leucocytosis is a certain indication of suppuration, and is a more reliable guide than palpation, or the state of the pulse and temperature. As the



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Pernicious anæmia.
Megalocyte with basophile granulation.

amount of pus increases, the leucocytes become correspondingly numerous; after the pus is evacuated, whether by operation or rupture into the intestine, they rapidly sink to normal. If after operation leucocytosis does not diminish, it may be assumed that drainage is defective.

Sill emphasizes the importance of a differential count, and the enumeration of the polymorphonuclear leucocytes, in purulent infections. He states that, if both the leucocyte count and the polymorphonuclear count rise together, it indicates that the infection is growing more severe, but that the resistance is rising, *pari passu*. If they both fall together, it indicates that the body has overcome the infection, and the latter is on the decrease. If the leucocyte count falls, while the polymorphonuclear remains high, or rises, it indicates that the infection is spreading, and the resistance is being overcome. The outlook, then, is unfavourable.

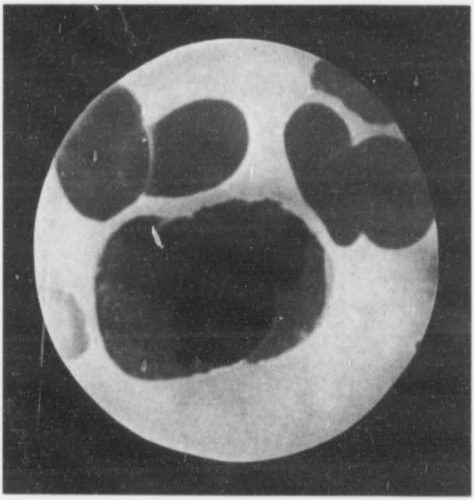
The leucocyte count, in appendicitis, is only of value to the surgeon, when positive.

Berndt thinks a continued high count above 25,000 can be relied on, as meaning the presence of pus formation, but the absence of an increased leucocyte count can never be considered a proof that pus does not exist.

Leucocytosis in pneumonia.

It is now a well known fact that, in most infective diseases, a polymorphonuclear leucocytosis is always to be regarded as favourable, while the absence of it is a very grave sign. Up to a certain extent, the leucocytosis increases with the extent of the infection, and is always an indication, that the leucocyte-forming tissues are functionally active. In those infections in which leucocytosis is the rule, its absence, diminution, or disappearance, without a corresponding improvement in the symptoms, must be considered a very grave sign.

Senega appears capable of producing a leucocytosis, and is worthy of a trial. The use of it has been advocated by Ensor, in Kala azar, in which there is a leucopenia. It is reported to be of benefit in certain cases.



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Megaloblast.
Megaloblastic phase of pernicious anæmia.

PHAGOCYTOSIS.

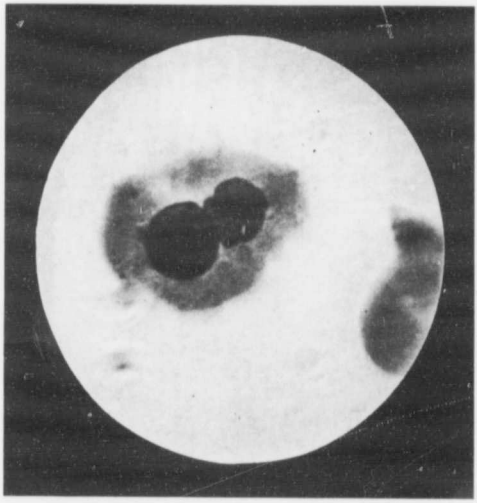
That many of the infectious diseases tend to run a definite course, ending in spontaneous cure, is well known. That such diseases run a specific course, and that their natural tendency, with few exceptions, is towards recovery, implies that, in some way or other, their presence in the body involves their ultimate extinction, and brings immunity. In the recovery from infection, phagocytosis plays an important part, but immunity is in no wise solely brought about by it.

For an active phagocytosis, it is essential that there should be a well marked leucocytosis. In estimating the power of the individual, to cope with infection, the leucocytes, as well as the serum, must be taken into account.

The disappearance of bacteria from the tissues of a naturally resistant animal is not explained altogether by phagocytosis. The relative value of the parts, played by the fluid constituents, and the cellular elements of the blood respectively, in combating an invasion of the body, by pathogenic micro-organisms, is still the subject of discussion and experiment.

The earliest observations leading to our knowledge of phagocytosis, was, that inert particles finding their way into the animal system, or introduced into the blood, are rapidly taken up by leucocytes. Attention was first drawn, in 1881, to the part played by the phagocytic cells, by Carl Roser, who gave examples of the possession of phagocytic power, by cells of both plants and animals, and of its importance in the resistance, offered by them to the attack of the pathogenic fungi, by which they are sometimes invaded. Hæckel, comparing the leucocyte of the newt with those of the lower amœboid organisms, indicated that this must be the remaining evidence of a normal process of nutrition, common to amœboid cells, in whatever position they may exist; these cells, in taking up inert particles, merely affording a better demonstration of what is always going on in most amœboid cells.

It is to Elias Metschnikoff, that we owe so much of our knowledge of the cellular activities of the body. He confirmed Hæckel's observations, and further demonstrated the fact, that certain amœbæ and ciliated, or flagellated, unicellular organisms, depend upon bacteria and fungi, under normal conditions, for much of their nutriment: these they destroy in large numbers, extracting from them nutritive material, and rejecting what they do not require.



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Megaloblast.
Megaloblastic phase of pernicious anæmia.

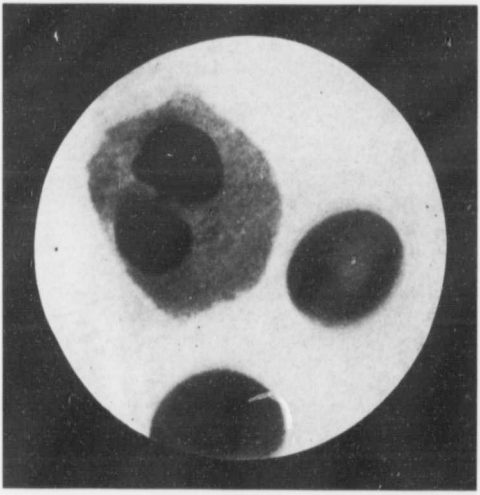
Phagocytosis is not an isolated function, brought into play for a solitary, or rare occasion, but a habit, upon which the animal cell depends for its existence.

Metschnikoff divides phagocytes into fixed (endothelial cells, etc.), and free phagocytes (leucocytes). The two forms of leucocytes, which are phagocytic are (1) the large lymphocyte—the *macrophage*—and (2) the polymorphonuclear leucocyte—the *microphage*.

In protecting the animal organism against infection, the *macrophages*, and the *microphages*, display differences in their phagocytic activity. The *macrophages* have a predilection for the infective organisms, which set up chronic diseases, such as leprosy, tuberculosis, and actinomycosis. The *microphages*, on the other hand, are especially concerned in the destruction of the bacteria, which produce acute infections, and play very little part in attacking the bacteria, which set up chronic diseases.

There is every reason to believe that phagocytosis is an important factor, in assisting to protect the body against local infection, but has little to do with the production of actual immunity. Since Metschnikoff enunciated his phagocytic theory of immunity, many facts have been found, which cannot be explained by it. One of these is the disappearance of bacteria from the tissues of a normally resistant animal, without any evidence of phagocytosis.

Bordet observed, that streptococci, injected into the peritoneal cavity of laboratory animals, set up a marked leucocytosis, which ended in the ingestion, and digestion, of almost the whole of the streptococci. There generally remained a few individuals, which resisted the action of the leucocytes, and were not ingested. Further injection of the organisms showed, that the leucocytes were still active, but more streptococci remained free. Thus a new generation of organisms was produced, which was able to resist the action of the leucocytes, or which was not actively phagocyted by them. Carrying the experiment further, Bordet established, that it was not a weakening of the phagocytic function of the leucocytes, which had taken place, for if he injected a rather feeble organism into the peritoneal cavity, just at the time that the ingestion of streptococci had ceased, the leucocytes at once became actively phagocytic to these new organisms. The leucocytes appeared to have a positive attraction for one kind of organism, and a negative attraction for another. Marchand showed that it was the more virulent strains of the organisms, in which the leucocytes did not act, and he concluded that an



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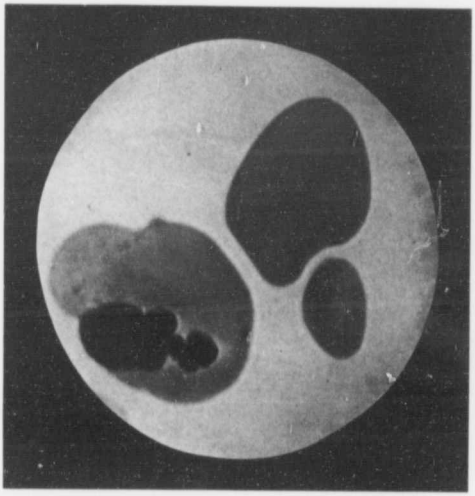
Megaloblast.
Megaloblastic phase of pernicious anæmia.

attenuated streptococcus is one readily devoured by phagocytes, and a virulent organism is one which is not phagocyted.

Numerous experiments have shown, that virulent bacteria are not phagocyted by the leucocytes, *in vitro*, but if certain bodies, produced during the process of immunisation, are added to the mixture of leucocytes and bacteria, phagocytosis almost immediately becomes a marked feature. Recent work has shown, that one factor in this process is a directly injurious action, on the bacteria of these antagonistic substances. In the animal body, Bordet observed that, when phagocytosis ceases, a certain influence still can be seen active against unenclosed organisms, in the phagocyte containing fluid.

Liakhovetsky next investigated the question of phagocytosis, by inoculation of the cornea with anthrax. Anthrax was used, because the effects of leucocytosis and phagocytosis, upon the bacilli, in refractory and insusceptible animals, can be investigated in the cornea, by direct observation. Some drops of a broth culture were injected into the substance of corneæ of dogs and rabbits. For control, India ink and salt solution were used. Liakhovetsky found that, though, in several cases, in rabbits the leucocytosis and phagocytosis, at the site of injection, plays a part, and perhaps an essential part in the recovery, in the remainder of the rabbits, and in dogs invariably, the bacteria are destroyed, without any share in the process being taken by the leucocytes, as phagocytes.

A series of investigations was conducted by Simon, on the action of leucocytes, suspended in salt solution, on streptococci. The exudate was obtained from the pleura of rabbits; the leucocytes were separated by centrifugalisation, and placed in physiological salt solution. Streptococci of different virulence were studied, and the activity of the unchanged exudate, the suspended leucocytes, the leucocyte free exudate, ordinary serum, and simple physiological salt solution, were compared, in regard to their influence on checking the growth of colonies. The suspended leucocytes always showed marked bactericidal action, the whole exudate a less marked activity, and the fluid, from which the leucocytes had been removed, no such action, in most cases. *In vitro*, the bactericidal power of the leucocytes was only active against the weaker strains of streptococci, and incapable of checking the growth of stronger types. Control observations were made, to guage the action of the salt solution itself, both alone, and mixed with defibrinated blood, and blood serum, on the streptococci; they showed that the activity



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Pernicious anæmia.
Megaloblast, megalocyte, and microcyte.

resided in the leucocytes. This action is extracellular, as well as intracellular; the salt solution extracts some substance from the leucocytes, with bactericidal power.

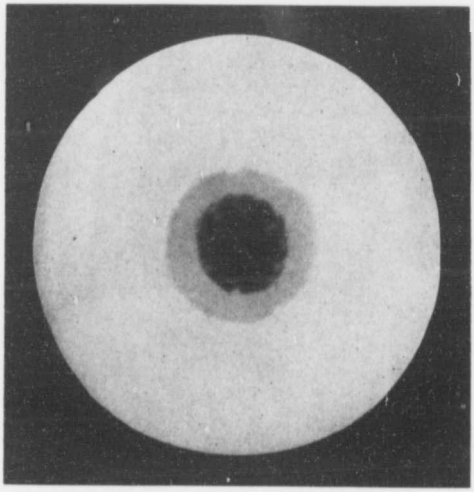
Bokenham experimented on rabbits, to determine the part played by phagocytosis, in the arrest of the inflammatory process in erysipelas. Minute fragments of sterile sponge, soaked, in a broth culture of *S. erysipelatis*, were inserted under the skin. After a time, the sponges were withdrawn, and the contained exudation examined. In this way, it was ascertained that phagocytosis was observable, in direct relation to the virulence of the original culture. With a culture, capable only of causing slight inflammation, in the rabbit's ear, phagocytosis was almost complete after 24 hours, and nearly all cocci were already enclosed in cells. With a more virulent culture, phagocytosis was still observable, but many cocci were not enclosed in cells, and those cells which contained cocci showed signs of having suffered greatly in the contest. With a very virulent culture,—one which would kill a rabbit in 2 or 3 days,—the exudate showed very few cellular elements, but extremely numerous free streptococci.

The absence of the active campaigning on the part of the phagocytes, in virulent infections, is a matter of frequent observation.

How soon, after infection, do the phagocytes appear at the seat of inoculation? Numerous experiments have been made to throw light on this interesting question. Petruschky and Fischel have shown that, within two hours after inoculation with anthrax, phagocytosis is not observed, and, even after three hours, the amount of phagocytosis is extremely small.

Klein and Homer did not find any phagocytosis, two hours after infection. Kanthack, after a large series of experiments, came to the conclusion, that phagocytosis rarely begins until four hours after inoculation. Fresh anthrax cultures were introduced under the skin, and every hour a little lymph was removed, by means of a capillary pipette, and examined microscopically. In this way, Kanthack found that the fourth hour is the usual time for phagocytosis to appear. The number of phagocytes, at this stage, is extremely small, and increases as time goes on. Two hours after inoculation, a large number of leucocytes had been attracted. These were chiefly lymphocytes and eosinophiles, which steadily refused to take up any of the bacilli.

When saprophytic micro-organisms were injected under the skin, Ruffer observed phagocytosis in active progress, in less than



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Young normoblast.
Normoblastic phase of secondary anæmia
(posthæmorrhagic).

half an hour. After the introduction of *B. pyocyaneus*, phagocytosis was observed in 25 minutes. When introduced directly into the blood, phagocytosis could be seen two minutes after inoculation.

There is every reason to believe, that bacteria become attenuated or weakened in their vitality, before phagocytosis begins.

Petruschky and others have demonstrated that, after a continued stay in the lymph sac of a frog, anthrax bacilli are greatly impaired in their virulence. The destructive action of the tissues of the frog, over anthrax bacilli, makes itself felt within five hours after inoculation, and this attenuation of the bacilli precedes phagocytosis.

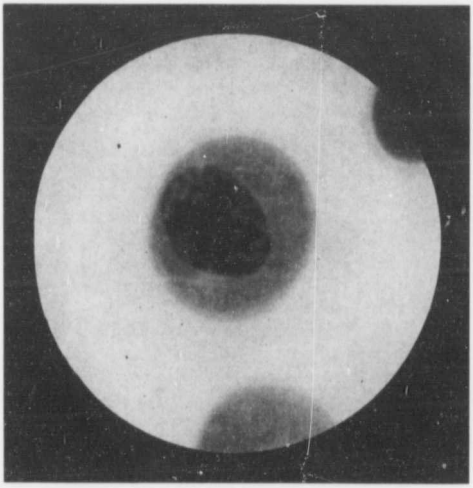
A remarkable case of pernicious anæmia, is reported by Rowley, in which all types of leucocytes were found to be actively phagocytic, for red and white cells. The most striking feature was the phagocytic power of the mononuclear cells, seen in smear on the warm stage. One cell, watched for an hour, destroyed twenty-seven red cells, and fourteen polymorphonuclears, and one, watched for three hours, was seen to engulf sixty-seven red blood cells, and twenty-four polymorphonuclears.

Reichenow describes the destruction of *Hæmogregarina stepanovi*, by a leucocyte. In its movement through the serum, the parasite comes in contact with a leucocyte, the movement to change the direction does not take place, and it remains stiff and stretched out. After a few seconds, large vacuoles appear in its nucleus; it has evidently been killed at once by the impact with the leucocyte. The leucocyte at once sets to work to surround its victim, and five minutes after the first contact, it has completely englobed the parasite.

The phagocytic index.

The phagocytic value of leucocytes *i. e.*, the average number of bacteria, phagocyted within a definite time, by the polymorphonuclears, is considered a fair and trustworthy indication of the patient's power of resisting, or overcoming infection.

The effect of tuberculin treatment is to increase both the number and phagocytic activity of the polymorphonuclear leucocytes, especially in the chronic tuberculous cases, in which the leucocyte count is below normal.



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Young megaloblast.
Megaloblastic phase of secondary anæmia
(posthæmorrhagic).

DEGENERATIVE CHANGES IN THE BLOOD.

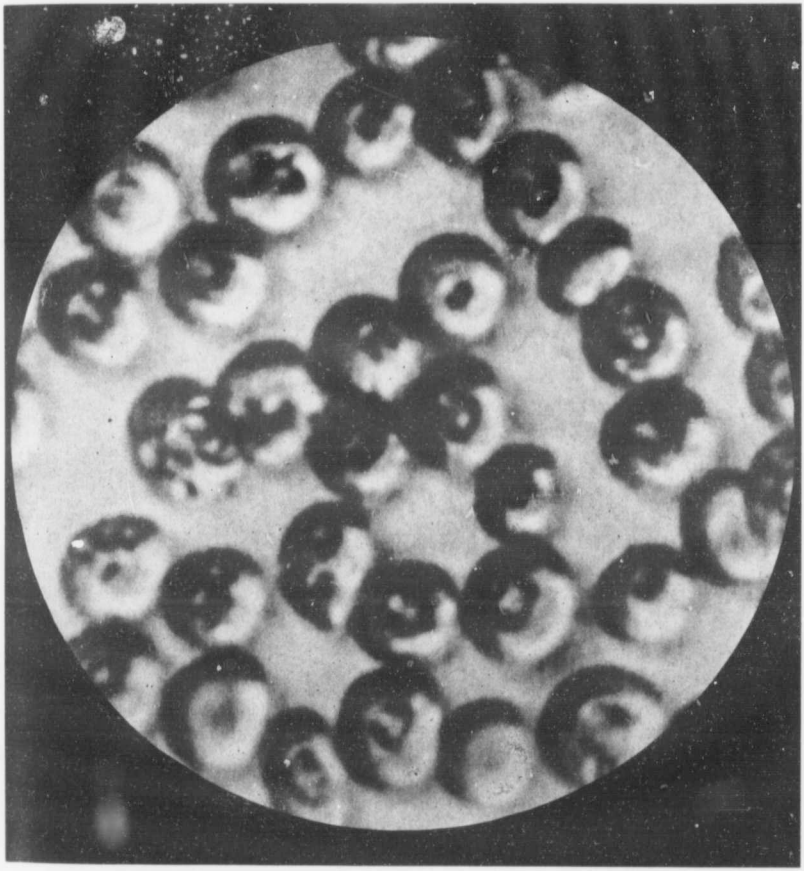
Hypochromemia.—Loss of hæmoglobin, or simple decolorization, is the earliest change affecting the red blood cells, and its intensity varies according to the intensity of the exciting cause. Diminution, in the amount of hæmoglobin, is seen in anæmic conditions, especially chlorosis, in which the corpuscles have entered the circulation, before receiving the normal quota of hæmoglobin. The lessened amount of hæmoglobin, in the corpuscles, is due to defective hæmogenesis, which leads to a disturbance of the normal uniformity, in the relation between the hæmoglobin and the number of blood corpuscles. In chlorosis, it would appear that the reduction, in hæmoglobin, always precedes the fall in the number of corpuscles.

The decreased amount of hæmoglobin, in the individual corpuscle, becomes evident in areas of decolorization. The light area appears first, in the central or thinnest part of the disk, and extends toward the periphery. The amount of decolorization is in proportion to the severity of the condition. Corpuscles, moderately poor in coloring matter, are recognised by the pronounced transparency of the central zone. In more marked cases, the peripheral zone alone is stained: these have been designated as ring forms. In the severe conditions, the corpuscles are completely decolorized, resulting in the shadow cells of Ponfick.

Among the agents, which have the power of inducing resolution of the chemical combination, between hæmoglobin and stroma, are snake poison, toad-stools, guaiacol, nitrites, nitro-benzol, arseniuretted hydrogen, potassium chlorate, pyrogallol, and high temperature. The coal tar derivatives are conspicuous, among medicinal agents, in common use, which exert a destructive action on the blood corpuscles. The effect of these substances, on the blood, is that of a hæmolytic poison. In a case of chronic poisoning, by the coal-tar preparations, observed by the writer, the most striking symptom was an intense livid colour of the skin.

When cobra poison is added to shed blood, in a test tube, two effects are noticed: (a) hæmolysis, meaning thereby destruction of the red corpuscles, and laking of the blood; and (b) delay or complete absence of coagulation. The cobra poison has a definite, hæmolytic action on the blood corpuscles, one result of which is to liberate the hæmoglobin.

Observations on the production of anæmia, by the action of



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Secondary anæmia.
Hydremia of red corpuscles.

bacterial toxins, are on the increase. Among the bacterial toxins, that of the streptococcus has the most destructive effect on the red corpuscles. In the very severe infections, by this organism, the destruction is so great, that the red cells may not exceed the number found in the severest anæmias.

Schistocytosis.

Degenerative changes, in the stroma, result in fragmentation of the corpuscles, with the formation of schistocytes. Irregularities in contour serve to distinguish these fragmentation products of the red corpuscles from microcytes proper, which arise by division of undersized mother-cells.

Schistocytes are constantly present, in pernicious anæmia. The action of the toxic agent, of pernicious anæmia, on the bone marrow, leads to the discharge, into the circulation, of cells less resistant than normal, to deleterious influences. The cells, thus formed, bear early evidence of various degenerative changes. The shortening of cell life requires increased cell production, to maintain the physiological balance between waste and repair.

Poikilocytosis.

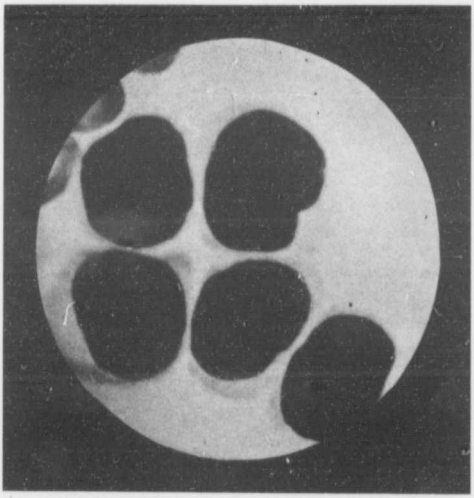
Deviation from the normal size, and shape, of red cells, is a feature of all types of anæmia. Deformities of shape and size are common to all pathological blood. As an indication of disturbances, in the bone marrow, poikilocytes are of about the same significance, as microcytes. Poikilocytes are functionally active, and may exhibit amœboid movement in fresh blood.

Polychromatophilia.

Polychromatophilia consists in an atypical staining, of the red cells, and betrays an impairment of function.

Schmidt believes it to be the result of a mixture of dissolved nuclear substance, with hæmoglobin, with or without basophilic granulation, as an intermediary stage.

Maragliano and Ehrlich advanced the theory, that it was due to a coagulation necrosis, affecting chiefly the older forms. The theory finds support in the fact, that polychromatophilic change, in cells, is associated with other signs of degeneration. This theory is op-



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Small lymphocytes.
Chronic lymphoid, or, lymphocytic leukæmia.

posed by Gabritchewski, Askanazy, Engel, Dunin, and others, who insist that they are not degenerating forms, but on the contrary the youngest cells of the blood. This view is supported by the abundance of such cells, in those conditions, in which red cells are being rapidly formed.

Maragliano and Castellino found that blood, after standing 10 to 12 hours, shows distinct alterations, one of which is the development of a basic staining quality, in a part, or the whole of the cell. They believe this change occurs in the circulating blood, and that it is evidence of destruction of blood.

Polychromatophilia occurs in various forms of anæmia, and is a sign of degeneration, in the affected cells. Instead of taking on the normal hæmoglobin colour, the affected cells show a violet, brown, blue-red, or even an intense blue, colour.

Granular degeneration.

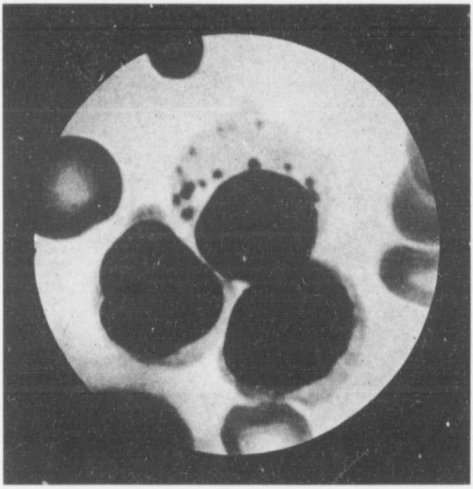
To Grawitz and Askanazy are due the credit for the first investigations, in this form of degeneration. The latter suggested, that these basophile granules are nuclear products, resulting from karyorhexis. Grawitz insisted, that they are derived from a degeneration of the cytoplasm.

The granules are constant, in lead poisoning, and appear very early before subjective or other objective symptoms can be demonstrated. The number of granular cells bears a direct proportion to the severity of the disease. In the severe cases, the coarse granules are generally in excess.

They can be produced experimentally, appearing in a few days, and increasing, as the intoxication becomes severe. No disease, that we as yet know of, causes granular degeneration of the erythrocyte, to the degree that is found in lead poisoning.

As against the theory of the nuclear origin of the granules, Ehrlich pointed out, that the granules were found, in some cases, in which no nucleated cells occurred in the blood, and that, on the other hand, they were absent when such nucleated cells were present. It was observed, that the granules were not stained by methyl green, as are the nuclei, and that the granules were not present, in the bone marrow, where nucleated corpuscles were abundant.

The granules were found in cancer, leukæmia, pernicious anæmia, sepsis, and lead poisoning, by Grawitz, who used the terms



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Small lymphocytes.

Chronic lymphoid, or, lymphocytic leukæmia.

"basic degeneration" and "granular degeneration." Grawitz considers the basophilic granules, as positive evidence of degeneration, and does not believe them the result of karyolysis of nuclei.

Plehn found them abundantly, in malarial blood, and regarded them as remnants of the parasites.

The evidence warrants the belief, that the granules are protoplasmic in origin, and result from a degenerative change, having no relation to nuclear fragmentation, or to polychromatophilia.

Basophile granules may be found in chlorosis, and all severe anæmias. They are usually seen in cells, whose hæmoglobin seems to be normal. They differ, not only in size, but in shape.

Vaughan found basophile granules, in normal blood, in percentages varying from 0.5 to 1.8. The percentage of cells, in pernicious anæmia, showing granules, varied from 7.7 to 18.8 per cent.

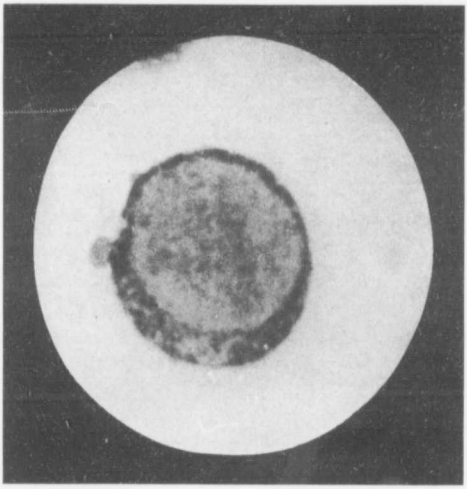
Hydremic degeneration.

Hydremic degeneration has been observed, by the author, in red corpuscles in septicæmia. The cells, in this case, were swollen and globular, and had lost their biconcavity. In some cells, the central depression had completely disappeared, while in others there was a faint impression. In the majority, the central depression varied between a quarter and a half of the diameter of the cell. Some corpuscles presented multiple depressions, which were considered to be due to unequal expansion of the cell. The hydremic condition of the erythrocytes, in this case, was attributed, by the author, to changes in the composition of the plasma.

Iodophilia.

In the normal polymorphonuclear cells, no free glycogen is present, yet, in certain diseases, cells are always found, which give the iodine reaction. Glycogen, in the blood, may be demonstrated by placing the preparations in a closed vessel containing crystals of iodine, where they assume a dark brown colour. A reddish-brown colour, in the polymorphonuclear leucocytes, is an indication of the glycogenic infiltration, indicated by the reaction.

Wolff believes, that some substance, susceptible to the action of iodine, probably cellular glycogen, is present in the circulating leucocytes, which, owing to its extreme solubility, is not present in



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Lymphoblast.

Acute lymphoid, or, lymphoblastic leukæmia.

dried films of normal blood, but is made insoluble, by certain toxins, and its presence is thus able to be demonstrated.

As in leucocytosis, toxæmia is the factor of the reaction.

Da Costa sums up his research on iodophilia as follows:—

1. In the dry film, intracellular iodophilia indicates a form of leucocytic degeneration, of toxic origin, and due presumably to an abnormal affinity, of the cell glycogen, for iodine. The same reaction, in the fresh wet blood film, is physiological. Extracellular iodine-stained masses, in the plasma, have no definite pathological significance, so far as can be determined.

2. The toxic factor may be absolute, and frankly demonstrable, as in pyogenic septicæmia, and in pneumonia, or, it may be indefinite, and masked, as in pernicious anæmia, and in cachectic states.

3. The reaction is restricted to the cytoplasm of the leucocytes, never affecting their nuclear structures. In fully 98 per cent. of all reactions, the polymorphonuclear neutrophiles are implicated; in about 20 per cent., other cells, notably the lymphocytes, and less commonly the myelocytes, also react, and, in exceptional instances, iodophilous eosinophiles are noted.

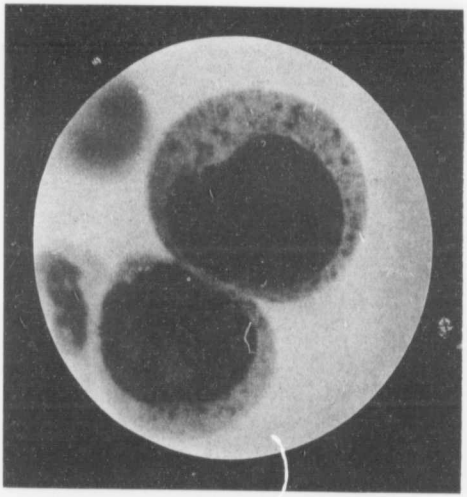
Diffuse and diffusely granular brown staining are the prevailing micro-chemical changes, pure granular stippling being exceedingly rare.

4. The number of iodine stained cells corresponds, roughly, to the colour intensity of the reaction; 50 per cent., or higher, of iodophilia, being generally found in a decided, and approximately 25 per cent., in a feeble, reaction.

5. Iodophilia has no direct relation to leucocytosis, to anæmia, or to pyrexia. Its relative frequency to high leucocyte figures is due to the fact, that such cases are generally toxic; a similar toxæmia, with leucopenia, excites just as intense a reaction.

The grade of anæmia in no wise corresponds to the incidence, or the intensity, of the reaction. Fever, *per se*, has absolutely no effect in causing iodophilia. Afebrile cases, and those with hyperpyrexia, show an equal percentage of positive results.

6. From a clinical standpoint, iodophilia is often a helpful, though, under no circumstances, a positive diagnostic sign, and to be of real service to the physician, it should be correlated with every other detail of the clinical picture.



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Myelemia.
Chronic myeloid, or, myelocytic leukæmia.
Neutrophile myelocytes.

A positive iodine reaction occurs, with considerable regularity, in—

(a) Grave anæmias.
(b) Pyogenic infections.
(c) Toxæmia of bacterial origin.
(d) Uræmia.
(e) Disturbances of respiration.

The iodine reaction is of value, as an independent indicator, in suppurative processes, without pyrexia, or leucocytosis.

Locke found, that no septic condition can be present, without a positive reaction. In appendicitis, with free drainage, the iodine reaction rapidly diminishes, and is usually gone in 48 hours. Locke found, that persistence of the reaction indicates incomplete drainage.

The diagnostic value of a negative reaction is great, as it excludes septic conditions of all kinds.

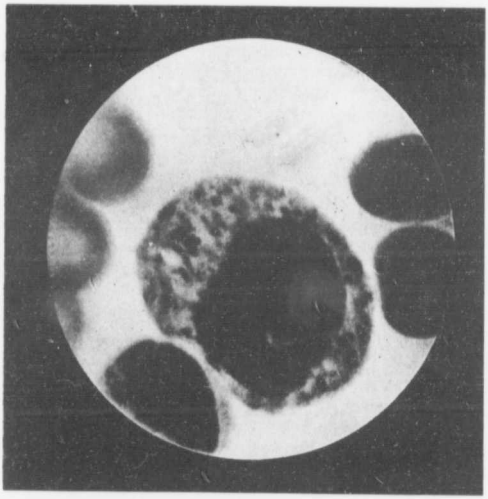
PRIMARY ANÆMIAS.

Chlorosis.

Chlorosis is essentially a disease of puberty, arising without obvious cause, and characterised by a diminution in the amount of hæmoglobin, in red blood corpuscles.

While numerous suggestions have been made to account for chlorosis, the essential factor in the evolution of the disease is as yet unknown. It seems probable that this affection is due to faulty hæmogenesis, either temporary, and occurring at the age of puberty, or congenital, and more or less permanent. This is the only theory as to the nature of chlorosis, consistent with the specific action of iron.

From observations of 23 cases, Stieda concludes that true chlorosis, not to be traced to external injury or to primary disease, is a disorder of development, like any other such disorder, or sign of physical degeneracy. He found it very frequently associated with infantile types of structure, in the adult patient, in whom it was only one of the symptoms of general ill development, being neither the cause nor the effect of any of the other symptoms.



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Myelemia.
Chronic myeloid, or, myelocytic leukæmia.
Neutrophile myelocyte.

Chlorosis is attended with disorders, which have been considered to bear a causal relation to the disease.

Menstrual disorders.—The almost complete immunity of males from the disease, and its occurrence in the female sex during the establishment of the menstrual function, have been considered to be of etiological significance. No satisfactory explanation can be given of this remarkable difference, in the liability of the sexes. One of the distinctive features of chlorosis is its association with amenorrhœa.

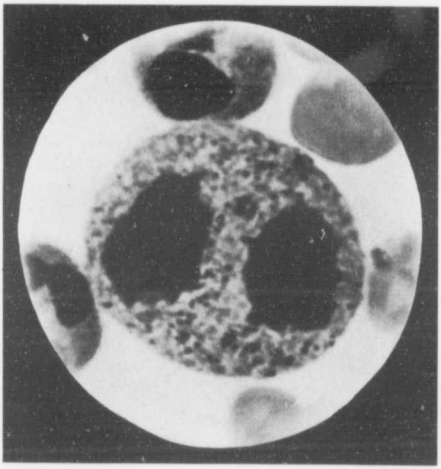
Stephenson (Aberdeen), in an analysis of 232 cases, did not consider that the affection was necessarily associated with an impairment of development of the body. In 58.7 per cent. of the cases, menstruation became scanty and irregular, and in many cases painful, while in 37.8 per cent., there was amenorrhœa for various periods. The number of cases of the disease presented a regular curve, beginning at 14, and rising steadily to a maximum, between 18 and 19, then rapidly falling to disappear altogether at 22. The tendency to secondary attacks manifested itself first at 24, rose to a maximum between 26 and 28, to again disappear at 32.

Most of the theories, from Hippocrates downwards, ascribed the condition to an intoxication arising from a disordered menstrual function. While an imperfect evolution of menstruation, as evidenced by scantiness of the flow, and irregularity of the periods, is a regular feature of the disease, it is generally subsequent, rather than antecedent to, the blood condition.

Intestinal disorders.—Andrew Clark expressed the belief that chlorosis, arising in nervous constitutions, with imperfectly developed sexual organs, is caused by fæcal retention, its decomposition, and the subsequent absorption of the poisonous products so formed.

Habitual constipation is a common complaint, and is often associated with anæmia. As against intestinal autointoxication, it may be stated that there are many cases of chlorosis, in which constipation does not exist, and in which intestinal decomposition is not greater than normal, and many instances of feculent retention, where anæmia does not result.

Arterial hypoplasia.—Congenital narrowness of the aorta was found by Virchow, and was considered by him to have some causative connection with the anæmia. As hypoplastic arteries have been found where no anæmia existed, the relation which was believed, by Rokitansky and Virchow, to exist between this developmental anomaly and chlorosis, is generally discredited.



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Myelemia.
Chronic myeloid, or, myelocytic leukæmia.
Mitosis in neutrophile myelocyte.

Nervous disturbances.—Trousseau considered it a neurosis, the blood changes being secondary. No evidence has been adduced in support of the theory, that chlorosis is a neurosis allied to hysteria.

Lloyd Jones has sought an explanation of chlorosis, in the changes which the blood undergoes at puberty. He says that, at puberty, the specific gravity of the blood, in males, becomes greater, whereas, in females, it becomes less; on the other hand, the specific gravity of the serum slightly increases in females, at this period, and that, therefore, the great fall in density is due to the diminution of hæmoglobin. For him, the loss of hæmoglobin, in chlorosis, is only the exaggeration of a natural process.

The blood in chlorosis.

A considerable degree of anæmia may be associated with a normal proportion of red cells.

In severe forms, may be noticed a moderate diminution in number, and variation in size and shape, of the corpuscles.

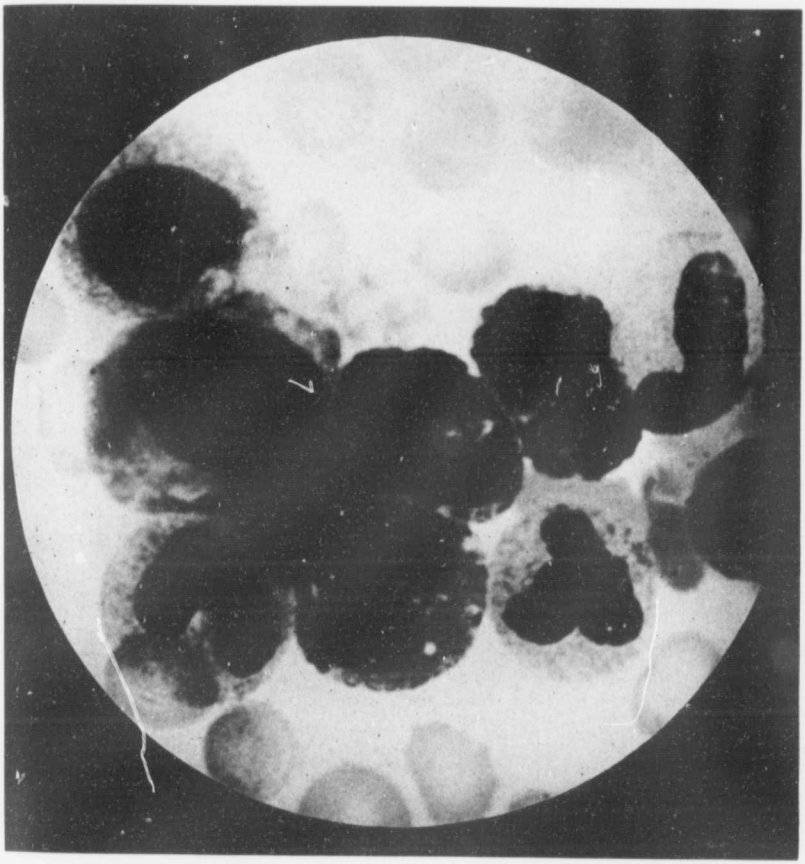
In the very severe cases, the red cells may number less than 2 million per c. mm. One would expect, in such cases, to find the red corpuscles imperfectly formed, and greatly altered in size and shape. Such was the condition of the blood, from which the microphotograms of chlorosis were obtained. The history of the case would indicate that the anæmic condition had been more or less permanent throughout life. The red corpuscles show the extreme alteration, in size and shape, which is so characteristic of the severe grades of anæmia, in its various forms. Microcytes were frequent; nucleated cells not found. The hæmoglobin was greatly diminished. The case had never received treatment, and terminated fatally in her 19th year.

In 80 cases of chlorosis, reported by Byrom Bramwell, the red cells averaged 3,437,300. Hayem reported a case with 937,360 red cells.

Hæmoglobin.—The essential blood change is a diminution in hæmoglobin, which may be reduced to 10 per cent. In Bramwell's cases, the hæmoglobin averaged 34 per cent.

The average colour index, in well marked cases of chlorosis, is usually about 0.5.

In 50 cases of chlorosis, Warfwinge found a reduction of the hæmoglobin to 15 per cent., while the red cells varied but little from normal in number. This characteristic disproportion, between the



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Myelemia.
Chronic myeloid, or, myelocytic leukæmia.
Polymorphonuclear leucocytes, and neutrophile myelocytes.

number of red cells and the amount of hæmoglobin, he regards as presumptive evidence, that chlorosis is a specific affection due to some toxin, which prevents the red cells from taking up substances, needed for the production of hæmoglobin.

Zickgraf makes a practice of applying the tuberculin test, in every case of persisting chlorosis, and states that a positive response was obtained, in 75% of 55 cases, in which there was nothing otherwise to suggest the existence of tuberculosis. He assumes, from these findings, that tuberculosis is responsible for chlorosis, in a surprisingly large number of cases.

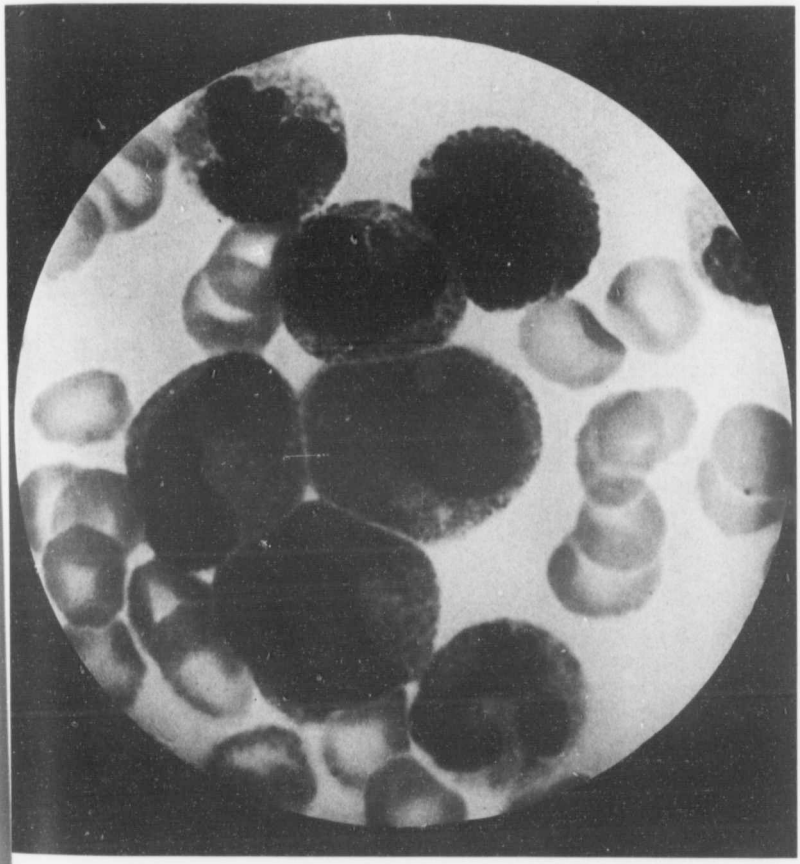
The chlorotic condition furnishes a favourable soil for tuberculous infection. The coincidence of the two diseases is probably attributable to unfavourable nutritive conditions.

The action of iron in chlorosis.

The causation of chlorosis has received some elucidation, by the investigation on the utility of iron, and its mode of action. The function of the red corpuscle, as an oxygen carrier, depends upon the iron containing element; the hæmoglobin index is the measure of the functional capacity of the individual red corpuscle. The administration of iron, in chlorosis, affords one of the most brilliant instances of the specific action of a remedy. It being accepted that iron, in any form, does improve the character of the blood, it would be interesting to know how it accomplishes its effect.

It would appear that the immediate effect of iron is to increase the number of corpuscles, without a corresponding increase in the amount of hæmoglobin. The first effect of iron is to stimulate hæmogenesis, and only secondarily does it add to the amount of hæmoglobin, in the corpuscles.

Hayem (Du Sang), from the study of the corpuscles during a cure, recognises three periods. During the first stage, there is an increase in the number of corpuscles per c. mm., without any increase in the corpuscular richness in hæmogoblin. In the second stage, there is a further increase in the number of corpuscles, and, at the same time, an increase in the amount of hæmoglobin, in each corpuscle. During this period, the number of corpuscles per c. mm. occasionally rises beyond the normal, and, in these cases, a last stage occurs, in which the number of corpuscles is gradually diminished, while the enriching in hæmoglobin of those remaining continues.



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Myelemia.
Chronic myeloid, or, myelocytic leukæmia.
Polymorphonuclear leucocytes, eosinophile leucocyte, and neutrophile myelocytes.

As to the cure effected by iron, it is improbable that it simply supplies the deficit, because every chlorotic absorbs sufficient iron for the purpose.

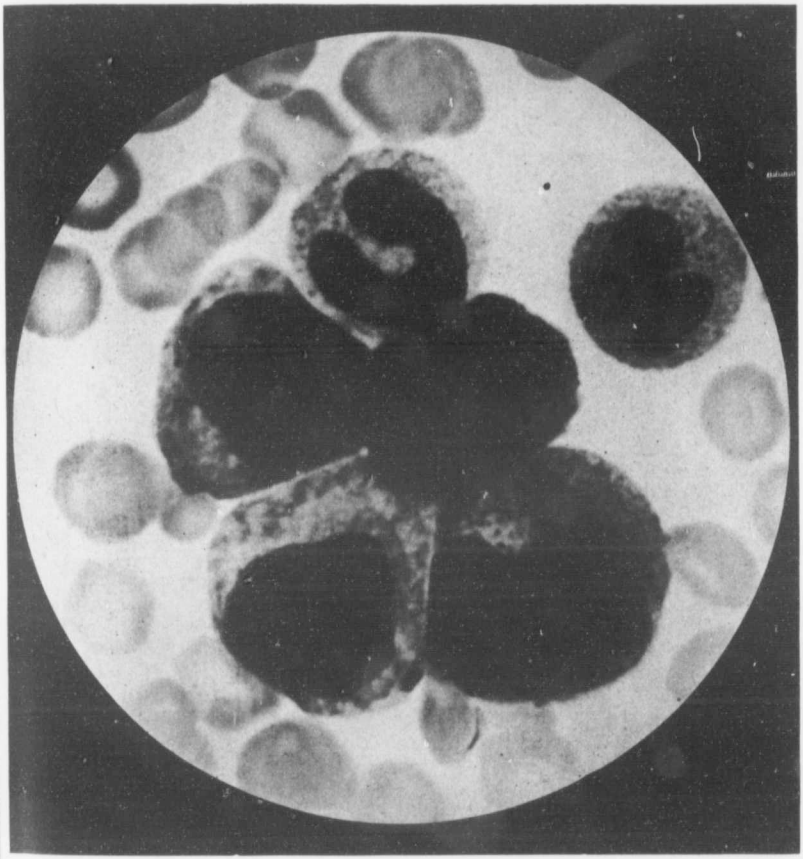
V. Noorden is of the opinion that iron only acts, like many other medicinal and hygienic agents, by stimulating the hæmatopoietic organs, and he does not attach any importance to its relation to the hæmoglobin molecule.

A. Hoffman (Halle), in continuing his investigations, as to the mode of action of iron, experimented on 98 rabbits. Particular attention was paid to the bone marrow, spleen, and lymphatic glands, as especially concerned in blood formation; liver, kidneys, and small and large intestine, were also examined. The blood corpuscles were counted, and the hæmoglobin estimated, and various preparations of iron and hæmoglobin, tested as regards qualitative and quantitative absorption. He found that all forms of iron were absorbed in the duodenum, and entered the circulation in transport cells, combined with albuminous matter, in a combination which had no toxic action. It could be so demonstrated, in large quantities, in the spleen, liver, and especially in the bone marrow, where crowds of these iron-laden cells were present in the tardy blood stream, in the parenchyma itself and in the network of vessels within it. This organ alone exhibited, after blood letting, a corresponding regenerative activity, an active hyperplasia of its parenchyma. The restoration of the red corpuscles was more rapid, the bone marrow richer in its contents, after the administration of iron while the spleen and lymphatic glands showed no difference. Hoffman concludes, that iron has a stimulating action on the physiological activity of the bone marrow, and accelerates the entrance, into the circulation, of the young cells therein produced.

Special preparations of iron are unnecessary, of hæmoglobin irrational; the action of iron depends entirely on the quantity of metal absorbed.

PERNICIOUS ANÆMIA.

The recognition of progressive, pernicious anæmia, as a distinct and separate malady, is due to Addison of Guy's Hospital, who first described its peculiar nature, in 1855, when he also discovered the disease of the adrenals, which still bears his name. The



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Myelemia.
Chronic myeloid, or, myelocytic leukæmia.
Polymorphonuclear leucocytes, and neutrophile myelocytes.

disease was known as Addison's anæmia, until Biermer, in 1872, gave to it the name by which it is since recognised. Addison is entitled to the credit of having first recognised pernicious anæmia, as a definite clinical disease. The disease was described by Addison, under the term idiopathic, and included only cases apparently primary. Biermer, in introducing the term—"progressive pernicious anæmia," regarded the element of fatality as the most important feature, and the absence of cause became of secondary importance.

There has been a large amount of discussion, as to whether the condition constitutes a distinct and separate disease, or whether it is simply a condition of extreme bloodlessness, secondary to numerous other conditions.

There is good reason, on the ground of etiology, for separating from the secondary anæmias those in which no cause is discoverable.

No classification of the anæmias can be made on the blood picture alone.

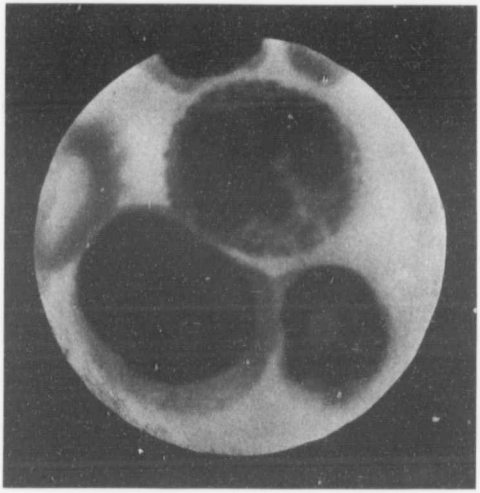
The merit of Addison's work consisted in the separation of what he considered a special disease. The attempt to group, under pernicious anæmia, all those cases, of known and unknown etiology, in which the blood changes indicate megaloblastic degeneration, has led to further confusion. Too much importance is attached to the appearance of megalocytes, and megaloblasts; they are found in other forms of anæmia and are not distinctive of pernicious or any one form of anæmia.

The characteristic blood picture of primary pernicious anæmia may be presented by patients suffering from malignant disease. The clinical symptoms, and the blood condition, are also induced by oft repeated hæmorrhages, and by intestinal parasites.

The different forms of anæmia, in their initial stages, possess certain features in common. Addison described pernicious anæmia as one "without discoverable cause." To this may be added the essential blood change, and we may define "pernicious anæmia" as an anæmia arising without discoverable cause, characterised by progressive reduction in the red corpuscles, and a high colour index.

Age incidence.—Pernicious anæmia is not often met with during the first 25 years of life, but no age is exempt.

D'Espine (Geneva) has reported pernicious anæmia in a girl aged 2, in which the symptoms did not endure for more than one month. The anæmia developed without discoverable cause.



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Anæmia infantum pseudoleukemica.
Neutrophile leucocyte, large and small lymphocytes.

Clinical course.—The most notable feature of the disease is the remarkable rapidity, with which the blood change is established, and its permanency. The age of the patient, the severity of the changes in the blood, and the progress toward a fatal issue, in spite of treatment, serve to distinguish pernicious anæmia from chlorosis and secondary anæmia. The term "*pernicious*" correctly represents the tendency of the disease, notwithstanding all modern therapeutic measures.

In the adult, it is seldom an acute disease. Generally speaking, the younger the patient the more rapid the course.

The course of the disease is marked by remissions and recurrences.

General etiology.

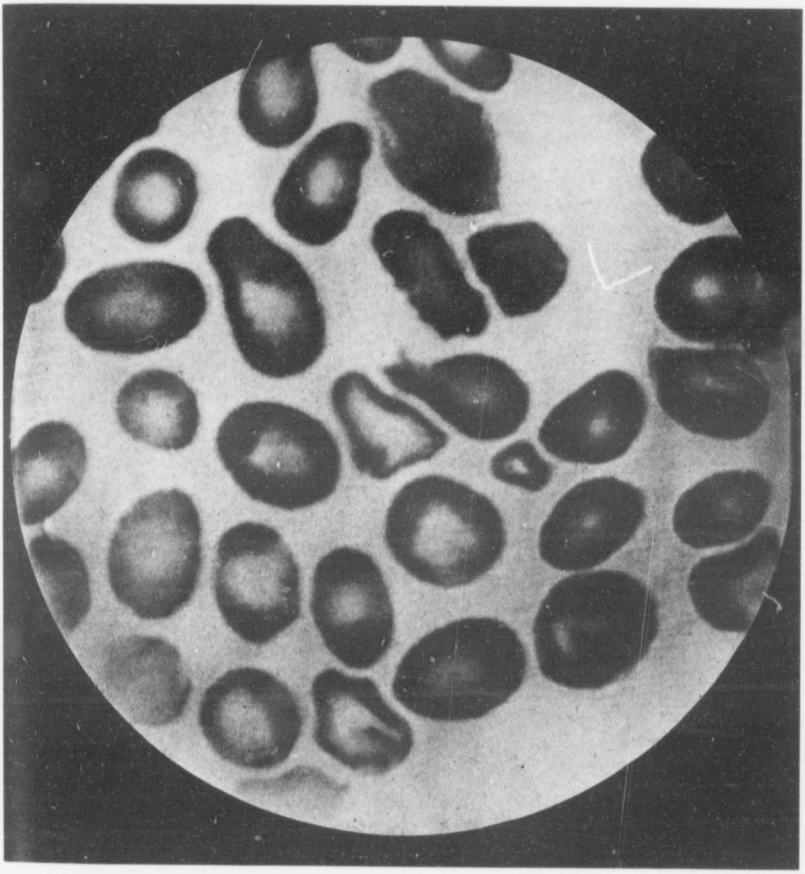
Quincke found an enormous accumulation of iron in the liver, and he suggested that the affection was probably due to increased hæmolysis.

To maintain the blood at the standard of health, an even adjustment between blood formation and blood loss is necessary. Instances, in which the normal balance between hæmogenesis and hæmolysis is disturbed, are furnished, among others, by chlorosis, and post-hæmorrhagic anæmia. In the former, is found defective blood formation with normal blood loss; in the latter (at first) normal blood formation with excessive blood loss. In chlorosis, there is defective formation, principally in the quality, but also in the quantity of red corpuscles. Pernicious anæmia is believed by some to result from defective hæmogenesis; others believe it to result from excessive hæmolysis, defective hæmogenesis being secondary.

Clinically, normal hæmogenesis is indicated positively by the character of the blood corpuscles, and negatively by the absence of excessive hæmolysis.

Excessive hæmolysis, on the other hand, is indicated by the deposit of hæmolytic debris in the liver, spleen, kidneys, and skin and, especially, when rapid, by the appearance of the dissolved elements in the urine.

Hunter (London), continuing Quincke's observations on the deposit of iron in the liver, believes that pernicious anæmia is due to excessive hæmolysis, resulting from a toxin acting within the portal area. This poison, Hunter concludes, is probably of a cadaveric nature, produced within the gastro-intestinal tract.



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Anæmia infantum pseudoleukemica.
Poikilocytes.

Mott and others hold that pernicious anæmia consists essentially in an excess of the normal, blood-destroying function, of the liver and the spleen. There is no special reason for believing, that either the liver, or the spleen, has an active blood destroying function.

The life of the red corpuscle begins in the bone marrow, and terminates in the liver. The corpuscles disintegrate, in the natural course of events, and the products of this disintegration are simply stored in the liver, or excreted by it as bile pigment, bile acids, etc.

Jacobi found that, when an iron salt was injected into the blood, no less than 50 per cent. was retained by the liver. The excess of iron in the liver is no proof, as some think, that the liver cells actually break down red corpuscles. Iron is also found in the spleen, kidneys, pancreas, and surface of the brain.

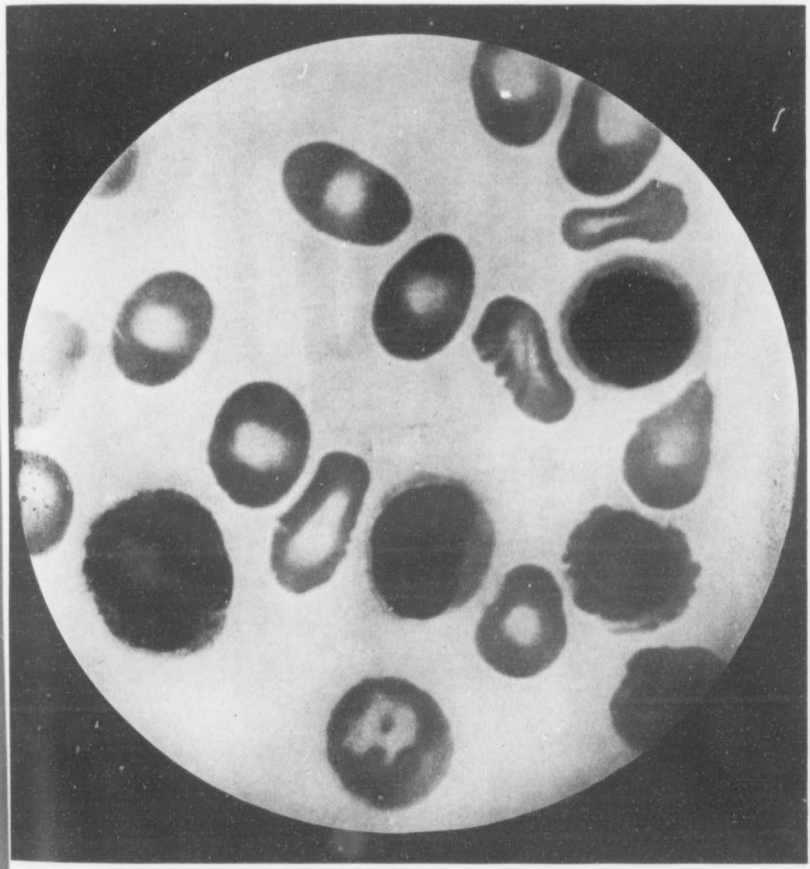
Minkowski and Naunyn, after poisoning with arseniuretted hydrogen, observed, in the liver spleen and bone marrow, large numbers of leucocytes, carrying partially disintegrated red corpuscles, whereas, in the blood of other parts, such leucocytes were rare. The explanation is, that a slowing of the blood stream is necessary, to enable the leucocytes to deal with the weakened corpuscles. This occurs, according to Quincke, in the hepatic capillaries, and, to a less extent, in the spleen and bone marrow.

That excessive hæmolysis is a constant feature of pernicious anæmia, most authorities are agreed.

The theory which most satisfactorily explains the condition is, that it is a process of defective hæmogenesis, in which excessive hæmolysis is a constant result.

The life of the tissue cell is short, and the blood corpuscle is no exception. By reason of defective hæmogenesis, the red corpuscles enter the circulation, predisposed to early disintegration—without sufficient vitality to resist deleterious influences.

The final, clinical picture of pernicious anæmia results from excessive disintegration, within the blood paths. The production of cells, which are individually less resistant to deleterious influences, presupposes a deficiency in the bone marrow. This weakness in the bone marrow may not result in the production of cells, in insufficient numbers. Nature compensates for excessive disintegration, by increased blood formation. The action of arsenic, in pernicious anæmia, is explained on the ground that it exerts a stimulative effect on the bone marrow, leading to the increased production of cells, and possibly to the production of more resistant cells. Gunn has



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Anæmia infantum pseudoleukemica.
Polymorphonuclear neutrophile leucocyte, small lymphocytes, and poikilocytes.

found that arsenic protects the red corpuscles from the hæmolytic action of distilled water.

That the hæmoglobin is not at fault, is indicated by the high hæmoglobin content of the corpuscles, and the fact that, as a remedial agent, iron is useless.

THE BLOOD PHASES OF ANÆMIA.

Widely different as the causes of anæmia may be, it is a striking clinical fact, that they present certain blood phases in common. The blood phases, hereinafter described, are applicable to all forms of anæmia. The blood picture of the mild anæmias is restricted to the first one or two phases; severe forms traverse most or all phases, according to their severity.

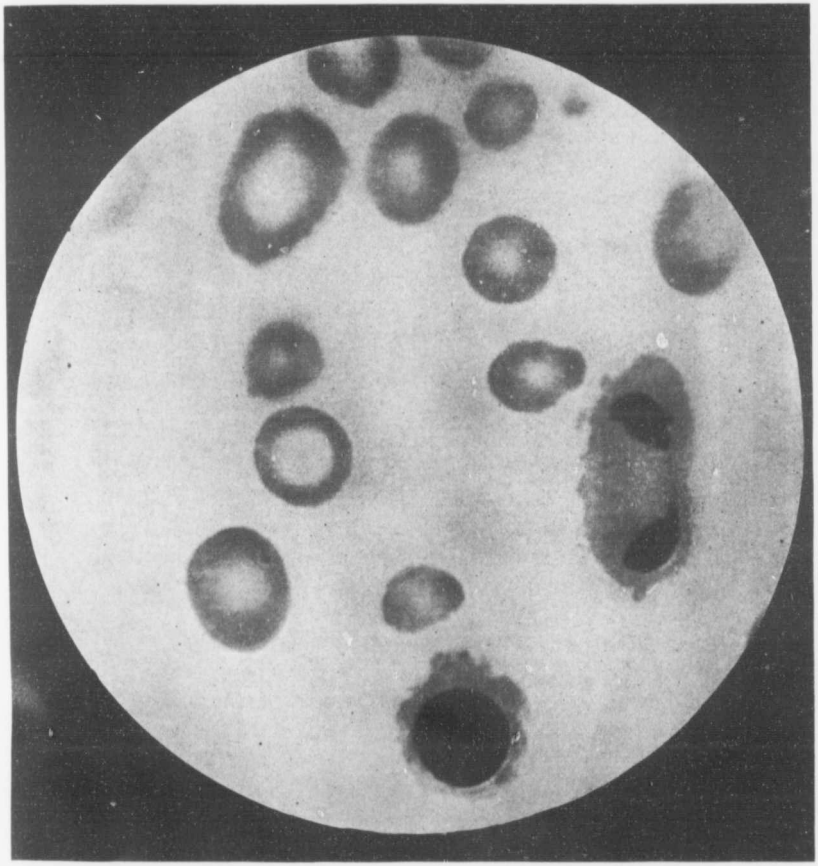
First or normocytic phase.

The first, or normocytic, phase begins with the reduction in number of the red corpuscles. This is the first stage in the development of all anæmias, whatever the cause. Reduction in the number of red cells results, when the blood formation fails to keep up with the requirements of the body.

The reduction in the number of corpuscles, which is the essential feature of the normocytic phase of anæmia, results either from insufficient production, to meet a normal demand, or from excessive blood loss, with an apparently normal production.

The reduction may be gradual (chlorosis), or sudden (hæmorrhage).

In pernicious anæmia, the oligocythæmia is more profound, in degree, than in any other form of anæmia. The decrease in the number of corpuscles is more marked, than the decrease in the percentage of hæmoglobin. The average hæmoglobin content may be greater than in the normal corpuscle, and still greater than in the corpuscle in chlorotic blood. Apparently, the disintegration of corpuscles, in pernicious anæmia, goes on faster than the destruction of hæmoglobin. The colour index is usually over 1, and may be double or treble.



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Anæmia infantum pseudoleukemica.
Mitosis in megaloblast.

Edgecombe (Harrogate) reports a case, with hæmoglobin 8 per cent., red cells 185,000, and colour index 0.84.

Handford (Nottingham) reported a case of pernicious anæmia, with corpuscles 154,000 per c. mm., hæmoglobin 10 per cent., and colour index 3. In 5 months, the hæmoglobin had increased to 50 per cent., corpuscles to 46 per cent., and the colour index had dropped to 1. This man was reported, 8 months later, as pursuing his occupation of hawker, in apparent good health.

It is stated, on the authority of Hayem, that anything under 300,000 corpuscles per c. mm., is incompatible with life, but Quincke mentions a case in which there were only 143,000.

Most cases of pernicious anæmia show from 1,000,000 to 2,000,000 corpuscles per c. mm., when they first come under observation.

Loss of strength is the symptom, which usually brings the case under observation. The weakness is not always in proportion to the degree of anæmia. It would appear that the cases with fewest corpuscles are not necessarily the most severe, nor those with more numerous corpuscles milder in type. One patient, with 500,000 per c. mm., may be following his usual occupation, while another, with 2,000,000, is mortally ill.

In most cases of pernicious anæmia, death occurs when the corpuscles are between 300,000 and 600,000.

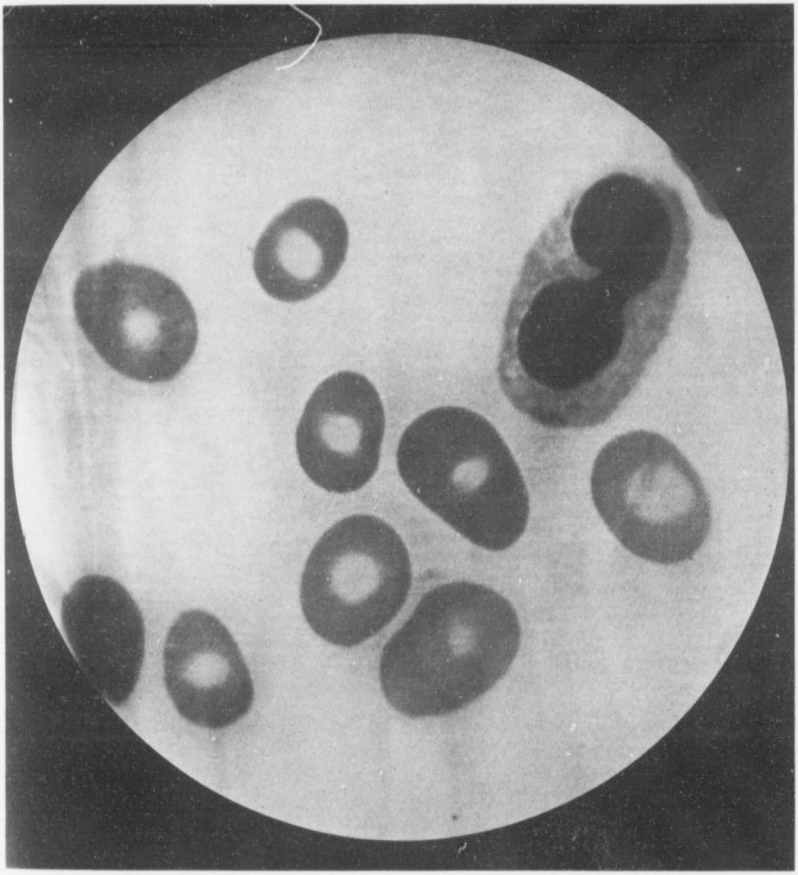
Second or poikilocytic phase of anæmia.

This phase begins with the appearance of poikilocytes.

Regularity in formation is the most striking characteristic of the normal red corpuscles. This uniformity in size and shape is retained, in the initial stages of chlorosis, and secondary anæmia. The red discs are also, in all respects, normal, in the quiescent periods of pernicious anæmia.

When pernicious anæmia comes under observation, the blood is already in, or has passed, the second, or poikilocytic, phase.

The distinctive feature of this phase is the great irregularity, in size and shape, of the corpuscles. These deformities are in no way characteristic of any particular type of anæmia. The corpuscles lose their uniformity, and, in pernicious anæmia, it has been noted that they have a tendency to become oval, or pear shaped. These are the most common forms for pernicious anæmia. In the severe grades of chlorosis, the most fantastic shapes are seen.



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Anæmia infantum pseudoleukemica.
Large lymphocyte and poikilocytes.

Poikilocytes show marked differences in their hæmoglobin content.

Microcytes, or small corpuscles of arrested development, are also a product of this phase. These are approximately half the normal size, or may be mere fragments, the result of schistocytosis. Several microphotograms, illustrating the production of microcytes, by schistocytosis, or fragmentation, appear in this volume.

In the various forms of anæmia, improvement towards uniformity of shape and size, of red cells, is a good indication of the progress of the blood to a normal condition.

In the primary attack of pernicious anæmia, the blood count may fall to a very low figure, before the appearances of morphological changes.

Third or normoblastic phase of anæmia.

This phase is marked by the presence of normoblasts, in the blood. It marks the stage of great regenerative activity, on the part of the bone marrow.

The nucleated cell of normal size, having a small deeply stained nucleus, is regarded, by Ehrlich and others, as the antecedent of the red corpuscle. With the exception of aplastic anæmia, they are to be found, at some time, in all forms of severe anæmia.

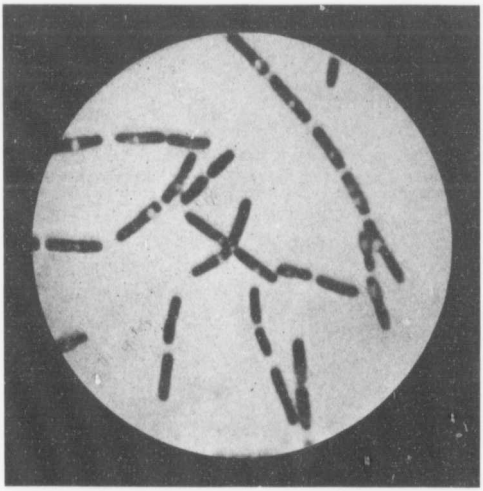
The sudden increase in the number of normoblasts is a regenerative phenomenon, and therefore of favourable import. They are most numerous in the acute anæmias, and are the sign of an extraordinary effort of blood renewal.

A periodical increase of normoblasts, in chlorosis, lasting 4 to 6 days, and accompanied by a marked increase in red cells, has been described by V. Noorden as "a blood crisis."

The phenomenon of the normoblastic phase indicates, that the type of blood formation is physiological.

Ehrlich describes a case of fatal posthæmorrhagic anæmia, in which he could find no normoblasts whatever. Autopsy showed that no regenerative effort had been put forth by the bone marrow. According to Ehrlich, therefore, a scarcity of normoblasts, in pernicious anæmia, would indicate the same failure of response, on the part of the bone marrow.

Microblasts, and poikiloblasts, are also products of this phase. In the remissions of the disease, normoblasts usually disappear from the blood.



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Bacillus anthracis.

Fourth or megalocytic phase of anæmia.

This phase is marked by the presence of megalocytes in the blood, and indicates a severe grade of progressive anæmia.

These giant cells are the immediate successors of the large, nucleated, red cells of the bone marrow, or megaloblasts. They measure up to 11, or 13, or even 16 to 20, microns.

The presence of megalocytes in the blood is pathological, and indicates a condition of exhaustion of the bone marrow.

The diameter of the blood cells is distinctly increased in this phase.

The high colour index, which is such a constant and characteristic feature of the megalocytic phase, in pernicious anæmia, is no doubt due to the large percentage of megalocytes, containing an unusually large amount of hæmoglobin. A high colour index is a sign, so constant, in all blood phases of pernicious anæmia, that, notwithstanding the absence of other morphological elements, it is sufficient to excite grave suspicion.

In chlorosis, the hæmoglobin is reduced, out of proportion to the reduction in the corpuscles, so that the hæmoglobin content of each cell may be greatly lowered. In posthæmorrhagic anæmia, the colour index remains unaltered, and the percentage of colouring matter corresponds with the percentage of the corpuscles.

With the relative increase in the number of large cells, containing an excess of hæmoglobin, the colour index rises, to descend in periods of remission. The number of megalocytes varies in different anæmias, and, from time to time, in the same condition.

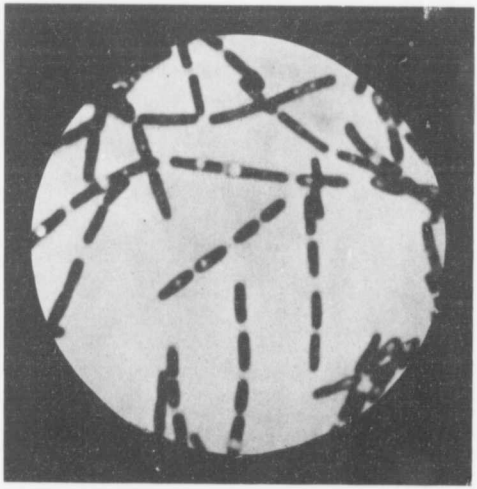
According to some writers, it is justifiable to class, as pernicious anæmia, a blood condition in which any considerable number (10 to 33 per cent.) of the red cells are megalocytes, with increased hæmoglobin index.

The characteristic feature of the megalocytic phase of anæmia is its persistence, when once established.

Fifth or megaloblastic phase of anæmia.

The megaloblastic phase is marked by the presence of megaloblasts in the blood. The entry of these cells, into the blood, is a sign that certain pathological changes are taking place in the bone marrow.

The megaloblast is the direct antecedent of the megalocyte,



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Bacillus anthracis.

into which it is transformed, by the disappearance of the nucleus. Their presence in numbers indicates a further, and final, stage of pathological blood formation.

The majority of megaloblasts display large pale nuclei, and are distinguished from normoblasts by the deeply stained nuclei of the latter. The nucleus of the megaloblast contains, as a rule, a well marked chromatin network; the nucleus of the normoblast is pycnotic. Size and age are the distinguishing marks of the nucleated red cells. Old normoblasts, and young megaloblasts, are the forms commonly encountered in the blood. The normoblast, containing a small dark structureless nucleus, is in fact an old cell; the megaloblast, containing a large pale nucleus, with delicate nuclear structure, is a young cell. The character of the nuclear network is a guide to the age of the cell.

Though normoblasts are found in all grave anæmias, and are known to be regenerative in function, practically, in no condition, other than pernicious anæmia, do the megaloblasts so constantly outweigh numerically the normoblasts. This is regarded as a distinctive feature of pernicious anæmia, and a point of differential diagnosis from secondary anæmia.

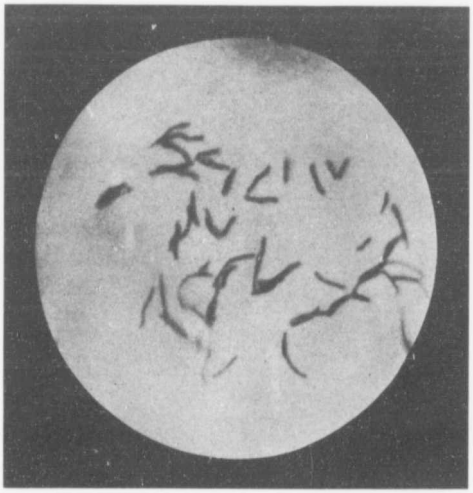
The fifth, or megaloblastic, phase is established with the preponderance of megaloblasts over normoblasts. The histological picture of pernicious anæmia is often of the megaloblastic phase, more often of the megalocytic. The onset of this phase of anæmia, though of serious import, does not of necessity prognosticate a fatal issue. Megaloblasts appear in the blood of severe forms of secondary anæmia, especially that present in ankylostomiasis.

Such are the phases, physiological and regenerative, or pathological and degenerative, which are presented by the various anæmias. Each phase represents a further step in the downward tendency, and is marked by the presence of an additional morphological element in the blood.

All anæmias, in their downward course, pass through some or all of these phases, according to the severity of the cause.

In the periods of remission, so common in pernicious anæmia, the red corpuscles rise, and the hæmoglobin-index falls. The megaloblasts disappear, normoblasts take their place, to disappear in turn. After the disappearance of the megalocytes, and poikilocytes, the blood is found in the first phase, with a reduction in number of red corpuscles.

In some remissions, the blood count increases to normal, or



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Bacillus tuberculosis.

may exceed even this, but mostly does not rise above 4,000,000. It is interesting to note that Quincke's celebrated case, in which there were only 143,600 per c. mm., improved greatly, and went through a typical remission, before she died.

Leucopenia, with a relative lymphocytosis, is the rule in pernicious anæmia.

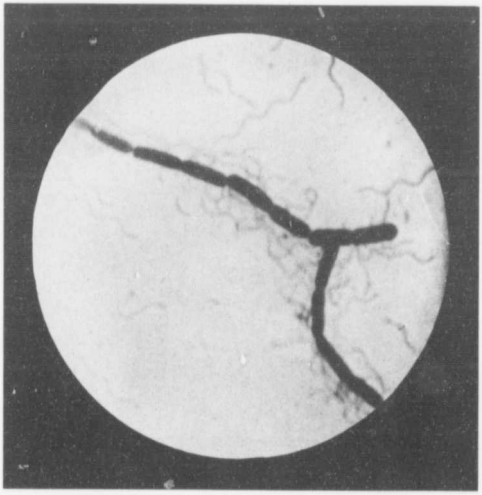
Aplastic anæmia.

In this rare form of fatal anæmia, the blood shows no evidence of regenerative activity. The bone marrow is found fatty, instead of hyperplastic. This failure of hæmogenesis has been observed after hæmorrhage, and is therefore secondary; in other instances, it is primary, or "cryptogenic," a convenient term, used by some writers to include all severe anæmias of unknown etiology.

Ehrlich (1888) described the first case. It was a case of post-hæmorrhagic anæmia, in which he could find no normoblasts whatever. Autopsy showed that no regenerative effort had been put forth by the bone marrow. According to Ehrlich, a scarcity of normoblasts, in pernicious anæmia, indicates a failure of response, on the part of the blood forming organs.

The disease usually shows the symptoms of progressive pernicious anæmia, but there are no signs of regenerative activity of the blood forming organs, and histological examination of the blood gives different results from those usual in pernicious anæmia; there are no nucleated cells; the leucocytes are diminished in number, and show an excess of lymphocytes; the medulla of the long bones is yellow, showing none of the transformation to red, usually found in severe anæmia.

A case of aplastic anæmia has recently come under the observation of the writer. A farmer and merchant, aged 59, who had always been a hard worker, suffered from progressive weakness, extending over two years. In the last six months, the loss of strength was rapid, ending in great prostration. Anorexia, which came on suddenly after the extraction of a tooth, was a prominent symptom during the last six months. The skin was a pale yellow colour, which gradually became deeper, until a few days before death, when it appeared to become lighter. The mucous membranes were bloodless. Drowsiness was noted for a week before death, but consciousness was retained to the last. The red blood cor-



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Bacillus typhosus.

puscles numbered 1,250,000. Examination of the red cells showed slight poikilocytosis, but there were no nucleated red corpuscles, either normoblasts or megaloblasts. While the patient was apparently holding his own, a great change came over him, in the space of a few hours; he was manifestly prostrated. A blood count revealed 682,500 red corpuscles per c. mm. He died the following day. In fourteen days, there was a loss of 567,500 corpuscles per c. mm. The rapid fall in the number of red blood corpuscles, which caused the sudden change in the physical condition, was attributed, by the author, to failure of hæmogenesis, from overstimulation of the bone marrow by arsenical preparations.

The essential features of aplastic anæmia are:

1. A rapidly fatal course.
2. Absence of megaloblasts and normoblasts.
3. Low colour index.
4. Leucopenia with a relative lymphocytosis.
5. A continuous and persistent fall in the number of red blood corpuscles.

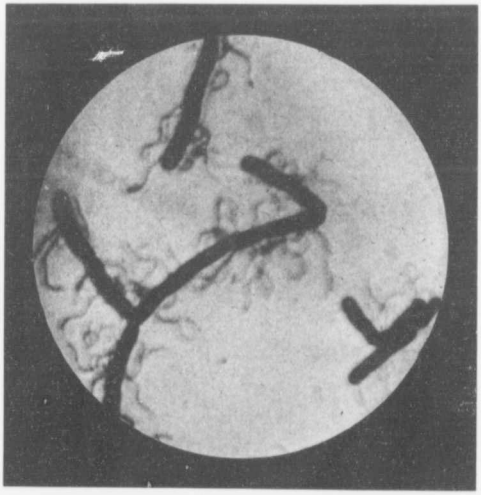
Polychromatophilia.

Under normal conditions, the red corpuscles are stained only with acid dyes. In anæmic conditions, the affinity for acid dyes is lost, to a greater or less extent, and an affinity for basic stains becomes evident. Instead of staining a light red, the cells take a bluish red, violet, or even a blue colour.

Polychromatophilia is referred, by Maragliano and others, to a progressive coagulation necrosis of the cell, which thereby loses its normal affinity for acid dyes.

Polychromatophilic degeneration may affect not only non-nucleated but also the nucleated red cells, and especially the megaloblasts.

Some writers believe that polychromatophilic corpuscles are not degenerating, but are the youngest cells of the blood. In support of this view, they point to the abundance of such cells, during the active hæmogenic process following severe hæmorrhage.



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Bacillus typhosus.

SECONDARY ANÆMIA.

The severity of the changes, in secondary anæmia, depends upon the duration and intensity of the exciting cause. Anæmias differ only in degree, and it is impossible to make a classification, from the alterations in the blood picture. The morphological changes in the blood, in pernicious anæmia, are identical with those found in the severe forms of secondary anæmia.

Secondary anæmia is not to be distinguished from primary, by the blood picture alone, because all phases are to be seen, from the chlorotic type to the extreme pernicious. The presence of a discoverable cause is the only reliable criterion, for the recognition of secondary anæmia.

Posthæmorrhagic anæmia.

Chronic loss of blood is much better borne than acute loss. Quincke has shown that almost double the entire amount of blood may be gradually withdrawn from dogs, in the course of four or five months, and be completely restored.

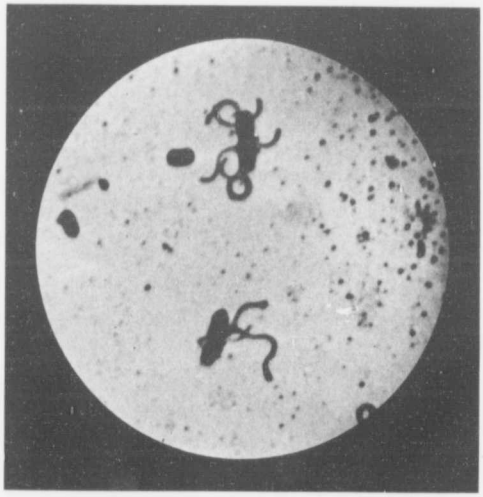
Alexandrew, a Russian physician, who was afflicted with phthisis, and had hæmoptysis, measured each time the amount of blood lost, and claims he lost, in six and a half months, about four times the entire weight of blood, yet, according to his own report, he recovered completely.

Continued small losses of blood lead to a much more profound anæmia, than a single large hæmorrhage.

As age advances, the recuperative power diminishes, so that a longer time is required, after each hæmorrhage, to make up the blood loss. Individuals differ in their blood regenerative power. A blood loss which, in one individual, would be replaced in weeks, would require months in another. The time required for restoration is greater, the more frequently the hæmorrhage is repeated.

Frequent large losses of blood produce no ill effects, when the intervals between hæmorrhages permit of complete restoration.

Every cause which can produce anæmia, may produce either a mild, or severe form; hæmorrhage is no exception to this rule. After complete restoration, a normal blood count, with diminished hæmoglobin percentage, is found, or reduced blood count with hæmoglobin approximately normal, or greatly reduced red corpuscles with colour index down to 0.5, resembling the chlorotic



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Bacillus coli communis.

type. Further, poikilocytes, and later normoblasts, are constant features of posthæmorrhagic anæmia; an anæmia having these morphological elements may be considered of moderate degree. In addition to the morphological elements just mentioned, we find, in profound posthæmorrhagic anæmia, megalocytes and megaloblasts. The blood, in severe posthæmorrhagic anæmia, may very closely resemble that seen in pernicious anæmia. Further, in various secondary anæmias, the blood phase is not distinctive of any particular form of anæmia, but is solely an index of the severity of the condition.

The effect of repeated hæmorrhages, in inducing a profound anæmia, is a matter of frequent observation.

Plumbism.

A description of an anæmia, peculiar to lead workers, appears in the works of the earlier Greek and Roman authors. Nicander, a century before the Christian Era, described acute poisoning by ceruse. Galen, in his De Medicina, condemned the use of leaden pipes, as also did the Roman architect, Vitruvius, who lived in the time of Cæsar Augustus.

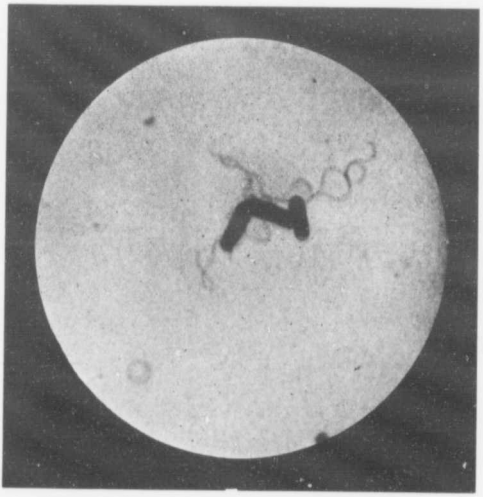
It is amongst the lead workers that the worst types of plumbism are observed.

Of the physical signs and symptoms of lead poisoning, anæmia is the most conspicuous. It is present from the beginning. Oliver never found the normal number of red corpuscles in lead workers. The average was from 2,500,000 to 4,000,000, with hæmoglobin as low as 45 or 50 per cent. of the normal. In severe cases, blood corpuscles may be reduced in number to 1,500,000, or less.

In the majority of cases, there is a greater relative decrease in hæmoglobin. Of ten cases, reported by Goadby (Cantab.), the lowest colour index was 0.6, the highest 3. Two of the ten cases had a colour index of 3; in one the red corpuscles numbered 1,334,000, in the other 1,347,000; in both the hæmoglobin percentage was 60.

Granular degeneration of the red corpuscles is a constant feature in all cases. The granules vary in size, from fine points to the size of eosinophile granules. They are found in cells of normal size, as well as in poikilocytes, and nucleated corpuscles, both megaloblastic and normoblastic.

The granules are present in chronic lead poisoning, at a time



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Bacillus coli communis.

when subjective symptoms are not yet manifest. They appear in the blood, within 24 hours of the experimental administration of acetate of lead.

Granular degeneration is more abundant in lead poisoning, than in any other condition, and, in a severe case, a large proportion of the red cells may be affected. When present, in a considerable proportion of the corpuscles, it is pathognomonic of plumbism. The number of the granular corpuscles is in proportion to the toxic condition.

The steps which mark the downward course of the blood in anæmia may be followed, as well in plumbism, as in pernicious anæmia.

The red corpuscles are diminished, in lead workers, as a general condition. The colour index in this stage is reduced, the blood presenting the chlorotic type. In addition, granular degeneration is abundant.

The first stage passes in plumbism without calling for treatment. Individuals get along very well, until the corpuscles fall to about 3,000,000. When they come under observation, at this period, all are poikilocytic. As the condition advances, normoblasts are found.

In the next stage, the corpuscles may fall below 2,000,000, and megalocytes appear in the blood. It is in the cases which have advanced to this degree, that the colour index is increased above normal.

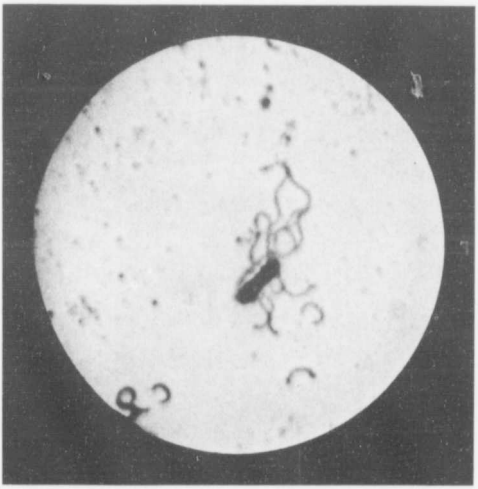
In the most severe forms, megaloblasts are found, and, in the megaloblastic phase, cases are seen, in which the resemblance to pernicious anæmia is very striking.

In the sign-manual of the blood, the megaloblastic phase is the precursor of a fatal termination.

Malaria.

The cause of anæmia in malaria is quite apparent, in the destruction of the red corpuscles by the specific parasites. Further investigation may possibly show, that the plasmodia, in addition to their power of directly destroying the corpuscles, may produce hæmolytic substances, which are also capable of inducing an anæmic condition.

The regeneration of the blood is usually rapid after tertian



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Bacillus coli communis.

and quartan attacks, but, in æstivo-autumnal fever, the anæmia may be very severe and persistent.

The condition of the blood generally corresponds with the first and second phases. In the former, the red cells may be reduced to 2,000,000 or 1,000,000. Numbers as low as 500,000 have been reported in malarial cachexia.

The hæmoglobin is reduced in about the same ratio as the corpuscles.

Anæmia, in the fourth blood phase, in which there was a preponderance of megalocytes, with increased hæmoglobin, has been observed in severe infections. The fifth blood phase of anæmia is also found, as a sequel of malaria; the megaloblasts having the same unfavourable prognostic significance, as in other severe anæmias.

Hæmogenesis is never sufficient to make good the blood destruction, with the rapidity of its occurrence in malaria. The degree of anæmia depends upon the number of parasites, and the rapidity with which they increase. The writer has blood films of æstivo-autumnal fever, obtained in Malay, in some fields of which every corpuscle harbours a parasite.

The enormous blood destruction, resulting from severe malarial infection, is equivalent to a large periodical hæmorrhage.

Fortunately, in malaria, the adjustment between blood loss and blood formation is recovered, by the destruction of the specific parasites.

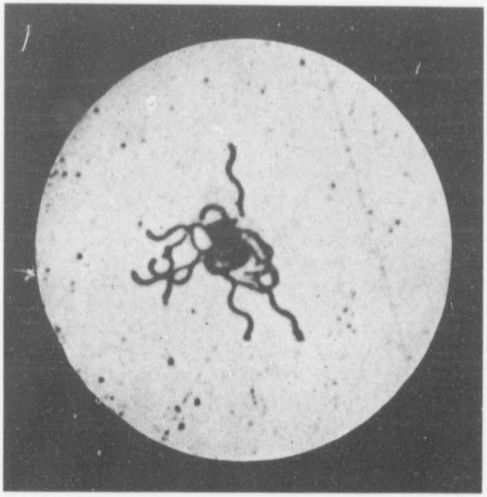
Typhoid fever.

The blood picture of typhoid fever is one, in which the red cells are moderately reduced in number, with proportionate diminution, in the percentage, in hæmoglobin. A reduction in the chromocytes, of 40 per cent., is usually not exceeded in uncomplicated cases.

Syphilis.

Syphilis, throughout its course, is productive of an anæmia of the first degree. During the primary stage, the red cells are slightly decreased. The hæmoglobin falls steadily, until treatment is begun.

In untreated syphilis, Justus found the diminution, in hæmoglobin, varies with the severity of the disease, and its tendency to spontaneous recovery. Under mercurial treatment, there is an in-



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Bacillus coli communis.

crease of hæmoglobin, and red corpuscles; the cure of syphilitic lesions begins with the rise in percentage of hæmoglobin.

Neumann and Konried find a loss of 25 to 30 per cent. of hæmoglobin, in the primary stage, without much change in the red cells. On the outbreak of secondary lesions, the red cells sink considerably in number. In untreated cases, the red cells may sink as low as 2,000,000, or less. The hæmoglobin continues to diminish, and may fall to 25 per cent.

The hereditary syphilis of infancy is productive of a more profound anæmia, with low blood count, great poikilocytosis, and nucleated blood cells.

Sepsis.

Septic infection is an important factor in the etiology of secondary anæmia.

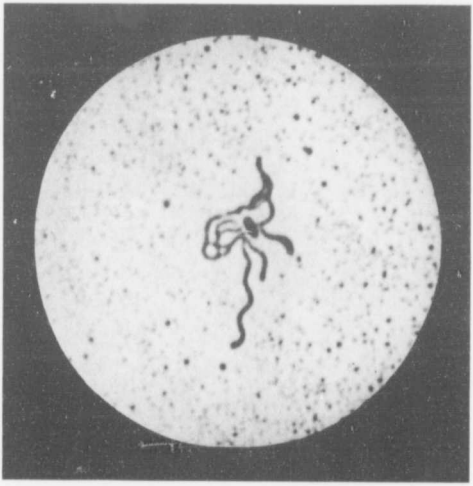
Dental decay, with pus formation, is a cause of anæmia which is frequently overlooked. There is not a more widespread affection than oral sepsis. It is present in a large percentage of patients, who come for treatment for any cause. All forms of septic involvement are noted, from simple hyperæmia to alveolar abscesses. The general condition is due to insufficient mastication, and toxæmia from pyorrhœa alveolaris.

Another prolific cause of anæmia is toxæmia, resulting from intestinal stasis, and the retention of scybalous masses. The removal of these two, prolific causes of ill-health, will mark the disappearance of many gastro-intestinal affections, in which anæmia is an incident.

Marked anæmia is present in all severe cases of septicæmia. In a case of acute puerperal sepsis, of 24 hours' duration, with profuse hæmorrhage, Grawitz found the red cells reduced to 300,000.

In septicæmia, the red cells generally number between three and four million, but may sink below two million.

There is a group of cases, recently reported, in which there was fever, great prostration, and especially marked greenish pallor of the skin, without localised visceral symptoms, other than enlarged spleen. In addition to giving the clinical picture of pernicious anæmia, the blood showed the presence of pathogenic micro-organisms. *B. typhosus, B. coli,* and *S. pyogenes* were isolated from the blood. The anæmia, accompanying these infections, is supposed to depend upon hæmotoxic substances, produced by the bacteria.



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Bacillus suipestifer.

Poikilocytes and normoblasts are found in the severest cases.

An increase in the depth, by obliteration of the central concavity, giving the red corpuscle a swollen hydremic appearance, is occasionally observed in secondary anæmia. This condition of the corpuscles was noted, by the writer, in a fatal case of septicæmia, from puerperal cystitis. The microphotograms show, that the red corpuscles have lost their flattened disc-like appearance, and have become globular. The central concavity, in those cells in which it is still retained, occupies a small relative portion of the cell. Other corpuscles appear gouged out, which is probably due to failure, of those portions, to expand with the remainder of the cell.

Tumours.

Malignant disease is one of the conditions, that may produce an anæmia, so profound as to bear a close clinical resemblance to pernicious anæmia.

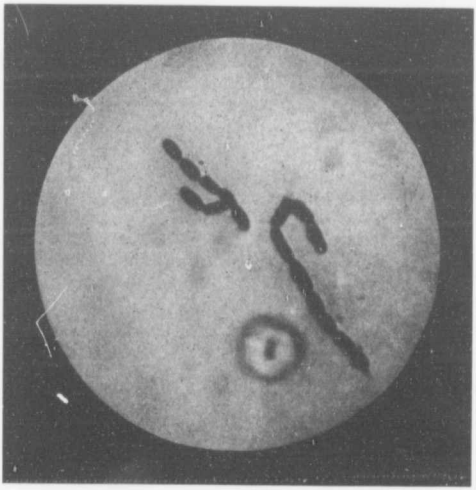
The lowest percentages of corpuscles, and hæmoglobin, are associated with gastric carcinoma. Of the diseases which simulate pernicious anæmia, gastric carcinoma is one of the most important. The difficulty, at times, of differentiating the two diseases, becomes evident in cases, diagnosed as pernicious anæmia, and in which gastric carcinoma is found at necropsy.

It is possible that either disease may complicate the other. As an aid in diagnosis, it has been pointed out that 1,000,000 red cells per c. mm. is the minimum for carcinoma.

The pallor of anæmia has generally been supposed to be due to deficiency of hæmoglobin. In primary anæmia, the colour of the skin is a fairly reliable sign of the deficiency of hæmoglobin, but in malignant disease, in patients having every appearance of a very profound anæmia, there is often only the slightest change in the blood. In a large sarcoma of the abdominal wall, of three years growth, in which there was every appearance of a severe anæmia, the writer found the blood almost normal.

Cases of malignant disease, which do not progress further than the first phase of anæmia, present (1) those with approximately normal blood, (2) those with diminution in hæmoglobin, and (3) those with diminution in both corpuscles and hæmoglobin.

In the severe grades of anæmia, accompanying malignant disease, poikilocytosis is marked, and nucleated cells, of both normoblastic and megaloblastic type, may be present. The red corpuscles



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Bacillus pestis.

are reduced to 2,500,000, and only in exceptional cases do they sink as low as 1,000,000 per c. mm.

Ankylostomiasis.

A severe type of anæmia may be produced, in every detail, by certain intestinal parasites, of which the most important are *Ankylostomum duodenale* and *Bothriocephalus latus*.

Ankylostomiasis is epidemic among the miners of Belgium, Hungary, and Germany, the tile and brick makers in the vicinity of Cologne, and among the population of the Southern States of North America.

This blood-sucking parasite is extremely prevalent in many parts of the globe, and is the cause of much of the debility seen in mines, and prisons. It was first detected by Dubini of Milan, in 1838, while making necropsies. It was discovered in Egypt by Bilharz, and Griesinger, who was working with Bilharz, came to the conclusion that it was the sole cause of the anæmia, which was at that time affecting one-quarter of the entire population of Egypt, known as Egyptian chlorosis. It was found in Calcutta by McConnell (1878), while making necropsies, and, in the same year, it broke out among the thousands of miners employed in the construction of the St. Gothard Tunnel.

At the present time, ankylostomata are distributed over about three-fifths of the habitable globe. The worm is a tropical parasite, and thrives best in conditions of heat and moisture.

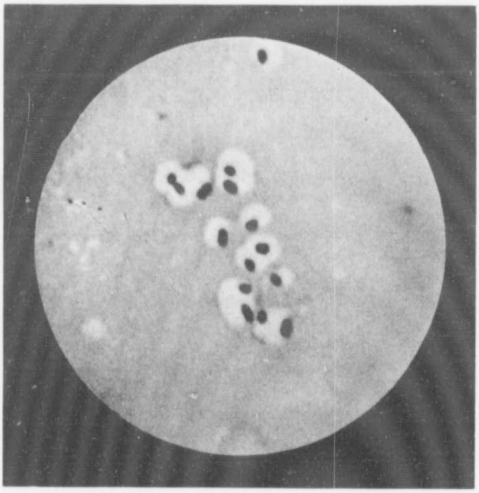
As a factor in the production of anæmia, in the tropics, the ankylostoma is second only to malaria.

It is stated that, although the negroes in South America may be the subjects of ankylostomiasis, they do not suffer from anæmia. The explanation offered of this circumstance is, that they have acquired an immunity to the toxins of the parasite, or that the parasites are less virulent, than those which infest white men.

Transmission of ankylostoma.

Infection may take place either by ingestion of ova, in the food, or drink, or by passage through the broken or unbroken skin.

Looss made the discovery (1898) that the larvæ could penetrate the unbroken human skin. Entering chiefly by way of the hair follicles, they bore their way into the dermis, occasionally get-



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Pneumococcus.

ting as far as the subcutaneous tissue. There they penetrate the lymphatic vessels, less frequently the cutaneous veins, and are then carried to the right side of the heart. Their passage is to some extent checked by the lymphatic glands, in which some of them are arrested, and perish. From the heart they are driven to the lungs, where they penetrate the alveolar walls, and so make their way into the bronchi. They then ascend the trachea, and reach the oesophagus, after which they finally reach their ultimate destination in the intestine.

The blood in ankylostoma infection.

Blood extraction, venom secretion, and secondary infection, have been advanced to explain the resulting grave anæmia.

Weinberg and Leger uphold the theory of secondary microbic infections, as explaining the gravest or malignant forms of anæmia, and advance experimental proof in favour of their belief. Warre has recorded a case of ankylostoma infection of this type, in which the red corpuscles were fragile, and there was jaundice of hæmolytic origin.

It is to the secondary infection, due to intestinal bacteria, taking place through the minute wound, produced in the mucosa by the parasites, that Castellani attributes the fever which frequently accompanies ankylostomiasis.

The anæmia is mainly toxic, and only secondarily due to small hæmorrhages. Alessandrini has shown that the parasites secrete a toxin, which hæmolyses the red corpuscles.

The degree of anæmia is, in general, in proportion to the number of worms present. Ernst of Cologne found 2,768 parasites in the intestinal canal, at the autopsy of a brick maker.

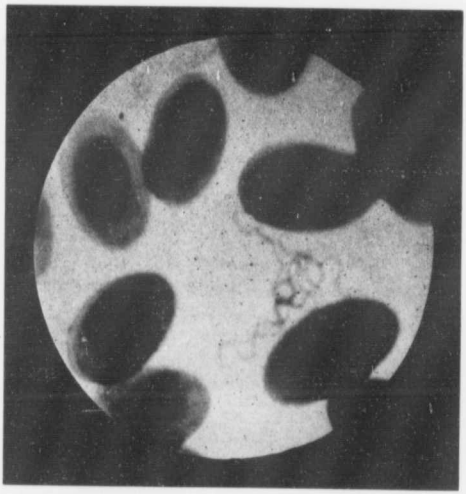
The ankylostoma is frequently found in persons otherwise healthy, but is always liable to produce anæmia.

The blood, in the majority of cases, is of the chlorotic type.

In other cases, the blood cells may sink below a million, with a low colour index, and marked poikilocytosis. As in chlorosis, the average colour index is found to be about 0.5. Normoblasts are common, and, in the severe grades, the blood enters the megalocytic and megaloblastic phases.

Eosinophilia in ankylostoma infection.

An ever present eosinophilia serves to distinguish the blood condition, in this infection, from pernicious anæmia.



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Spirochæta gallinarum.

Brehaut made observations, in Egypt, on blood changes in ankylostomiasis. He found the eosinophilia was not great, a fact which he attributed to a tolerance of the toxins, which produce the eosinophilic change. His average was only 10 per cent.

The number of eosinophiles varies from 5 to 72 per cent. The latter percentage was found, by Leictenstern, in a very anæmic patient. After removal of the worms, the eosinophiles fell at once to 11 per cent.

Boycott and Haldane found the highest percentages in recent cases, and the lowest in chronic cases. They also noted that a fall in eosinophiles, with no improvement in physical signs, was unfavourable.

Eosinophilia seems to be much more constantly associated with nemotode worms, than with tapeworms, or flukes. It is a constant symptom of ankylostomiasis, so constant, and to such an extent, does its degree indicate the severity of the infection, that it has been recommended, by Boycott, as the most important sign, next to the presence of ova in the fæces, in endemic areas.

Calamida claims to have proved, that certain entozoa undoubtedly produce toxins, which not only possess active hæmolytic properties, but are positively chemotactic, as regards eosinophile leucocytes.

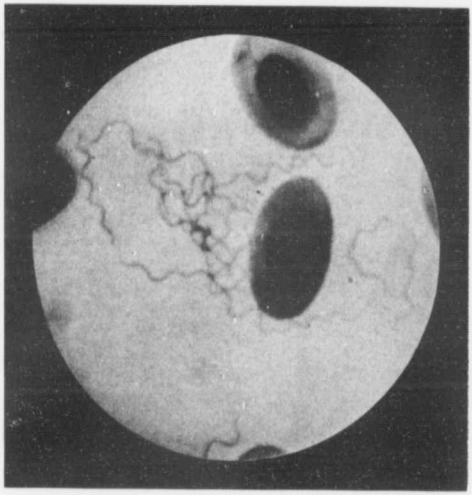
Bothriocephalus anæmia.

Bothriocephalus latus is accredited with the production of the most profound forms of anæmia. No other human tapeworm is known to give rise to an anæmia of a pernicious type.

Tallqvist has extracted hæmotoxic substances from the tissues of bothriocephalus. Amongst these substances are found a hæmolysin, which acts *in vivo* and *in vitro*. When injected into a normal animal, Tallqvist was able to reproduce an anæmic condition, resembling to some extent true bothriocephalus anæmia.

Repeated attempts have failed to isolate, from other tapeworms, a hæmotoxic substance, in demonstrable quantity.

The reduction in the red blood corpuscles, in this form of anæmia, is extreme, reaching the minimum in Schauman's case of 395,000 per c. mm. Schauman's average, for 38 cases, was 1,290,000, with an average colour index of 1.09. Poikilocytosis was marked, and nucleated red cells were present, in all cases examined for them. Megaloblasts predominated, in over half the cases. In



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Spirochæta gallinarum.

one case, normoblasts only were present, and, in five cases, megaloblasts only appeared. Schauman found that bothriocephalus anæmia, in every respect, even to remissions and exacerbations, resembles true pernicious anæmia.

In this particular form of secondary anæmia, the blood can be followed in the downward scale, through all the phases of anæmia, and back again to complete recovery.

LYMPHADENOMA.

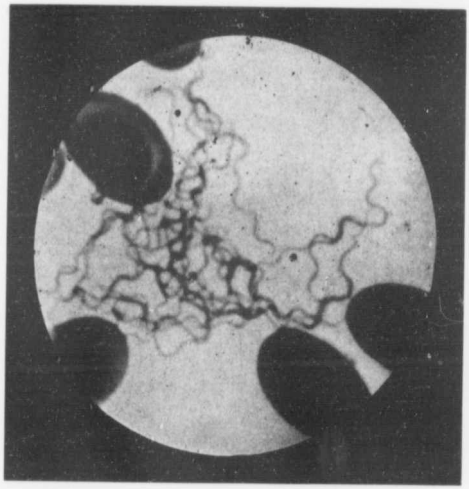
Under this generic term, may be conveniently grouped those affections of unknown etiology, characterised by primary involvement of the lymphatic apparatus, with anæmia of secondary type.

It includes—

1. Lymphoma or Hodgkin's disease.
2. Anæmia infantum pseudoleukemica.
3. Splenomegaly or splenic anæmia.

Hodgkin's disease.

To Hodgkin, of Guy's Hospital, is due the credit of having first described this malady in a communication, in 1832, to the Pathological Society of London "On some morbid appearances of the absorbant glands and spleen." The first case Hodgkin described was that of a boy admitted to the hospital in 1826. He died of dropsy and peritonitis. There was enlargement of the bronchial and mesenteric glands, and a continuous chain of enlarged lumbar glands around the abdominal aorta, and along the iliac vessels. The liver "contained a few tubercles somewhat larger than peas, white, semi-cartilaginous, and of an uneven surface. The spleen was large, and contained numerous tubercles." Arguing against the inflammatory character of the disease, he concludes: "Notwithstanding the different characters which this enlargement may present, it appears nearly in all cases to consist of a uniform texture throughout, and this rather to be the consequence of a general increase of every part of the gland, than of a new structure developed within it, and pushing the original structure aside, as when ordinary tuberculous matter is deposited in these bodies." The lapse of nearly a century,



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Spirochæta gallinarum.

since this communication, has verified the accuracy of Hodgkin's observations, and added but little to our knowledge of the disease.

The main features of Hodgkin's disease are painless, progressive, glandular enlargements, usually starting in the cervical region, with a relative lymphocytosis.

As a rule, the disease runs a chronic course; occasionally, however, it runs a very acute course, terminating in so short a time as nine weeks from the first distinct appearance of the complaint.

Clinically, two types of the disease are recognised. In one type, the superficial glands are found enlarged; in the other, the intra-thoracic glands are prominently affected, the superficial glands showing no change.

In most cases, the enlargement commences in the cervical glands, spreads to the axilla, and to the glands in the groin. Internally, the retro-peritoneal glands are the next to be affected, followed by the anterior and posterior mediastinal and the mesenteric.

The glandular masses are connected together by chains of lymphatic nodules, in the course of the lymph channels.

The superficial glands are freely movable, and painless. One or two groups of glands may enlarge, and remain for a long time at a standstill.

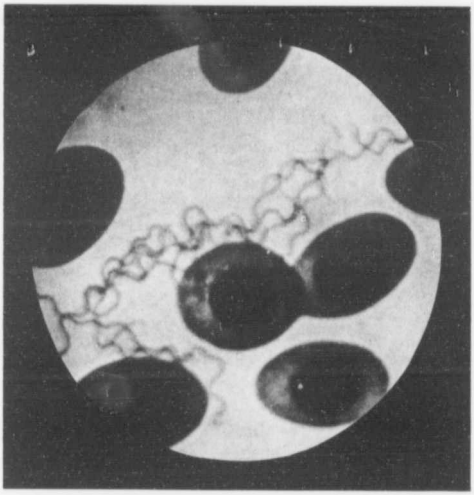
Difficulty of diagnosis is apt to occur, where at first there is only a single mass of enlarged glands. All doubt as to the nature of the ailment vanishes, when the disease spreads rapidly.

The enlargement of intra-thoracic glands may cause pressure on the trachea, or larynx, internal jugular vein, or recurrent laryngeal nerve. Pressure effects on the cervical arteries have been noted in the great tumour masses in that region.

As a rule, the spleen is only slightly larger than normal, but it may be as large as in any form of leukæmia. Pappenheim comes to the conclusion, that when only the spleen and lymph glands are involved, Hodgkin's disease results, while with implication of the bone marrow, true leukæmia is produced.

Microscopically, the appearance is more nearly that of a chronic inflammatory process than a malignant neoplasm. There is great increase of fibrous tissue, and hyperplasia of lymphoid cells.

The prognosis is fatal. The course of the disease is marked in some by the development of tubercle as a terminal infection, in others by obstruction to respiration by the immense tumours about the air passages, or by a slow cachexia or intercurrent disease.



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Spirochæta granulosa penetrans.

The blood in Hodgkin's disease.

The blood shows a fairly well marked anæmia with a relative increase of lymphocytes. The red cells may be reduced to between two and three million; microcytes and poikilocytes may be present in varying proportions. The blood presents the poikilocytic, more commonly the normocytic, phases of anæmia.

The hæmoglobin is in all cases diminished. The reduction in hæmoglobin exceeds that of the red cells, giving the low colour index common to most secondary anæmias.

A relative increase of lymphocytes is the most constant feature of the blood in this disease. The proportion of lymphocytes may reach 95 per cent.

The total leucocytes in the blood may be either slightly increased or diminished, and in either case the lymphocytes are relatively increased. A leucocytosis of inflammatory type is occasionally seen toward the close of the disease; this may be dependent on suppuration in the glands or intercurrent infection, such as pleurisy; in other cases, its origin is not clear.

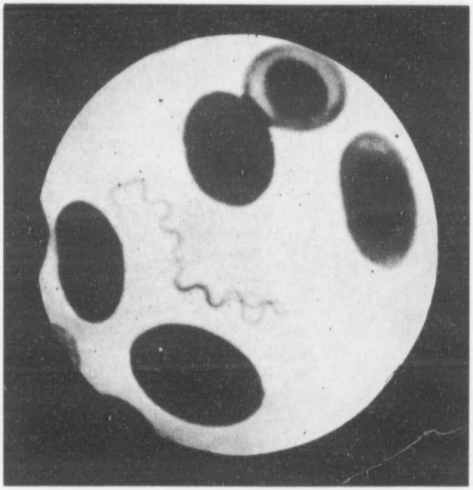
Anæmia infantum pseudoleukæmica.

This is an infantile disease, characterised by splenomegaly, and a high grade of anæmia. The disease affects young children, between the ages of nine months and two years.

Since the first description of this disease by Von Jaksch, in 1889, the knowledge of the condition has not been greatly extended, and opinions regarding its significance are still at variance.

The theories held regarding the nature of the malady are as follows:—

1. That it is an early stage of leukæmia.
2. That it is a form of secondary anæmia, following rachitis, tuberculosis, or syphilis.
3. That it is pernicious anæmia, referring the leucocytosis to the special tendencies of infants' blood.
4. That it is an infectious disease.
5. That it is due to an organism described by Löwit as "*Hæmamœba leukæmia magna.*"
6. That it is Hodgkin's disease, with leucocytosis.
7. That it is a primary disturbance of the spleen.



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Spirochæta gallinarum.
Duplication of terminal flagellum-Multiplication by longitudinal fission

Some writers assert that all we are justified in concluding, about the anæmias of infancy, is, that in some cases there is enlargement of the spleen, and in other cases there is not.

After accounting for the cases of pernicious anæmia, leukæmia, rachitis, tuberculous and syphilitic infections, grave anæmia with leucocytosis, there remain sufficient cases to justify, at least for the present, the creation of a separate clinical entity.

Wolff contends that this affection is the result of some primary disturbance of the spleen. The case upon which he bases this theory yielded the following data. The patient was one year old, and weighed 14 lbs. Hæmoglobin was 40 per cent., red corpuscles 467,000, leucocytes 37,800. Cachexia was marked, and the spleen was greatly enlarged. In ten days after splenectomy, the child had gained two pounds in weight, and the red corpuscles had increased to 1,000,000 per c. mm., and from then on, the improvement was progressive.

The spleen is much enlarged and firm. It may reach the anterior superior spine. Histologically, the changes are those of hyperplasia of all elements. The liver has been found moderately enlarged, usually less so than the spleen. Similar histological changes may take place in the lymph glands, but in no degree comparable to the changes of leukæmia.

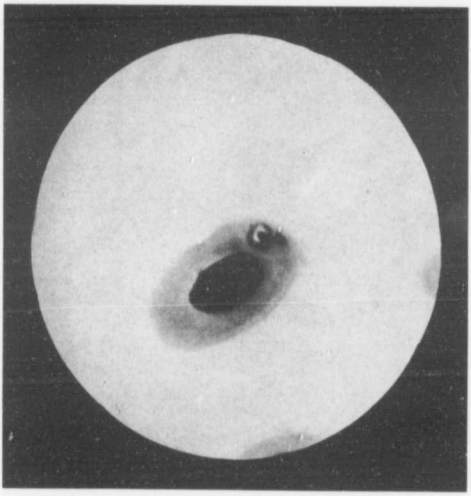
The blood in anæmia infantum.

The blood in *anæmia infantum pseudoleukemica*, in the different stages of its course, presents the morphological features of the five blood phases of anæmia.

The diminution of red blood cells rarely exceeds one million per cubic millimetre. The cachexia is frequently out of all proportion to the degree of anæmia; the patients die with a higher blood count than in pernicious anæmia. Several of the cases reported, have terminated without any complication or intercurrent disease, when the red cells stood between two and a half and three and a half millions.

The poikilocytic phase of anæmia is pronounced, in the early stage; later, large number of nucleated corpuscles are to be found. Microblasts are a feature of anæmia infantum; occasionally, they exceed in number the normoblasts.

The excessive abundance of nucleated red corpuscles is one of



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Spirochæta granulosa penetrans.
Infective granule-After-phase of spirochætal infection.

the most characteristic features of this disease. In severe cases, the megaloblasts in number may exceed the normoblasts.

In the majority of cases, the hæmoglobin is between 40 and 60 per cent., the colour index between 0.6. and 0.8.

Leucocytosis in anæmia infantum.

Extensive leucocytosis, with a preponderance of lymphocytes, is an important characteristic of the blood, in anæmia infantum. The leucocytes vary in number within wide limits. They may exceed 100,000 and may be as low as 4,000 per c. mm.; usually, they are between 20,000 and 50,000.

In the differential estimates, the lymphocytes are slightly in the majority; sometimes the large forms, and sometimes the small forms, are in excess. An increase in eosinophiles is not constant. Myelocytes up to 10 per cent. have been reported.

In a differential estimate of 20 cases, Cabot reports the following averages: lymphocytes 59.1 per cent., polymorphonuclears 36.9 per cent., eosinophiles 1.2 per cent., myelocytes 2.8 per cent.

Summary.

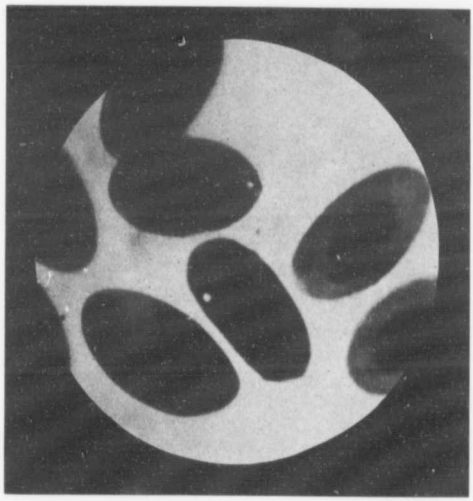
The characteristics of *anæmia infantum pseudoleukemica* are (1) anæmia of various phases; (2) high leucocytosis with preponderance of lymphocytes; (3) colour index below 1; (4) greatly enlarged spleen; (5) very slightly enlarged lymphatic glands.

Anæmia splenica.

The characteristic features of splenic anæmia are primary splenomegaly, and progressive secondary anæmia, with leucopenia.

The first recorded case was by Woillez in 1856. Gretzel, in 1866, described a case to which Griessinger gave the name anæmia splenica.

The existence of this condition, as a pathological entity, is considered by some a matter of uncertainty. As against it, they state that the mere occurrence of a splenic enlargement, which cannot be accounted for, does not constitute sufficient grounds for the assumption that there is a specific disease process. According to this view, splenomegaly is not a pathological entity, and there is no



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Infective granule.

Corpuscular inclusions from infection by Spirochæta granulosa penetrans. (After-phase).

reason for separating this condition from other diseases. Enlargement of the spleen is expected in cirrhosis of the liver, and there must be, in certain instances, special causes that operate to make the enlargement excessive.

On the other hand, Simmonds and Umber believe it to be a disease, *sui generis*, because they observed that the metabolism was disturbed in Banti's disease, and not in splenic anæmia. Nevertheless they state, positively, that they cannot make the diagnosis *post mortem*. Their observations lead them to believe that the removal of the spleen is beneficial, because it eradicates the source of a poison.

It is the contention of those, who hold to the pseudo-leukæmic nature of this condition, that the splenic enlargement takes the place of the ordinary lymphatic enlargement. They do not pretend that considerable enlargement of the spleen occurs, in ordinary cases of Hodgkin's disease. They classify splenic anæmia, as Hodgkin's disease, with enlarged spleen.

Sippy considers it quite possible that an analogy may be drawn between this disease, and exophthalmic goitre, the enlarged spleen having a deranged function, and producing toxic substances, which cause nutritional disturbances.

As to whether the splenic condition causes the anæmia, it is difficult to say, because as yet little is known of the function of the spleen. However, it seems certain, that the enlargement of the spleen precedes the anæmia.

The spleen is intimately connected with the etiology of the disease, since good results follow splenectomy.

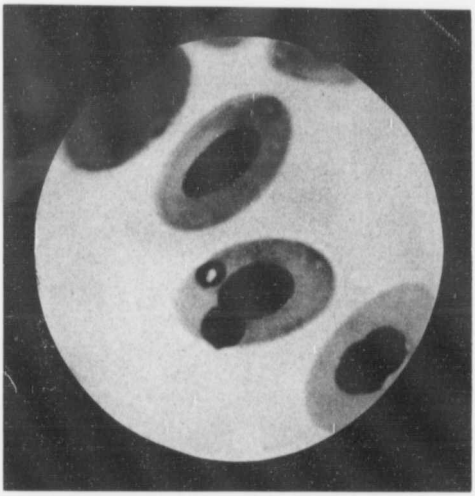
Studies in pathological anatomy have shown hypertrophic cirrhosis, an overgrowth of the trabeculæ, and supporting tissue of the spleen, with atrophy of the Malpighian bodies, caused by overgrowth of the connective tissue about the central artery. There is no special involvement of the true splenic tissue.

The affection may occur at any age, but is commonest in adults, and most frequent by far in males.

The course of the disease is continuously progressive, though there appear to be periods of temporary arrest. The duration is from six months to two years, but it is occasionally more prolonged.

The *diagnosis* is to be made from Hodgkin's disease, leukæmia, malignant disease, pernicious anæmia, and from other forms of splenic enlargement, as rachitis, syphilis, and ague.

There is nothing characteristic in the initial symptoms; they



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Spirochæta granulosa penetrans.
Infective granule-After-phase of spirochætal infection.

are those common to all forms of severe anæmia. Increasing pallor and loss of strength bring the case under observation. The spleen is then found to be considerably enlarged and tender. Epistaxis is frequent, and is often one of the earliest symptoms. Although usually slight, it is of importance, chiefly on account of its frequent occurrence. Hæmorrhages from other localities are met with, but are rarer. In the last stage of the disease, the hæmophilic symptoms may be unusually pronounced.

The blood first shows a loss in hæmoglobin, not shared in by the corpuscles to the same extent. Later there is reduction, both in corpuscles and hæmoglobin. The reduction in red corpuscles is seldom extreme. The corpuscles average over 3 million, and the hæmoglobin between 40 and 50 per cent.

Later still, occur changes in size and shape of red corpuscles (second phase), and, finally, normoblasts may be present (third phase).

Hypoleucocytosis, of less than one thousand per c. mm., has been reported (Cabot).

Although the anæmia is a marked and characteristic symptom, it is not invariably present, even when the spleen is greatly enlarged.

The diagnostic value of the blood, in this disease, consists in the absence of special characteristics.

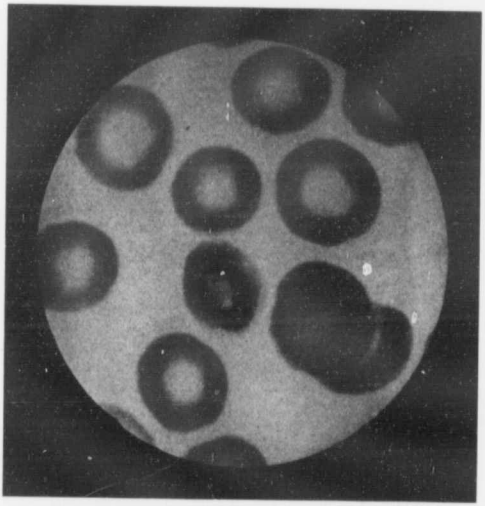
The cachexia, as in Hodgkin's disease, is out of all proportion to the degree of anæmia.

LEUKÆMIA.

Leukæmia is a disease of the hæmogenic organs, characterised by a great increase of leucocytes, in the circulating blood.

Much of the uncertainty, regarding leukæmia, is due to our defective knowledge of the histology of the blood, to the difficulty of separating the different elements, and of finding their seat of origin.

Before the discovery of the blood-making properties of the bone marrow, Virchow recognised two varieties of leukæmia, *i. e.*, lymphatic, and splenic. The small lymphocytes, found in lymphatic leukæmia, were attributed to the lymph glands, and the larger leuco-



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Hæmamœba quartana.

Peripheral arrangement of granules in quartan parasite.

cytes, found in other forms of leukæmia, were supposed to originate in the spleen. The spleen and lymph glands alone were considered the seats of origin, of the blood corpuscles, until Bizzozero and Neumann discovered the hæmogenic function of the bone marrow.

The rôle played by the spleen, in the production of leucocytes, has been a matter of uncertainty, since the early days of hæmatology. This question has been partly cleared up, by the observation of the behaviour of the blood, where splenectomy has been performed on healthy people, as the result of trauma. The observations in human beings, the subjects of splenectomy are important, as corroborating Kurloff's investigations, in the behaviour of the blood, in splenectomised animals.

In Kurloff's investigations, guinea pigs were employed, on account of the constant composition of their blood. Kurloff concludes as follows:

1. In the guinea pig, the spleen is not indispensable to life, since the animals, which survive a splenectomy, progress normally, and even increase in weight.

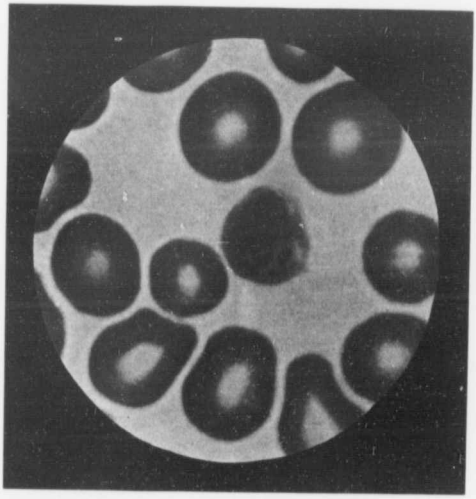
2. The hypertrophy, and hyperplasia, of the lymph glands, especially of the mesentery, which develop after the operation, are associated with a lymphocytosis, that occurs so constantly in the course of the first year, after the operation, as to constitute a characteristic of the absence of the spleen. The increase of lymphocytes may amount to double, or more. It must be concluded, that the removal of the spleen is compensated by the lymph glands. The lymphemia may persist for years, though, in the majority, it subsides, during the course of the first year, to a condition in which the percentage is less than normal.

3. In contrast to this, the pseudo-eosinophile, polynuclear cells show no variation, during the first year. These cells, corresponding to the polymorphonuclear cells of man, are therefore independent of the spleen, and associated with the bone marrow.

4. The group of so-called mononuclear, and allied leucocytes, show no evident increase.

5. Most interesting is the increase of eosinophile cells, which is found constantly, in the second year after the operation. This percentage increased once to 34.6.

It is apparent, therefore, from Kurloff's investigations, that the spleen plays a very insignificant rôle, in leucocyte production. What, then, is the function of the spleen, since it is not indispensable to life? In the lower vertebrates, the blood-making power of the



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Hæmamœba quartana.

Quartan parasite containing coarse pigment granules.

spleen is of great importance, while, in mammalia, its chief function seems to be phagocytic,—to take up the fragments of the blood cells, broken up in the circulation.

The discovery of the origin of the blood cells rendered obsolete the division of leukæmia into splenic and lymphatic. Under normal conditions, the part played by the hæmogenic organs, is as follows: The lymphocytes are furnished by the lymph glands, the granular leucocytes by the bone marrow.

Inasmuch as leukæmia is a disease of the blood-making organs, in which the leucocyte producing function is mostly concerned, we recognise two varieties, *lymphoid* and *myeloid*, the number and character of the cells in the blood acting as a guide to the organs at fault.

Etiology.—As to the nature of the stimulus, which excites these organs to greater activity, we are utterly in the dark. That there is an over-production, there can be no doubt.

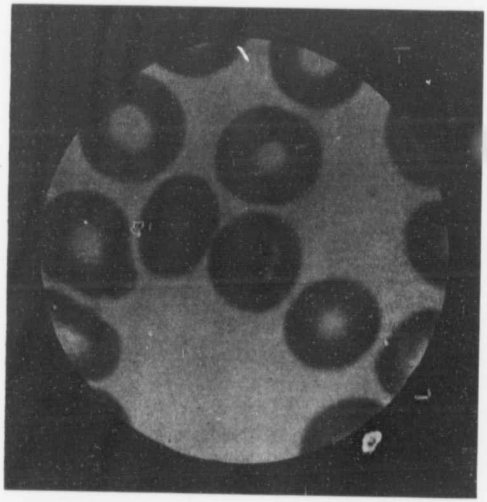
Lymphæmia.

Lymphæmia, or lymphoid leukæmia, is a primary disease of lymphoid tissue, the principal feature of which is a great increase of lymphocytes in the blood.

The comprehension of the pathogenesis, of lymphæmia, requires the recognition of the ubiquity of lymphoid tissue. What is designated lymphoid tissue embraces, not only the lymph glands, the lymph follicles found in the stomach, intestines, tonsils and elsewhere, but also the less well defined, irregular masses of tissue resembling that of lymph follicles, which, as Arnold has shown, is widely disseminated in variable amounts, in different parts of the body, in the lungs, beneath the pleura, in the interlobular septa, and elsewhere; in the liver, kidneys, spleen, etc.

The pathogenesis of lymphoid leukæmia consists in a widespread tendency to hyperplasia of lymphoid tissue. This is seen particularly in the lymph glands, but also in the smaller masses of lymphoid tissue called lymph follicles.

The onset of the disease is marked, by a gradual enlargement of the lymph glands, over different regions of the body, or more frequently limited to one or several groups. Any, or all, of the visible glands may be enlarged; they seldom reach the size seen in Hodgkin's disease. The only sign may be enlargement of the tonsils, in which their removal may prove fatal from hæmorrhage.



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Hæmamœba quartana.
Quartan parasite containing large blocks of pigment.

In another class of latent leukæmia, as pointed out by Nægeli, the most prominent symptom is gangrenous stomatitis, or tonsillar ulceration, with or without hæmorrhage, into the skin, or elsewhere.

The spleen, as a rule, is moderately enlarged. The liver is not greatly enlarged, but occasionally reaches to the navel. The serous membranes, mucous membranes, the skin, heart, lungs, kidney, pancreas, and sexual organs, may any or all be affected.

The bone marrow, which contains but a trace of lymphoid tissue, in adult life, participates in the general lymphoid overgrowth. The invasion of the bone marrow, by lymphoid cells, results in the suppression of the other variety of hæmogenic tissue,—the myelogenous —hence the absence of granular leucocytes from the blood.

Among the various theories, that have been advanced regarding the disease, are—

1. That it is an infectious process. This is insisted upon by many writers.

2. That it is a disease, primary in the lymph glands, with metastases in the various organs.

3. That it is a primary disease of the lymph glands, which shows the characteristic blood picture, after the bone marrow becomes involved.

4. That it is a disease of the lymphatic tissues, in general.

The types of lymphemia.

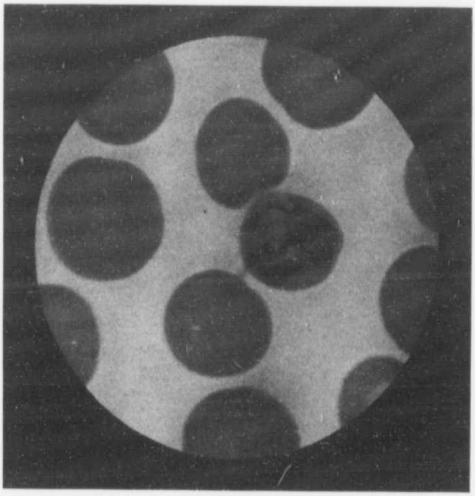
There are good reasons, both clinical and histological, for recognising two forms of lymphoid leukæmia:

(a) Lymphocytic leukæmia.
(b) Lymphoblastic leukæmia.

Lymphocytic leukæmia.

A great relative increase, of the small lymphocytes, is characteristic of this type of lymphatic leukæmia. It is also distinguished, clinically, by its greater chronicity.

The increase, in lymphocytes, is both relative and absolute. The relative increase is easier to determine, and more important in diagnosis. The lymphocytes may be increased, to the exclusion of nearly all other varieties. Increase in small lymphocytes up to 99.9 per cent. has been reported (Cabot).



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Hæmamœba quartana.
Full grown quartan parasite.

While mostly the small lymphocytes make up the leucocyte formula, cases occur, in which the large lymphocytes predominate, with every gradation from the smallest to the largest.

The lymphocytosis varies, in different cases, and in the same case from time to time. Leucocytosis as high as 1,500,000, and as low as 171 per c. mm. has been noted (Cabot); in the latter case, which was complicated by sepsis, the lymphocyte percentage was 94.7.

A fall in the number of leucocytes, in lymphemia, complicated by intercurrent disease, is referred to leucocytolysis. In instances of lymphatic leukæmia, in which excess of polymorphonuclears has been found, there is a complicating infection, grafted on a primary leukæmia.

In lymphocytic leukæmia, we expect a leucocytosis from 25,000 to 150,000, and small lymphocytes approximating 80 per cent., or more.

The red blood cells are seldom reduced below 2,000,000. The hæmoglobin percentage about corresponds to the corpuscle percentage. Myelocytes, normoblasts, and megaloblasts are usually not seen.

Pathological histology.

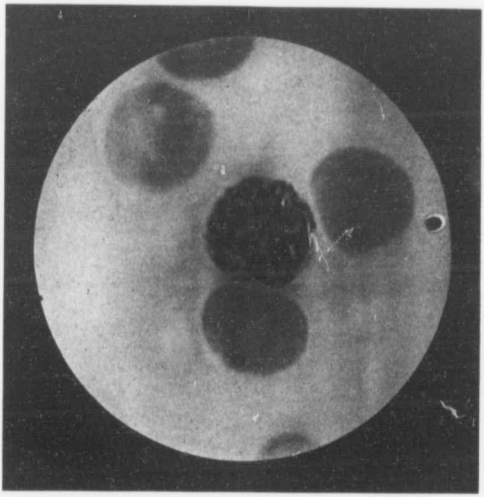
The bulk of cellular constituents, in the bone marrow, spleen, lymph glands, etc., like those of the blood, is made up of small lymphocytes. In the bone marrow, the normal elements are crowded out by the lymphocytic overgrowth. The usual myeloid cells are greatly diminished, in the marrow, as well as in the blood.

Lymphocytic accumulations, in the form of solid grayish nodules, are found in the liver, kidneys, spleen, and skin; they resemble in appearance metastatic sarcomas.

Lymphoblastic leukæmia.

The lymphoblast is the characteristic cell of this type of leukæmia. The feature of lymphoblastic leukæmia is the discharge, into the blood, in large numbers, of lymphoid cells, before their normal metamorphosis is finished.

The lymphoblast is the ancestral form of the lymphocyte. This cell has a faintly, and regularly, stained nucleus, filling almost the entire cell, and a small amount of perinuclear protoplasm, devoid of granulation. The nucleus shows a delicate network, with large clear areas. The protoplasm exhibits the same affinity for basic dyes, as



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Hæmamœba quartana.
Quartan pre-segmenting body.

the nucleus, and is therefore inconspicuous. The margins of the cells are often fringed, or crenate.

Lymphoblasts range, in size, from 12 μ to 23 μ, are deficient in chromatin, and look like mere bluish expansions, showing little difference between nucleus and protoplasm.

The lymphoblasts are the primitive lymphoid cells, and are identical with those found at the germ centres, in lymphoid tissue.

The number of lymphoblasts, in the blood, depends upon the intensity of the changes in the lymphoid tissue. In a case, which proved fatal in ten weeks, there were 42 per cent. of lymphocytes, and 56 per cent. of lymphoblasts.

In this type of leukæmia, usually over 90 per cent. of the white cells are of lymphoid origin.

Compared with myeloid leukæmia, lymphoid leukæmia is attended with less anæmia, and less pronounced leucocytosis. The leucocytes are usually between 50,000 and 200,000; it is exceptional for the latter number to be exceeded. Leucocyte counts, up to 918,000, are recorded for lymphemia.

The hæmoglobin percentage is between 25 and 35 per cent. The colour index remains approximately normal.

The red blood corpuscles vary from 1,750,000 to 2,250,000; they do not often fall below 1,000,000. Nucleated red cells are occasionally present, but not abundant.

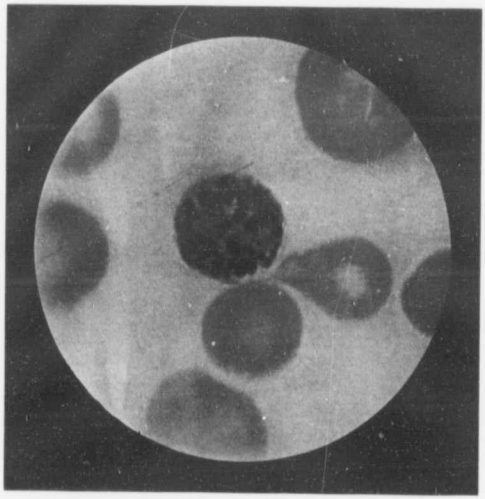
The secondary anæmia becomes more marked, as the disease progresses.

Pathological anatomy.

The spleen is normal in size, or moderately enlarged. In children, it may reach the largest size observed in other leukæmias.

The lymph glands are moderately enlarged. Complete absence of any palpable enlargement has been noted. Lymphoid tissue, wherever situated, throughout the body, may take on abnormal activity. There is no organ, in which lymphomas may not be found. In lymphoblastic leukæmia, they are usually very small, and visible only when confluent. They are to be found wherever there is hæmorrhage. The whole alimentary tract has been found, studded with accumulations of lymphoid tissue; the intestinal lesions simulate, and no doubt have frequently been mistaken for, the lesions of typhoid fever.

The most striking feature, *post mortem*, is the large number of



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Hæmamœba quartana.
Quartan segmenting body.

hæmorrhages. They occur in the mucous membranes, the skin, the pericardium, the peritoneum, the pleura, the retina, the genito-urinary tract, intestine, and brain.

Pathological histology.

Histologically, all the lymphatic structures show a great accumulation of cells, of the same variety as those found in the blood. These cellular elements occur in all the lesions, in whatever locality they are found. The bone marrow shows great cellular accumulations, particularly in the long bones; hæmorrhages are frequent. The most remarkable feature about the marrow is that it contains few, or no, granular cells, of any kind. The suppression of the myeloid elements, in the marrow, accounts for the absence of the granule cells from the blood.

Diagnosis of lymphoblastic leukæmia.

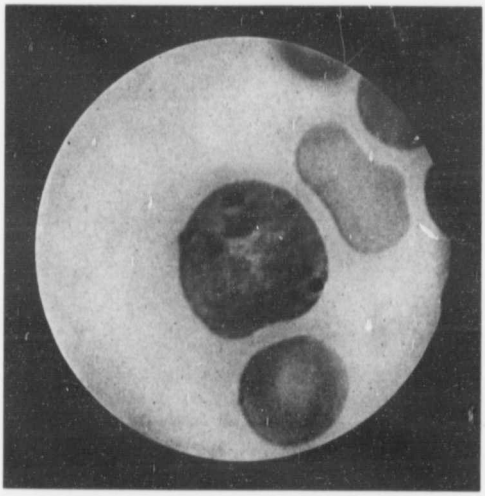
The diagnosis of lymphoid leukæmia can be made from morphology, and leucocytosis. In those cases, in which the leucocyte count is normal, the characteristic features of leukæmia are only brought out by a differential count.

In the cells of lymphoid leukæmia, all grades of proportional increase are observed.

The lymphocytic, or chronic, type of lymphoid leukæmia is frequent; the lymphoblastic, or acute, type is relatively infrequent.

Lymphoblastic leukæmia presents the following clinical features:—

1. Rapidly fatal course.
2. Fever, weakness, and hæmorrhages.
3. Moderate glandular enlargement.
4. Progressive anæmia of secondary type (first and second phases).
5. Extreme rarity of granular leucocytes.
6. Leucocyte formula, mostly made up of primitive lymphoid cells.



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Hæmamœba tertiana.
Early stage of infection of corpuscle by four tertian amœbulæ.

MYELEMIA.

Myelemia, or myeloid leukæmia, is a disease of myeloid tissue, characterised by great increase of granule-bearing cells, in the blood.

Leucocytes are products of growth, and evolution. In the development of the finished cell, the intermediate stages are not seen in the circulating blood; with disturbances of the blood-forming organs, any or all of the transition forms may appear in the circulation. Two types of myeloid leukæmia may be recognized:—

(a) Myelocytic leukæmia.
(b) Myeloblastic leukæmia.

Myelocytic leukæmia.

This is the chronic form of myeloid leukæmia. Myelocytic leukæmia is characterised by great increase of granular leucocytes, and by the presence, in the blood, of a large proportion of myelocytes.

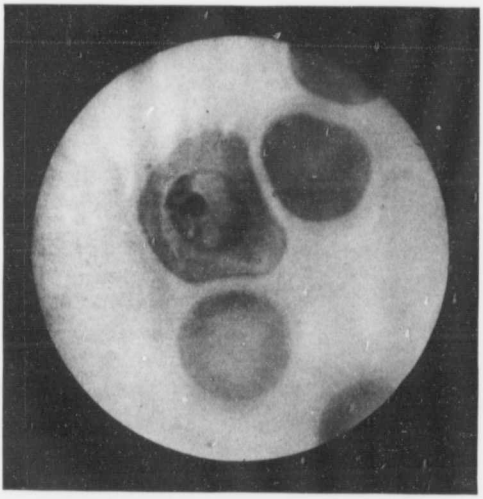
The neutrophile myelocyte is the forerunner of the polymorphonuclear neutrophile leucocyte; it is a mononuclear cell, with neutrophile granules. It differs from the large lymphocyte, in having granules, and from the polymorphonuclear, in the shape of its nucleus. In size, the neutrophile myelocyte varies from 8 μ to 25 μ in diameter. The nucleus is round, or oval, and often excentrically placed. The myelocyte fails to exhibit amœboid motion.

The presence of myelocytes, in the blood, is always pathological. In addition to leukæmia, they appear in the blood during the course of infectious diseases. Rieder reports 3.6 to 14.4 per cent. of myelocytes, in diphtheria, in children; Engel found 12 per cent. of myelocytes, in the crisis of pneumonia.

Neutrophile myelocytes make up from 20 to 60 per cent., of the white cells, in myelocytic leukæmia, with an average of about 35 per cent.

The eosinophile myelocyte,—the ancestral form of the eosinophile leucocyte,—is found regularly in myeloid leukæmia. These cells are not found in the blood, under normal conditions. They are of constant occurrence, and of great diagnostic value, in myeloid leukæmia, in which they are more numerous than in any other disease. The eosinophile myelocyte is a mononuclear cell, with eosinophile granules.

The neutrophile leucocytes in myelemia show greater variation, in size of cell, and of granules, greater difference in staining affinities,



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Hæmamœba tertiana.
Large ring form of tertian parasite.

and more unusual shapes in the nuclei, than in any other condition. They may be smaller than red corpuscles (4 μ), or as large as myelocytes (20 μ).

While the absolute number of neutrophile leucocytes is enormously increased, the percentage is reduced. They may be as high as 70 per cent. or as low as 20 per cent.

The mast cells are increased, up to 18 per cent. (Löwit), with an average of about 5 per cent. A high relative mast cell count is constant in myeloid leukæmia.

The eosinophile leucocytes are greatly increased in number per c. mm.; a percentage increase is inconstant.

The total leucocyte count is usually so high, that the diagnosis is unmistakable. Cases are on record, in which the whites actually exceeded the reds. Lerch has reported the remarkable blood count of 2,020,000 red cells, and 3,570,000 whites. There was a large number of myelocytes. It would appear that 300,000 per c. mm. is an average leucocyte count, for myeloid leukæmia.

As the disease progresses, a secondary anæmia develops; the anæmic condition depends upon the length, and character, of the primary disease, and the presence of complications. The red cells may reach 1,000,000, or lower, before death.

The liver is considerably enlarged, the spleen enormously enlarged, and the glands slightly.

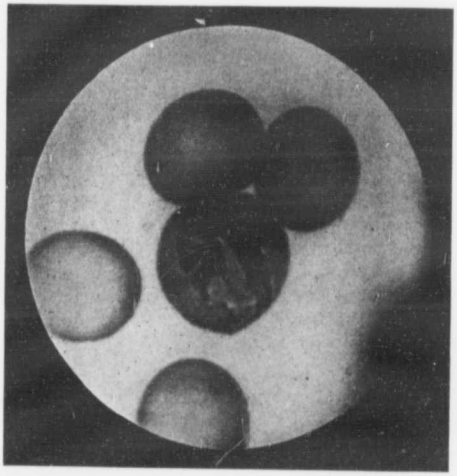
Histologically, the bone marrow shows excessive increase of neutrophile myelocytes. The spleen, liver, and glands, are infiltrated with cells of myeloid origin, similar to those in the blood.

Myeloblastic leukæmia.

This is the acute form of myeloid leukæmia. It is recognised by the presence, in the blood, of the myeloblast, which is the ancestral form of the myelocyte.

While the recognition of the lymphocytic, and myelocytic, or chronic leukæmias, is comparatively simple, depending mostly upon finding lymphocytes in one, and myelocytes in the other, the separation of lymphoblastic and myeloblastic is more difficult. The primitive leucocytes, which are poured into the circulation, in lymphoblastic leukæmia, are of lymphoid origin, while in myeloblastic leukæmia they are of myeloid origin. Myeloblasts, and lymphoblasts, exhibit no marked morphological differences.

As described by Buchanan, the myeloblast is a spherical cell,



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Hæmamœba tertiana.
Amœboid form of tertian parasite.

with a large nucleus, almost filling the cell, so that in some, only a thin rim of cytoplasm is seen. The nucleus is finely reticulated, stains feebly, and may contain one or two small vesicular-looking nucleoli. The perinuclear protoplasm is finely reticulated, and, with basic stains, appears darker than the nucleus. The youngest variety has the basophile protoplasm stretched tightly around the nucleus. As the cell develops, the nucleus becomes excentric and reniform, the cytoplasm more abundant, and less responsive to basic stains. At this stage of development, the cell appears as a non-granular myelocyte, in which the specific granulation will determine the class to which it will belong.

A proteolytic ferment is found in cells of myeloid origin, which is said not to be present in structures of lymphoid origin. Schultz has proposed a modification of a reaction, originally used by Winkler for the detection of pus cells, which depends upon the presence of an oxydising ferment in the myeloid cells.

The oxydase reaction.

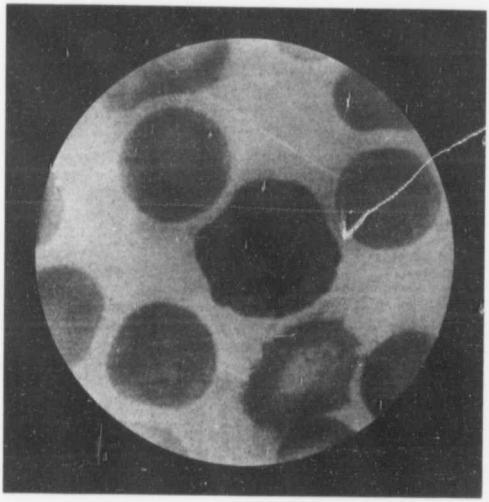
This serves to distinguish myeloid cells from those of lymphoid origin. A 1 per cent. solution of naphthol, and a 1 per cent. watery solution of dimethyl-phenyl-endiamin are freshly mixed in equal proportions, and the tissue or blood smear, to be examined, is placed therein. The granular leucocytes, the myelocytes, and the myeloblasts take on a distinct colour, due to the reaction of the oxydase, in these cells.

In myeloblastic leukæmia, there appear, not only the cells, characteristic of this type of leukæmia, but also a slightly later cell, described by Port as the premyelocyte, in which a few neutrophile granules can be made out.

In myeloblastic leukæmia, there is difficulty in distinguishing myeloblasts from myelocytes, because so many transitional cells, with faint indistinct granulation, are present.

In blood films, from myeloblastic leukæmia, the author has observed an occasional mononuclear leucocyte, in which some of the granules were eosinophilous, and some basophilous; the former were identical with those seen in the eosinophile leucocyte, and the latter resembled the granules of the mast cell.

In myeloblastic leukæmia, the myeloblasts make up about 15 per cent., or more, of the leucocyte formula, while myelocytes vary from 8 to 60 per cent.



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Hæmamœba tertiana.

Pigment-forming tertian parasite. Schüffner's granules.

Small lymphocytes are relatively diminished. Eosins may be present in small numbers, or increased.

Pathological anatomy.

The lesions are most marked in the bone marrow, less marked in the spleen, and still less in the lymphatic glands. Certain authors report that, in very acute cases, they found only hyperplasia in the bone marrow, and nothing at all pathological, in spleen or glands.

In the spleen, the pulp is chiefly affected; the Malpighian corpuscles are recognisable, the general structure of the organ is preserved, and the pulp is full of mononuclear, nongranular cells, of which the nuclei are clear, and the protoplasm basophilous. In the very acute cases, these changes are not marked, owing to the changes in the whole hæmogenic system taking place so rapidly. The bone marrow is red, congested, and even hæmorrhagic.

Pathological histology.

In the bone marrow, there is extreme proliferation of the one element,—the myeloblast. The myelocytes are fewer in number, and the polymorphonuclears still less abundant.

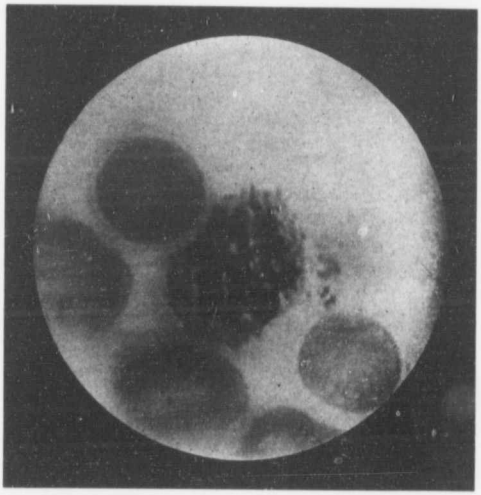
Course and duration.

The clinical course of myeloblastic leukæmia is of short duration. Von Leube's case lasted 4 days. Of the leucocytes, in this case, 14 per cent. were myelocytes, 40 per cent. neutrophiles, and 40 per cent. were reputed as "lymphocytes." Gullman's (Berlin) case terminated in four and a half days, after the onset of the first symptoms.

Meyer and Heineke believe their observations demonstrate that the blood changes in leukæmia are the result, not of perverted blood formation, but of reaction of the blood-forming organs, to some toxic influence.

Roentgen ray in leukæmia.

The application of the *x* ray, in myeloid leukæmia, is marked by a temporary amelioration of the symptoms. In the majority of cases, in which complete detailed blood examinations have been re-



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Hæmamœba tertiana.
Tertian segmenting body.

corded, there has been an increase in hæmoglobin, and red blood cells, with a distinct diminution of the myelocyte percentage, and a corresponding rise in the polymorphonuclear percentage. The essentially leukæmic character of the blood has shown a tendency to disappear, but not entirely.

In myelemia, under the influence of the *x* ray, there can be brought about a nearly normal condition of the blood. There is a marked decrease in the size of the spleen, and a coincident amelioration of all symptoms.

Lymphoid leukæmia is apparently not influenced by the ray.

The history of all cases of leukæmia, whether treated medicinally or by *x* ray, records that at first they do very well, but soon grow worse, and die.

Gramegna and Quadrone made animal experiments to decide the action of the *x* ray, on blood corpuscles. While no alterations, either in the colour or form of the red cells, were observed, the leucocytes showed marked degeneration phenomena, particularly in the direction of fragmentation of the nucleus. In other leucocytes, the protoplasm was degenerated, so that it stained badly, and assumed an indistinct outline, and, in yet other forms, the protoplasm was broken up into small masses, which quite failed to take up the staining reagents. There was almost always a decrease, in number of leucocytes, polynuclear, and mononuclear.

Lensir and Hilber came to the following conclusions, regarding the effect of *x* ray on the blood.

1. The white blood cells are affected, in an elective manner, by the *x* ray, the lymphocytes being most susceptible to its influence.

2. By the action of the rays, there arises in the circulating blood, and also in the blood treated outside the body, a leukotoxin, which, when the serum is injected into an animal, causes a destruction of leucocytes.

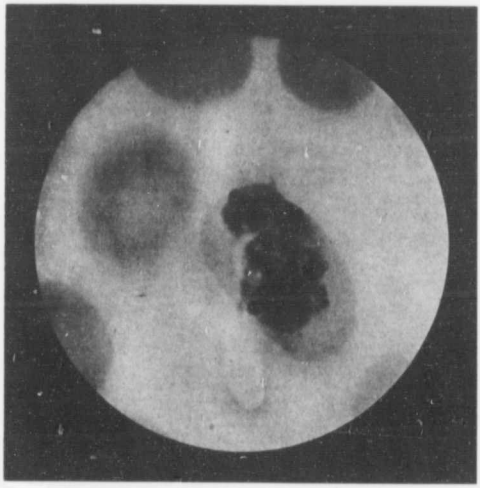
3. This leukotoxin produces an immunity against itself.

4. This leukotoxin produces nephritis, by its elimination by the kidneys.

5. On the erythrocytes, the blood platelets, and hæmoglobin, the *x* ray has little or no effect. The coagulability does not suffer.

Curschmann and Gaupp, in experiments on animals, arrived at similar conclusions:—

1. Through the action of the *x* ray on leukæmic patients, there appears in the blood a specific leukotoxin, that exerts an elective de-



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Hæmamœba tertiana.
Dehæmoglobinized corpuscle containing tertian segmenting bodies.

structive power, on the leucocytes of the circulating blood, of experimental animals, and normal persons.

2. It is inactivated at 60° C., and completely loses its faculty of destroying leucocytes in the circulating blood.

3. The injection of leukæmic blood, into normal animals, causes an immediately appearing leucopenia, of one to one and a half hour's duration, followed by a reactive hyperleucocytosis, and, five to six hours later, a hypoleucocytosis.

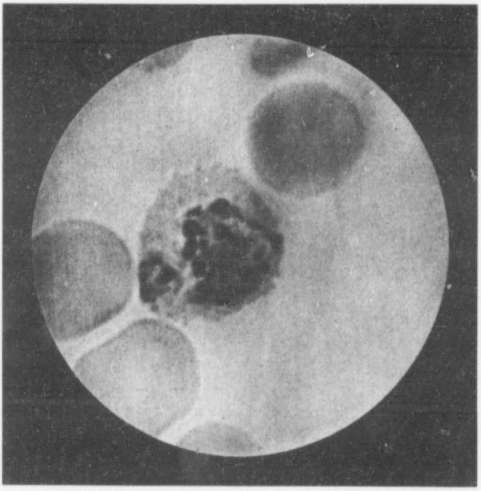
Musser and Edsall think, that the *x* ray exerts its influence, not by a direct effect on the leukæmic tissue, the blood making organs, or on the blood, but by a stimulation of the autolytic powers of the organism. They think great care should be exercised in the application of the *x* ray, and especially in individuals suffering from kidney trouble.

J. Smith's study and experience of leukæmia have convinced him that the treatment reduces the consumption of neutrophiles, eosinophiles, and mast cells, in the circulating blood. The extent of the reduction, depends on the duration, and intensity, of the exposure, which may lead finally to far reaching, although never quite complete, restoration of the blood to normal.

Joachim believes the *x* rays have an elective action on the myelocytes. He believes the behaviour of the myelocytes is of the greatest prognostic value, much more so than the fall in the total number of leucocytes. The lower the relative myelocytic value, the more hope for the preservation of the patient; the higher the percentage of myelocytes, the more unfavourable is the prognosis. In relapsing cases, he noted that the increase of myelocytes preceded the total increases of leucocytes, by several days.

Maragliano found, in a typical case of myelemia with enlarged glands, that those glands far removed from the area of the body exposed to the *x* ray, promptly subsided. When exposures were made, over the spleen and cervical glands, and not over the bones, the inguinal glands diminished in size, parallel with the diminution noted in the exposed cervical glands. The glandular change preceded the effect of the rays on the blood. Maragliano is of the opinion, that a more radical, beneficial influence on leukæmia would result, if larger areas were exposed to the *x* rays. In order to eliminate the danger of skin injury, he urges the filtering of the rays through 4 layers of diachylon, which excludes from the skin the more harmful non-penetrating rays, but allows the really curative rays to penetrate.

Joachim and Kurpjuweit, by *x* ray treatment, extending over 14



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Hæmamœba tertiana.
Tertian segmenting bodies. Schüffner's granules.

weeks, reduced the leucocytes from 693,000 to 6,300. Later, the white cells again increased in number.

Bozzolo finds that, even in relapses, the *x* ray applications are able to act promptly, and speedily, in bringing back the blood to its normal condition, and improving the general condition of the patient. It was frequently noted that, although the patient appeared quite well, in his general health, and the spleen much reduced, yet the blood condition still showed pathological alterations, and, in these cases, the *x* rays soon reduced the percentage of leucocytes, and increased the hæmoglobin. Bozzolo found the state of the blood, in all these cases, was liable to considerable fluctuation, from time to time.

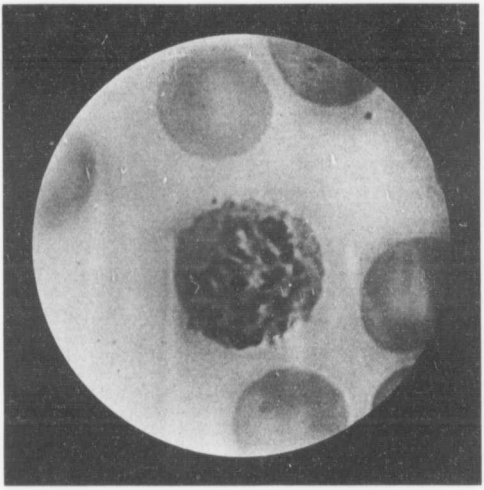
Aubertin and Beaujard submitted a case each, of myelemia and lymphemia, to identical treatment. In the myelemia, they noted an increase in the red corpuscles, in the course of three months, from 2,000,000 to 3,000,000 per c. mm., and a fall in leucocytes, from 320,000 to 60,000. In the lymphatic case, the leucocytes were reduced from 350,000 to 10,000. In the case of myeloid leukæmia, there was noticed a marked increase in the leucocytosis, after each of the earlier séances, reaching to 450,000, occurring three to five hours after the application of the rays, and lasting three to four hours. The polynuclear leucocytes were responsible for the principal increase. In the myeloid case, the improvement in the leucocyte state was established only after a long period of increase, with marked oscillations. In the lymphatic case, a similar increase of leucocytes was noticed, a few hours after the application.

Œthinger, Fiessinger, and Sauphar, draw attention to the dangers, and say there is always the peril, with radiotherapy, that the chronic myeloid type may be transformed into the acute type, and therefore the technique should be cautious with intervals, especially when the patient reacts markedly to the exposures.

Warthin is in accord with other observers, in the realization, that Roentgen irradiation, in leukemia, is symptomatic treatment, which does not affect the essential disease-process. He concludes:

1. The experimental work proves that the Roentgen rays have a selective action on lymphoid, myeloid, and epithelioid cells, causing nuclear disintegration, fatty degeneration, and necrosis.

2. Exposures of five hours, or more, kill mice, rats, young rabbits, and guinea pigs in from two to ten days. The symptoms leading to death are uniform and characteristic, and are probably to be interpreted as an intoxication, resulting from the disintegra-



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Hæmamœba tertiana.
Tertian segmenting body. Schüffner's granules.

tion of cell-proteid. The greater the destruction of lymphoid tissue, the more marked the symptoms of intoxication.

3. By prolonged exposures, practically all the lymphoid tissue of the spleen may be destroyed.

4. The destruction of lymphoid tissue is always more marked in the spleen, than in the lymph-glands, or bone-marrow.

5. The cells, chiefly affected by the Roentgen rays, are the young forms, the small and large lymphocytes, and the myelocytes. These cells are destroyed in greater numbers, than the polymorphonuclear leucocytes.

6. Regeneration of lymphoid tissue is slow, after prolonged or repeated exposures, but more so in the case of the former.

7. The therapeutic application of Roentgen irradiation, to leukemia and pseudoleukemia, finds a pathologic basis in the selective action, which the rays have for cells of the lymphocytic and myelocytic types, and for their parent cells. The improvement, noted in the majority of cases, so treated, is due to the removal of leucocytes from the general circulation, and from the spleen and other organs where they collect, and to a delayed production of new cells.

8. It is extremely doubtful if the essential disease-process is affected to the point of a cure.

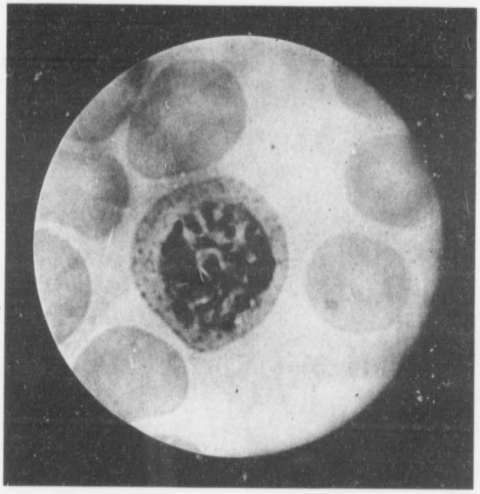
9. The destruction of enormous numbers of leucocytes, in the circulation, by means of Roentgen-ray treatment, may in itself be dangerous. From the disintegrating cells, poisons may be formed, and these may cause a fatal intoxication.

10. Based upon these studies, the therapeutic use of Roentgen rays, in leukemia, seems of doubtful value, or even dangerous. Careful clinical, and pathologic studies, will be necessary to establish the fact of a positive cure in any case.

Chloroma.

This rare and interesting disease, which also goes by the name of green cancer, was first described by Alan Burns, in his "Observations on the Surgical Anatomy of the Head and Neck" (1823), who regarded it as a condition differing from any morbid affection hitherto described. Burns considered that the new growth originated in the lachrymal gland, and was propagated secondarily to the other regions of the head and body.

Huber defines the condition as a metastatic, periosteal sarcoma,



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Hæmamœba tertiana.
Tertian rosette-Segmenting form of tertian parasite.

and maintains that the tumours always originate in the bones of the head and face, and that the growths in other organs are secondary, and originate by metastasis.

Recklinghausen pointed out that the tumours, found in cases of chloroma, differed in many respects from periosteal sarcomas, chiefly in their deficiency of bone formation, and in their development from the outer layer of the periosteum. He insisted upon the intimate relationship which exists between chloroma and leukemia. He demonstrated that the structure of all the tumours, in his case, was of a purely lymphomatous character. Recklinghausen is supported in this belief, by many writers, with the result that the growths are now generally regarded as belonging to the lymphosarcomas.

Chloroma appears to be a disease of children, and adolescents; the average age of onset is below 20 years.

The disease is rarer than acute leukemia, to which it bears an extraordinarily close resemblance.

The first striking symptom is usually exophthalmos, due to development of retro-bulbar lymphoma, which is accompanied by intense pain and disturbances of vision.

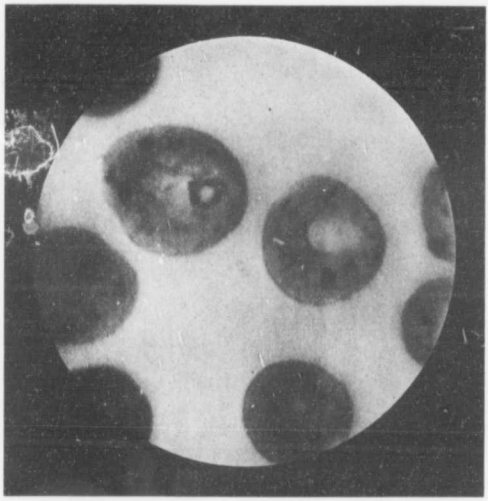
Lymphoid deposits develop in the conjunctivæ, corneæ, temporal fossæ, and periosteum of the bones of the skull. The temporal fossæ are bulged out by firm, or semi-fluctuating swellings. The periosteal lesions are apparently most marked in the region of the skull and face. The tonsils are often enlarged, and infiltrated. Great swelling of the gums, palate, epiglottis, and larynx, has been described. The glands are enlarged from lymphoid infiltration. Lymphoid deposits produce nodular swellings of the skin.

Post mortem, nearly every organ has been found invaded,—the nervous system forms the exception. The huge tumours, which completely fill the orbits, are traversed by the optic nerves, which are found quite unaltered. The brain may be compressed, but its substance is not invaded.

While the peculiar green, tumour-like growths, show special predilection for the skull, almost any organ or tissue may be involved.

The colour of the tumours varies from a yellowish green to a bright grass green. The colour quickly disappears on exposure to air.

Huber ascribed the colour to minute molecular granulations, possessing great refractile power, and of great brilliance, placed in



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Hæmamœba subtertiana.

Small refractive ring-like bodies. Maurer's granules.

and between the cells, and which he considered communicated an intense colour to the tumours.

Pathological histology.

Histologically, the primary and secondary growths are composed of a closely arranged connective tissue stroma, the spaces of which are packed with cells, which in size and structure correspond with those found in the circulating blood. Scattered amongst the cells are rounded clusters of granules, which stain faintly with osmic acid, and are refractile. They disappear, when the sections are treated with solvents of fat.

The blood in chloroma.

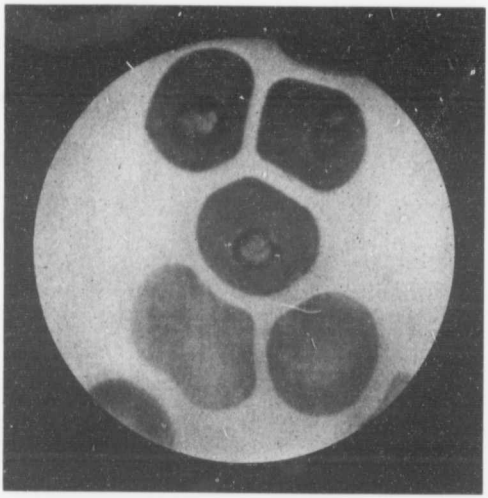
The blood, in every case examined, has been characterised by a very marked lymphocytosis, and diminution of red blood corpuscles.

As in lymphemia, the anæmia is marked, and progressive, and accompanied by petechial extravasations under the skin, epistaxis, and hæmorrhages into the conjunctivæ and retinæ.

The predominant white cell is one which has the morphological characters of the lymphoblast. The most important change is a relative and absolute increase in cells of lymphoid origin; the increase may reach 95 per cent., or more, of the total leucocyte count.

In many cases of chloroma, the blood resembles that of acute lymphoid, or lymphoblastic leukemia. The prevailing cell is identical with those of the primary growth, and the metastases. The growths, for which Ribbert proposed the name *lymphocytomas*, have, as their essential elements, either mature lymphocytes, or parent cells, such as are found in the germ centres. Many of them have no visible protoplasm. Others have a narrow rim of protoplasm, the outer layer of which often stains deeply. The protoplasm may be more prominent on one side, sometimes ragged, or with knob-like processes. Transition forms, between the large lymphocytes and the parent cells, are numerous.

From 79.6 to 82.6 per cent. of all leucocytes, in a case of chloroma, are reported, by Dock and Warthin, to resemble the undifferentiated lymphocytes of the bone marrow. They find that the blood picture, in chloroma, may be very varied.



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Hæmamœba subtertiana.
Early ring forms of æstivo-autumnal parasite.

The typical lymphocytes, *i. e.*, those regularly found in the blood, are only slightly increased above normal.

The diminution in granular leucocytes, and the extreme anæmia observed in chloroma, result from replacement of normal red marrow, by lymphoid tissue; the normal marrow elements are replaced by cells of the large lymphocyte type. The formation of red cells is greatly diminished, and the extreme anæmia is thereby explained. No evidence exists of any marked hemolysis. The anæmia, to which the chief symptoms of the disease are probably due, is one of deficient hæmogenesis, and not one of excessive hæmolysis. The differences, in blood pictures, are explained by the affection of the bone-marrow.

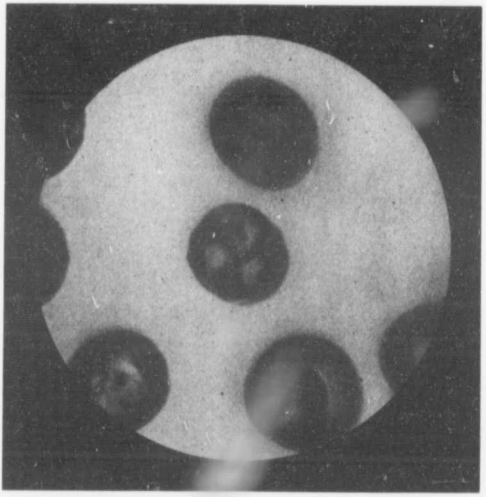
ANTHRAX.

The history of anthrax dates from 1843, when Bourgeois, in Provence, France, published his observations on *Oedeme Malin*. Bourgeois wrote afterwards a very complete description of the disease, in his book on *La Pustule Maligne et l'Oedeme Malin* (1861).

Anthrax is prevalent among those engaged in the manipulation of wool, and it appears that the wool-working industries have been centres, from which the knowledge of anthrax has been spread.

When the disease was brought prominently into notice by John Spear (1881), internal anthrax was the form which was most commonly recorded amongst woolsorters. Since that time, there has been a remarkable change in the type of the disease prevalent, the external and internal forms having changed places, as regards frequency of appearance. The change in the type of the disease is due to improved regulations, which require that the dangerous wools, alpaca, pelitan, Cashmere, Persian, camelhair, mohair, shall only be sorted at a place where a constant draught of air carries the dust downwards.

No animal plague is more widespread than anthrax. The germs of the disease are conveyed by the hairs of animals, that have died of the disease, or have been contaminated with blood, or discharges from such animals. The process of sorting simply pollutes the air with germ-laden dust; while the hands and other exposed parts of the workers are covered with dirt from the hair.



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Hæmamœba subtertiana.

Three æstivo-autumnal parasites developing in red corpuscle.

Anthrax is one of the most virulent of the blood parasites. While the bacillus is easily destroyed, on the other hand, the spore, in the dried state, is the most resistant of known organisms. Kübler found the spores capable of development, after three hours' boiling; Koch found that they retained their vitality for ten days, in a 5 per cent. solution of copper sulphate. The spore retains its vitality, long after the fabric, to which it is attached, has been absolutely burned.

The mode of infection determines the type of the disease of which three forms are recognized:—

1. Cutaneous.
2. Pulmonary.
3. Intestinal.

Cutaneous infection.

The bacillus is introduced through an abrasion in the skin, or even when no point of inoculation can be seen.

The primary lesion begins with a pale, soft, painless swelling, followed, after several days, by vesicles and eschar.

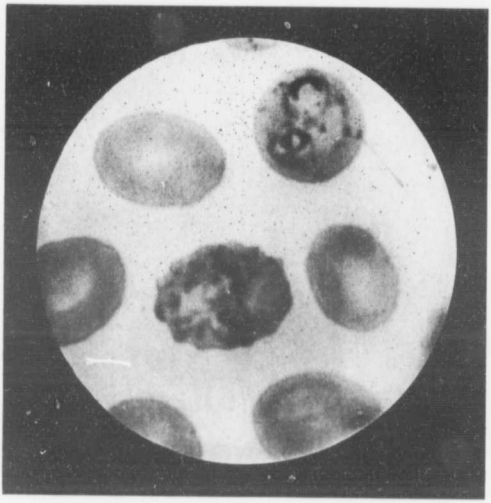
The development of the pustular form may be counted upon, if the bacilli have not invaded the lymphatics, and been carried beyond the point of inoculation. The infection remains essentially local, for a considerable time; penetration of the deeper parts of the dermis, by the bacilli, occurs very slowly and in relatively small numbers.

A second form of cutaneous anthrax is the œdematous,—described by Bourgeois as malignant œdema,—the course of which is on lines so nearly parallel with erysipelas, that the difference might easily be overlooked. The œdema, in this form, is extensive, and may extend from the scalp to the pubes. Of six cases of diffuse cutaneous anthrax, reported by Bell (Bradford), three recovered.

Pulmonary infection.

Pulmonary anthrax is due to inhalation of dust, laden with anthrax germs. The internal form of anthrax, known as wool-sorter's disease, was known for many years among wool-workers, before cutaneous anthrax was recognised. The pulmonary form bears such a close resemblance to an obscure pneumonia, that it has escaped detection, except by those familiar with it, in districts where it is prevalent.

The early onset of cardiac failure, evident on the first day of



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Hæmamœba subtertiana.

Early ring forms of æstivo-autumnal parasite. Maurer's dots.

the illness, in the rapidly fatal cases, is characteristic of pulmonary anthrax.

In an ordinary case, where life is prolonged for four or five days, the symptoms are so slight, that diagnosis is difficult. The patient may be sitting up without pain, feeling of illness, or appreciation of the serious condition, and still be pulseless at the wrist.

Intestinal infection.

The intestinal form results from ingestion of flesh of diseased animals.

The symptoms are those of poisoning, accompanied by toxæmia.

As a result of his feeding experiments, Nikolsky concludes that (1) anthrax develops as well after ingestion of spores in the food, as after any other method of infection; (2) that the spores develop in the intestine, in spite of the antagonism of the intestinal bacteria, and penetrate the mucosa, to enter both the lymphatics and the blood vessels.

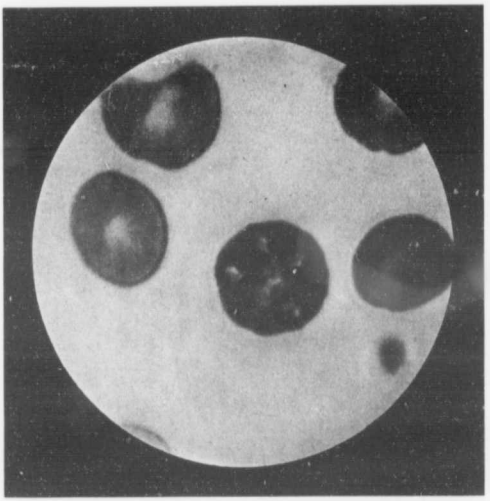
Hæmic infection.

Hæmic infection or anthracæmia is ushered in with restlessness and meningeal symptoms, terminating with convulsions and coma.

In the pustular form, bacilli are present in the serum of the vesicle, but may be entirely absent from the blood taken at the base. In the pustules, the bacilli are found in the cells, and free in the tissue.

In the intestinal infiltrations, the bacilli are always present in the mesenteric glands, and in larger numbers than in the spleen.

Anthrax bacilli are obtained from pericardial, pleuritic, and ascitic fluids, from spleen, liver, kidneys, and heart muscle. It may be difficult to find bacteria in the blood; when absorbed, they may be deposited in parts where the circulation is slow, as in the liver, spleen, and marrow of bones. Sometimes *Bacillus anthracis* is present in the blood, in large numbers, but, it is stated that, in the pulmonary and intestinal forms, no large development of the organism seems to occur, till just before death.



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Hæmamœba subtertiana.
Red corpuscle containing four subtertian parasites.

BACILLUS TUBERCULOSIS.

Among the many important facts, which bacteriological investigation has brought to light, is the persistent power of living in the body, which is exhibited by the tubercle bacillus, and other pathogenic bacteria.

The specific organisms of disease have more or less difficulty in gaining entrance into the living body, and maintaining an existence therein. Mechanical barriers of defence are presented by the skin, and, to a less extent, by the mucous membranes. Some parts of the mucous surfaces, such as those of the tonsils, fauces, bronchioles, and Peyer's patches, are highly vulnerable, and pathological changes in these parts diminish their protective capacity.

The respiratory and digestive tracts are the two main paths of infection, of the tubercle bacillus.

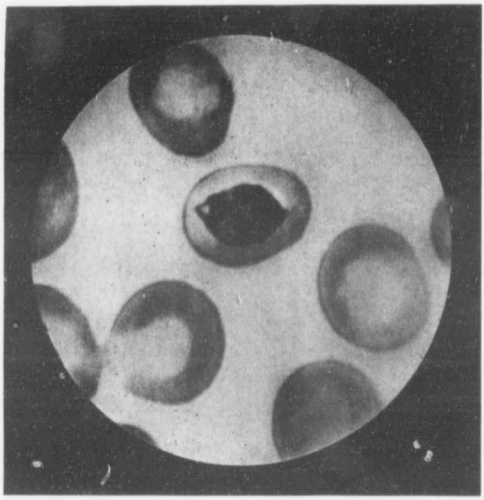
Tonsillar infection.

The importance of the tonsils, as a point of entrance for infection by the tubercle bacillus, is now fully recognised.

The structural characters of the tonsils render them liable to infection. Ample evidence has been brought forward to prove that, in tuberculous infection of the cervical glands, the tonsils have been often, if not mainly, responsible for the entrance to, and infection of, the cervical glands by the tubercle bacillus.

The tonsillar path of tubercle infection, especially in children, must be a comparatively frequent occurrence. Dieulafoy (Paris) made an experimental investigation, to ascertain whether hypertrophy of the tonsils and adenoids of the pharynx are, in any cases, of tuberculous nature. Portions of tonsils, and adenoid vegetations, which had been removed from 21 cases, on account of overgrowth, were inoculated into guinea pigs, and 3 became tuberculous. Thus 1 in 8 of the cases of simple hypertrophy of the tonsils, and 1 in 5 of the cases of adenoids, were tuberculous.

Out of 34 consecutive post mortems, Walsham (London) found the tonsils more or less affected in 20. There was nothing, during the life of these patients, to call attention to the tonsils. In the majority of the cases, the tonsils were atrophied, in only one or two, was there anything approaching hypertrophy. The necropsies were made in patients, who had died of visceral tuberculosis. In such



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Hæmamœba subtertiana.
Non-pigmented stage of æstivo-autumnal parasite.

cases, the tonsillar lesions may be either a primary infection, or a secondary hæmic infection, or, more probably, an auto-infection from the passage of bacilli-laden sputa, over the tonsils.

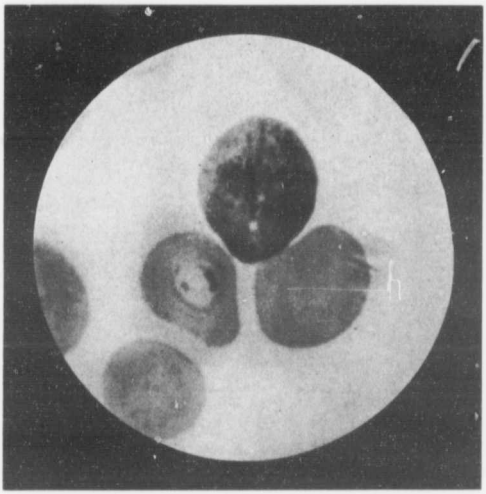
Phedini injected an active emulsion of tubercle into the tonsils of animals, with a view to ascertaining the route which tonsillar infection takes. At the autopsy, fifty days later, numerous tubercles, in various stages of development, were found in the tonsils, palatine arches, and adjoining mucosa, in the nearest lymphatics, also in the subclavicular, peribronchial, and mediastinal lymphatics, and corresponding lymphatic glands. It was quite clear that the disease had spread chiefly through the lymphatic channels. Similar results followed, after injection of tubercle into palatine arches, gums, and dental alveoli.

Both clinical experience, and bacteriological evidence, emphasize the fact, that, as a portal of entry for the tubercle bacillus, the tonsils are of prime importance.

Pulmonary infection.

Infection of the lungs, by way of the lymph channels, appears to be particularly common in infancy. Frænkel refers to the frequent swellings of the cervical glands, in scrofulous children, and to the still more significant fact, that, in infantile tuberculosis, the bronchial glands are almost invariably affected. Frænkel does not go so far as to advocate the extreme view, that the lungs in infants may not, in a certain proportion of cases, be directly infected by inhalation. In the adult, where the bronchial glands are frequently less affected than in the child, the occurrence of direct infection by the respiratory tract is undoubtedly common.

All attempts to produce pulmonary phthisis, as distinct from miliary tuberculosis, experimentally, have failed. The longer the time, between inoculation and the fatal issue, the more chance there is of the occurrence of caseous degeneration and cavities. Baumgarten (Wien) for a long time unsuccessfully attempted to obtain a product which, when inoculated, would produce phthisis. Bacilli, of varying virulence and in varying doses, were employed. At last success was obtained by accident. He was experimenting as to the paths by which tuberculosis of the urogenital tract progresses, and found that virulent tubercle bacilli produced typical apical phthisis, with large vomicæ and caseating nodules, when they entered the system from the intact urethra, or bladder. The reason is probably that



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Hæmamœba subtertiana.

Small ring form and large non-pigmented spherical body.

the bacilli have to penetrate a layer of stratified pavement epithelium, before reaching the connective tissue and lymphatics, and that therefore only a few, or even a single one, can arrive in any given part of the lung simultaneously. By this slow and gradual method of infection, so different from the intravenous injections commonly practised in experimental inoculation, the tuberculous predisposition of the apices has full play; if, however, the lungs are flooded simultaneously with crowds of bacilli, the universal infection overshadows the greater predisposition of the apices. Baumgarten is convinced, that some such process plays the preponderating part in the production of phthisis, and while admitting the possibility, denies the probability of the frequent occurrence of direct aërial infection, that is, he believes that phthisis is usually of hæmatogenous origin. The more one compares tuberculous lungs, the more one sees that there is every gradation between acute miliary tuberculosis and chronic ulcerative tuberculosis, or ordinary phthisis. Ribbert, who also believes in the hæmatogenous origin of phthisis, does not discard the inhalation theory; the bronchial glands are first infected aërially, then the lungs through the blood. Baumgarten goes further, and believes, that even the bronchial glands are usually infected hæmatogenously.

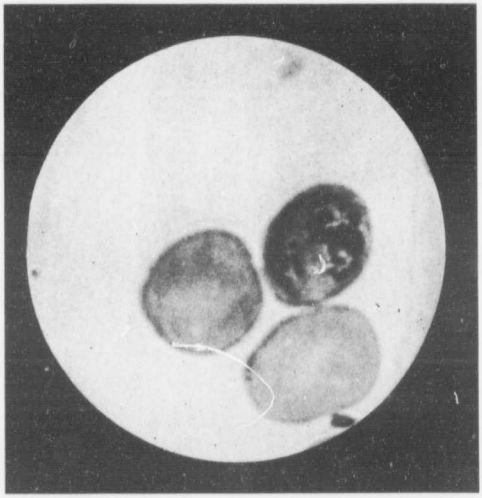
Intestinal infection.

There can be no doubt that, in a considerable proportion of cases of pulmonary tuberculosis, the infection has been introduced by the alimentary tract. This is particularly true of infantile pulmonary tuberculosis.

Bristowe found 167 cases of tuberculous ulceration of the intestine, out of 324 fatal cases of gastro-intestinal ulceration. Twelve of these had small tuberculous cavities in the liver.

Direct infection by the respiratory tract is undoubtedly common in the adult, where the bronchial glands are frequently less affected, than in the child. Evidence of the course of intestinal infection is afforded by the artificial production of tuberculosis, in animals, by the ingestion of tuberculous material. The lesions, thus produced, are miliary tubercles of the small intestine, particularly the ileum, of the trachea and bronchial tubes, of the peritoneum and lungs, indicating a widespread hæmic dissemination of the virus.

Flügge states that the number of bacilli necessary to tuberculise an animal, by ingestion, is greater than that which suffices for infection by inhalation.



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Hæmamœba subtertiana.
Intracorpuscular pigmented body.

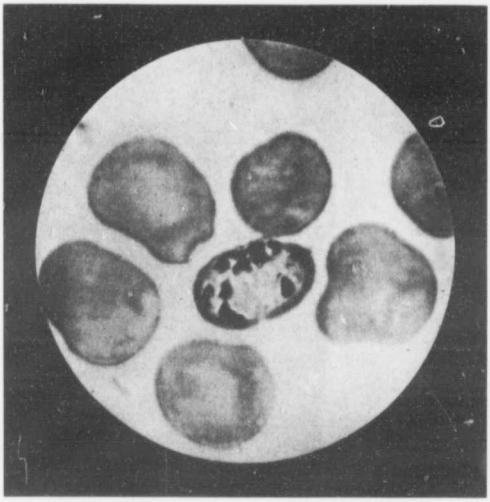
Calmette affirms definitely that, in an immense majority of cases, in man, the specific infection takes place in infancy, and early childhood. In most of these cases, the lesion remains localised in the lymphatics, without causing the occurrence of any morbid symptoms. Notwithstanding the large number of people who react to tuberculin, not more than 25 per cent. of these carriers develop tuberculosis, as a consequence. Calmette cites the following factors, as determining the virulence of tuberculous infection in man: (a) When infection occurs from a case of rapidly developing phthisis, it is much more virulent than infection from a bovine source. (b) It is much less virulent, when the bacilli have previously undergone exposure to light, and especially the ultra-violet rays. (c) It is more virulent, when the bacilli are introduced into the organism in massive doses and at short intervals, than when the doses are smaller and the intervals longer. In the latter case, the cellular defences of the body have time to accomplish their work and increase the resistance of the organism. (d) The infection is less severe when the patient already has latent tubercle.

The occurrence of tuberculous infection, through an intact epithelium, apart from any necessary primary lesion, or diseased infection site, has been established (Shattock S. G., Sidney Martin). The infective agent gains access between the epithelial elements of an intact surface, by means of wandering or carrier cells. The pigment, commonly found in the bronchial glands, is an example of this kind of conveyance. It is believed that normal leucocytes pass the mucous membranes, particularly those of the digestive tract, carrying bacteria into the lymphatics, or small veins of the portal system. The lymphatic glands, which act as bacterial filters, contain many an inhaled or ingested bacterium, which is destroyed where the soil is unsuitable for its growth.

Hæmic infection results in consequence of the extension of a periarteritis, to the inner coat of the vessel. This is especially liable to occur in the smaller arterioles, by invasion of the vessel wall, by tuberculous disease in the tissues contiguous to it.

Tuberculous endocarditis.

Étienne finds that an acute form of inflammation of the cardiac valves is sometimes found associated with tubercle. Careful examination of cases throws doubt on the specific origin of many; septic conditions, such as are frequently found in the later stages of tuber-



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Hæmamœba subtertiana.
Full grown pigmented parasite.

culous disease, manifest themselves by endocarditis. After a careful study of the course of tuberculous affections, Étienne concludes, that tuberculous endocarditis is certainly a pathological entity, though a rare one.

The presence of tubercle bacilli, in endocardial lesions, has been frequently verified; the difficulty of staining the bacillus, in section, will perhaps account for some of the negative results which have been obtained.

Leyden draws special attention to the presence of living bacilli, within the cells, and he thinks that such cells may be transported elsewhere, and form new foci of tubercle.

Hereditary transmission of tubercle.

The question of the direct transmission, from mother to fœtus, of a disease, so prevalent as tuberculosis, is one of considerable importance. Whether the fœtus was born, not only capable of receiving the bacillus, but actually containing it, was a matter of doubt, until Birch-Hirschfeld and Schurl put on record a case, in which it has been definitely proved that, in the human subject, tubercle bacilli pass from mother to fœtus.

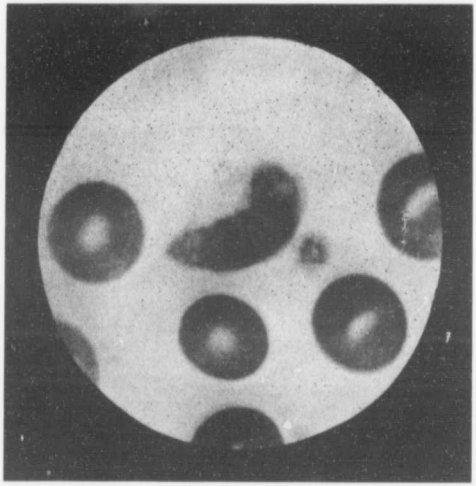
Landouzy protests against looking upon all cases of tuberculosis, as arising after birth; nor does he think, that the question of heredity is one of suitability of soil alone, but also one of actual bacillary infection.

Landouzy and Martin proved experimentally that inoculation from a fœtus, born of a phthisical mother, and yet with no naked eye tuberculous lesions, would produce tubercle in animals.

Novak and Ranzel have been able to demonstrate, in four out of six cases of tuberculous women, the presence of tubercle bacilli in the placenta.

Schmorl and Kochel, on three occasions, examined the placentæ of women, who had died of tuberculosis. Tuberculous changes were present in all three placentæ. They find the villi present a great obstacle to the entrance of tubercle bacilli, for they remain for a long time completely, or almost completely, intact, after they have been entirely surrounded by tuberculous new growth. Finally, however, when the surrounding tissue has become entirely caseous, and when the epithelium of the villi has been lost, the bacilli effect an entrance.

In the majority of cases, the bacilli come to the placenta, in the



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Hæmamœba subtertiana.

Male crescentic form of æstivo-autumnal parasite.

blood stream; but, in cases of tuberculous peritonitis, infection may also occur through the Fallopian tubes.

Londe thinks that the likelihood of getting positive inoculation results from the placenta, etc., increases with the gravity of the mother's tuberculosis, and that the placenta seems to act as a filter to the tubercle bacilli, so that inoculations with it are more likely to give results, than inoculations with the umbilical blood or fœtal viscera.

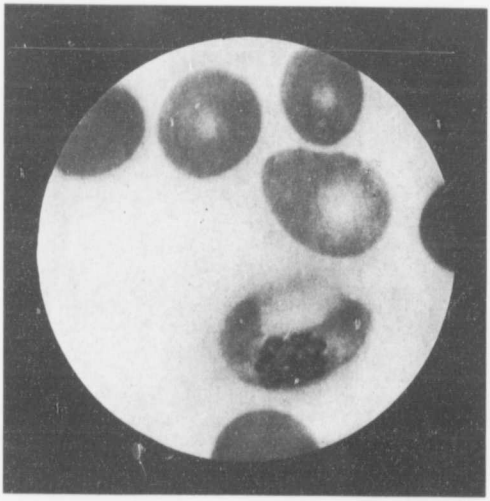
Lehmann (Berlin) observes that an organ containing as much blood as the placenta, ought to show the tuberculous lesion, quite as readily as the liver and kidneys do. He believes that such tuberculous lesions, as occur in the bones and glands, during childhood, are better explained by hereditary transmission, than by aërial infection.

The rarity of tuberculous lesions, in the fœtus, is perhaps not so astonishing. The fœtus is infected in utero, but time is required to develop the lesions. Passage of tubercle bacilli into the fœtal circulation has been proved, for they may be found, though only in small numbers, in placentæ of phthisical mothers, and in the fœtal villi.

BACILLUS TYPHOSUS.

A new element, discovered by Loris-Melikov, has entered into the etiology of typhoid fever,—namely, an anærobic bacillus. This investigator found a non-motile Gram-positive, sporing, strictly anærobic bacillus, which has a specific action on lymphoid tissue, and in particular on Peyer's patches in the intestine, on which it exercises a distinctly necrotic action; unmistakable swelling and ulceration result. These bacilli were found only in fæces, from typhoid patients, and not in normal stools. They were agglutinated, by typhoid patients' serum, in a dilution of as much as 1 in 100. Loris-Melikov considers that this organism has a local necrotic action, and that it adds to the septicæmic effect of the typhoid bacillus.

Bacillus typhosus enters by way of the intestine, passing thence through the lymphatics of the intestine, and mesenteric glands, into the thoracic duct and blood stream. Thence it becomes distributed to all the organs, and tissues, but finds, in the spleen and bone marrow



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Hæmamœba subtertiana.
Female crescentic form of æstivo-autumnal parasite.

alone, places where it can develop and thrive. They may be carried to the liver, and become eliminated in the bile, or be destroyed or eliminated by the kidneys.

The existence of typhoid fever, without any lesions in the intestines, is now recognised. In these cases, the bacillus is found in the blood, while the characteristic lesions of the micro-organism, in the intestine, are absent. There is the strongest evidence that, sometimes, though rarely, the typhoid bacillus enters through the intestinal tract, passes into the blood, and becomes generalised in the organs, without causing any lesions in the intestine. In these cases, the intestine is normal in appearance, but the mesenteric glands are enlarged, and show necrotic foci.

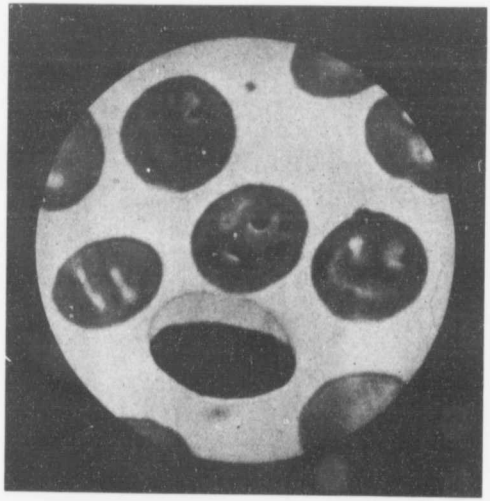
Bacteriological investigation of the blood shows that, with improved methods of technique, the bacilli can be demonstrated in most cases, in the first three weeks of the disease.

Schottmueller, in a systematic examination of the blood of patients, suffering from enteric fever, found the bacilli in 84 per cent. In one case he was able to examine the blood, on the second day of the illness, and found bacilli, while, in another case, the examination was made on the first day of a relapse, also with a positive result.

In 85 examinations, made in the first week of the disease, Coleman and Buxton got positive results in 93 per cent. Particular attention was directed to the periods of the disease, in which the bacilli were found in the blood. In the second week of the disease, examinations yielded positive results in 76 per cent., in the third week, 56 per cent., in the fourth week, 32 per cent. The interesting information, brought out by this analysis, is the large percentage of positive results obtained in the first week, and the steady decline in later periods of the disease.

Bacteriological examination of the blood, in cases of typhoid fever, is more valuable than Widal's reaction, since the former is able to allow of definite conclusions being formed, long before the latter. The method is of decided value, in those examples of the disease, in which the clinical manifestations are difficult of interpretation, and when the serum reaction fails to give a positive result.

Longcope studied the histo-pathology of the bone marrow in typhoid fever, and other infections, paying especial attention to the fact that, in enteric fever, there is leucopenia, as contrasted with the leucocytosis, present in most infections. In the typhoid cases, the lesions were constant and characteristic, closely resembling the changes met with in Peyer's patches, the mesenteric glands, and



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Hæmamœba subtertiana.
Severe infection in æstivo-autumnal fever.

the spleen. The most prominent features were a marked preponderance of lymphoid cells, over granular myelocytes,—an observation of significance, in view of the relatively high proportion of lymphocytes, in typhoid blood.—foci of necrosis, and the presence of large phagocytes. In the cases of pneumonia, peritonitis, septicæmia, etc., on the contrary, necrotic and degenerative changes were not observed, and large phagocytic cells were absent, while granular myelocytes over-shadowed lymphoid cells, as might be expected from the polymorphonuclear type of leucocytosis, met with in such infections.

Quincke's researches show, that the bone marrow contains the greatest number of bacilli, during the first week of the disease, and that, at this time, the bactericidal cells are few. Later on, the bacilli decrease in numbers, and there is a proportional increase in their antagonists.

At the end of the disease, the bacillus disappears, last of all from the spleen and the bone marrow; it may remain longer, as Guizzetti has pointed out, and then is confined to infarcts, abscesses, etc.

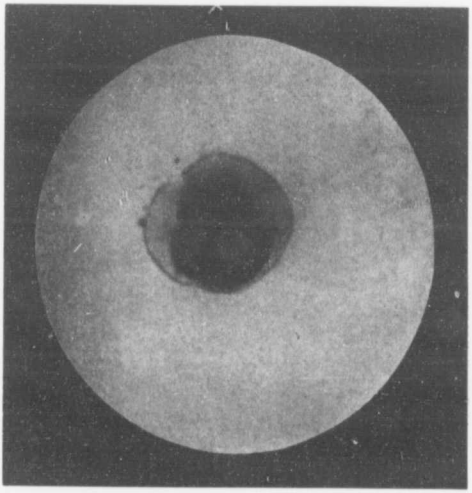
Busch suggests, that the post-typhoidal bone diseases may be due to the retention of the bacilli, in the marrow, after the rest of the body has become immune.

Barling reported a case, in which typhoid bacilli had set up a periosteal abscess, after remaining latent for three and a half years. The bacillus of Eberth was obtained in pure culture.

Bacillus typhosus may remain in the gall bladder, long after it has disappeared from other organs, and cases in which it has been found, after some years, are referred to by Pratt (J. H.). The presence of the bacillus, in the gall bladder, does not necessitate any cholecystic change. It is possible that invasion of the gall bladder occurs in two ways; one by an ascending infection, by the biliary passages, from the duodenum; secondly, by descending or hæmatogenous infection. Were infection to take place, from the biliary passages, it would probably be a mixed infection, whereas, in typhoid fever, the evidence seems to point to hæmatogenous infection, as the organism is nearly always found in pure culture.

The typhoid eruption.

Until quite recently, the general opinion was that the spots in typhoid were not due to a local growth of the bacilli, but were



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Hæmamœba danilewskyi
(Halteridium).

more probably due to the absorption, of the typhoid toxins, into the general circulation. Observers, for the most part, were unable to demonstrate the presence of bacilli, in the skin lesions.

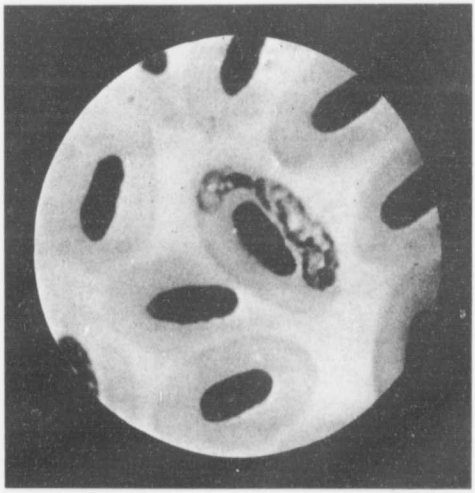
Neuhaus (1886) obtained nine positive results in fifteen cases. Neufeld (1899) explained the discrepancies, in the results of the various observers. He argued that, if the bacilli really were the cause of the skin lesions, it was evident that they were only able to obtain their foothold in the skin, and subcutaneous tissue, for a very short time, otherwise the spots themselves would not be so fleeting; hence, to find the bacilli, spots should be examined quite early in their development. To eliminate, as far as possible, the bactericidal power of the blood itself, which would come in contact with the bacilli, as soon as the spot was opened, he advocated the use of liquid culture media, in order to dilute the blood, and so diminish this source of error. Neufeld's results showed the value of these suggestions. He examined the spots, in fourteen cases, and in thirteen he obtained a positive result. It would appear that the negative results, obtained in many cases, were due in part to the selection of spots already beginning to fade. Richardson (Boston) isolated bacilli from the spots on an average of six days, before the Widal reaction was obtained.

Typhoid septicæmia.

Typhoid septicæmia produces a condition, analogous to that found in the severe anæmias. Among the symptoms reported are, a general depression, and signs of weakness, associated with extreme pallor, skin of a yellow colour and waxy, and mucous membranes colourless. The red corpuscles are reduced to about one million, colour index about normal, poikilocytes and nucleated corpuscles present. Leucocytes are normal in number, with relative increase in lymphocytes. Blood cultures show *Bacillus typhosus*, and Widal reaction shortly becomes positive.

Typhoid thrombosis.

Occlusion of a blood vessel may be a sequel to, or a complication of, typhoid fever. It is generally recognised, that thrombophlebitis depends on an infection of the vein wall with typhoid bacilli. Thrombo-phlebitis, as a sequel, is less grave than when it occurs as a complication. While venous occlusion is probably al-



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Hæmamœba danilewskyi
(Halteridium).

ways the result of thrombosis, it would appear that occlusion of an artery may result from either thrombosis, or embolism. The theory that gangrene, of this type, is due to a primary arteritis, leading to thrombosis, has been largely taught by the French school of pathologists. However, Virchow, in 1848, directed attention to the important part played by embolism, in the mechanical obstruction to the circulation. The special liability to bacterial invasion, in the epithelium, in the neighborhood of the cardiac valves, apparently favoured the theory of embolic origin. But, against this, is urged the infrequency of endocarditis, as a complication of enteric fever, and the absence of a discoverable cause of emboli, and no sign of their lodgement elsewhere. Although, in some cases, the obstruction may be of embolic origin, a bacterial invasion of the arterial wall is the essential cause of the gangrene, accompanying typhoid fever. Endarteritis, of typhoid origin, may lead to occlusion of the vessel, or it may not be sufficient to cause complete obstruction, and therefore gangrene does not supervene. Hawkins has collected 17 cases of hemiplegia, as a complication of enteric fever, in which the gradual onset of the symptoms bear out the view of a thrombus, formed *in situ*.

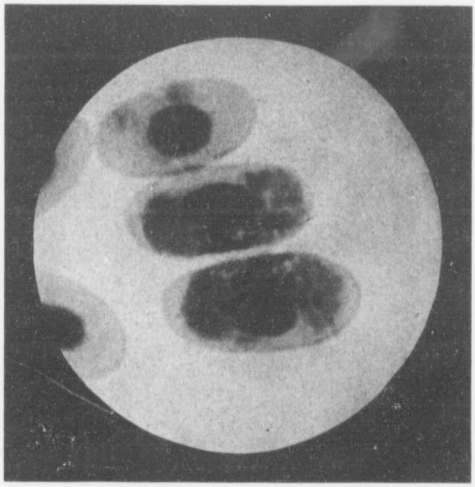
Of the complications and sequels of typhoid fever, arterial thrombosis, resulting in gangrene, is one of the rarest. On the other hand, venous thrombosis is not uncommon, and is especially frequent in the femoral vein, during convalescence.

The gangrene, which complicates the infective diseases, such as enteric fever and pneumonia, is the result of bacterial endarteritis, due to stagnation of the circulation, at a time when the blood contains living and virulent micro-organisms.

BACILLUS COLI COMMUNIS.

This organism, constantly present in the intestine, ordinarily inoffensive, becomes at times an active invader. Certain conditions are necessary in order to permit the transparietal invasion of *B. coli;* (1) a breach of surface of the alimentary canal, which need not be very advanced; (2) increased virulence of the bacillus. Enteritis, in its various forms, satisfies both these requirements.

The influence of *B. coli,* in the intestinal affections, is a difficult



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Hæmamœba danilewskyi
(Halteridium).

question, especially the problem whether the bacillus becomes more virulent, or whether the effects are due to different strains.

Neisser and Opitz concluded, from the results of their experiments, that, in the healthy animal, a passage of bacteria through the intestinal wall does not take place. Ford obtained precisely opposite results, which he attributed to differences in culture methods.

In strangulated hernia, *B. coli* is found in great abundance in the fluid contained in the sac, although no decided inflammatory change can be found in the confined loop of intestine. That *B. coli* actively invades the intestinal wall, and is the most regular cause of peritonitis, of intestinal origin, is generally recognised.

The points of entrance of *B. coli* are in order of frequency, the intestine, the biliary passages, the urinary tract, and the female genital organs.

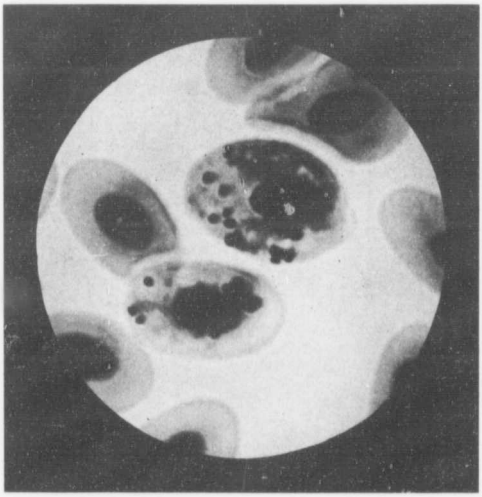
The ascent of the colon bacillus, along the biliary passages, may cause (1) cholangitis, and (2) cholecystitis. An ascending infection, up the pancreatic duct, by *Bacillus coli*, and other intestinal bacilli, is probably a frequent cause of pancreatitis, and a predisposing factor in the production of glycosuria. The infection of the urinary tract is more frequent from below, *i. e.*, ascending, or direct infection. In ascending infection of the urinary tract, the disease starts with cystitis; pyelitis and pyelonephritis follow. The greater frequency of this infection, in women, is accounted for by the shorter urethra, rendering an ascending infection easier in pregnancy, and diseases of the genital organs.

Albarran and Macaigne early recognised hæmic infection of the kidneys with *Bacillus coli*, and described parenchymatous nephritis, and miliary abscesses.

Hæmic infection accounts satisfactorily for cases, in which the parenchyma of both kidneys is affected. Conditions, such as trauma, calculus, torsion, rotation, and obstruction, which reduce the resistance in one kidney, may determine unilateral disease of hæmic origin.

In febrile disturbances, during the puerperium, *Bacillus coli* is found in about 15 per cent. of the cases, sometimes alone, but frequently associated with other organisms. That it is a frequent cause of infection is not surprising, when it is remembered how easily contamination may occur from the rectum.

Malvoz has pointed out, that it is not always possible, in cases of supposed puerperal peritonitis, to show that the case had its origin in the generative organs. In this form of purulent inflamma-



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Hæmamœba danilewskyi
(Halteridium).

tion, one would expect to meet only with *Streptococcus pyogenes*. The absence of this bacterium, and the presence of *Bacillus coli*, in the exudation following a miscarriage, would indicate that the inflammation was an incidental affection, having its origin in the intestinal tract, and not in the uterine organs.

No doubt, many infections arise from changes in the intestinal mucous membrane, inflamed through compression by the gravid uterus, or through retention of fæces, irritating the coats of the bowel. These changes allow *Bacillus coli* to pass into the peritoneum, setting up infection which is intestinal, and not, strictly speaking, puerperal.

Sevestre advances reasons for believing that, in infants, and probably also at other ages, in consequence of enteritis, a general infection with *B. coli* might occur, and, in particular, pulmonary congestion and broncho-pneumonia. Bacteriological examination was made in 5 cases, in which pulmonary lesions occurred, as complications of enteritis. In all cases, *B. coli* was found; from patches of broncho-pneumonia, it was obtained in pure culture, and was therefore assumed to be the only microbe in those areas.

Cases of hæmic infection with *Bacillus coli* are reported, in which there was nothing in the history to indicate the channel of infection, nor was any primary lesion found at autopsy. The symptoms are those of malignant endocarditis, in which pyrexia of all types is constant.

Cases of general hæmic infection with *Bacillus coli* have been classified by Jacob into three groups:

1. Those running a course somewhat similar to typhoid fever.

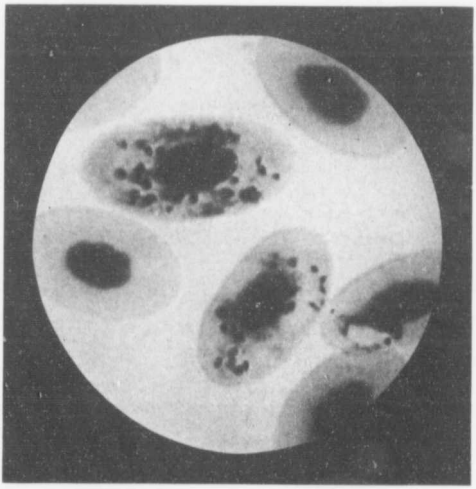
2. Cases with secondary abscesses,—a pyæmia. As compared with other infections, hæmic infection with *Bacillus coli* appears less prone to give rise to secondary abscesses.

3. Cases of terminal infection with *Bacillus coli*, in which the organism is removed from the blood, a short time only before death.

Bacillus suipestifer.

Bacillus suipestifer, a member of the para-typhoid group of bacteria, was discovered by Salmon and Smith. It is the cause of hog cholera, or pig typhoid, a particularly destructive disease of swine.

The disease is contracted through the alimentary tract; the first effect is upon the intestines, with secondary invasion of the lungs.



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Hæmamœba danilewskyi
(Halteridium).

The disease is contagious, and almost invariably fatal. At the outset, infected animals are languid; there is fever, cough, and loss of appetite. There is whitish, mucous, horribly offensive diarrhœa, which sometimes continues throughout the illness, and at other times is replaced by constipation. The affection lasts from 20 to 30 days.

The metastases to the lung are of the nature of a generalised broncho-pneumonia.

The pathogenic organism is found in the lungs, glands, intestinal tumours, liver, spleen, kidneys, urine, fæces, bile, and blood.

Bacillus suipestifer is always potentially dangerous to man, and is of importance in connection with bacterial food poisoning. In outbreaks of food poisoning, associated with this organism, the source of the infection is food derived from diseased animals.

There is evidence that food containing *Bacillus suipestifer* can sometimes be eaten without ill effects. When ingested it causes an infection, of the nature of an acute enteritis. The symptoms are nausea, vomiting, diarrhœa, weakness, fever, and prostration. The illness lasts from 3 to 5 days in mild cases, and about four weeks in severe cases.

Bacillus suisepticus.

Bacillus suisepticus, or bacillus of swine plague, so closely resembles that of chicken cholera, that at one time they were thought to be identical.

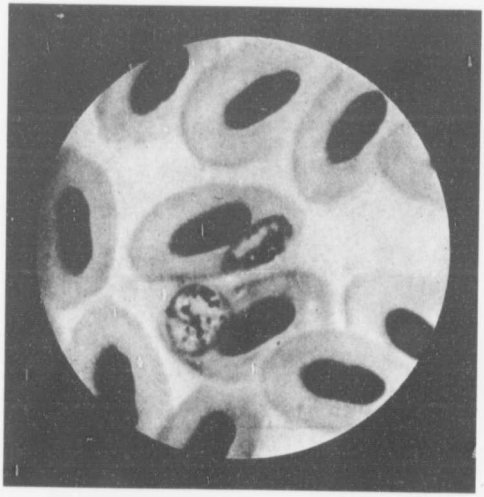
The pathogenesis of *Bacillus suisepticus*, while similar to that of *B. suipestifer*, presents some marked differences, especially in the duration of the disease, which is much shorter.

The course of the disease is usually rapid, a fatal result often occurring in one or two days. The symptoms are those of a hæmorrhagic septicæmia.

Bacillus choleræ gallinarum.

The bacillus, which is responsible for chicken cholera, was first observed by Perroncito (1878).

When the bacilli are introduced subcutaneously, a true septicæmia with hæmorrhagic exudates results. If, on the other hand, the disease is produced in the ordinary way by feeding, the bacilli are chiefly to be found in the intestine. The bacillus is pathogenic for rabbits, and use is made of it for their extermination.



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Hæmamœba relicta
(Proteosoma).

Bacillus typhi murium.

An epidemic among mice, in his laboratory (1889), enabled Loeffler to discover the bacillus of mouse septicæmia. It is pathogenic for mice of all kinds, destroying them, in from one to two days, when injected subcutaneously, and in 8 to 12 days, when fed upon material containing the bacillus.

Bacillus typhi murium multiplies rapidly, in the blood and lymph channels, and causes death from general septicæmia.

Following out Loeffler's suggestion, use has been made of the bacillus, in ridding fields and premises of mice. While field mice are successfully exterminated, in this way, the bacilli are not pathogenic for other animals, nor do they affect man in any way.

Bacillus psittacosis.

Psittacosis is an infectious disease of parrots and paroquets, communicable to man.

An extensive epidemic occurred in 1892, and Nocard found a pathogenic organism in the bone marrow of parrots which had died of this disease. More than 50 people were attacked.

Bacillus psittacosis is the cause of a specific infectious disease of parrots, resembling cholera, in its clinical characters, and *materies morbi*, which is transmissible to man. The symptoms, in infected parrots, are diarrhœa, ruffled feathers, refusal of food, etc.

Infection is easy, as the bird's feathers become soiled with discharges, crowded with Nocard's bacillus.

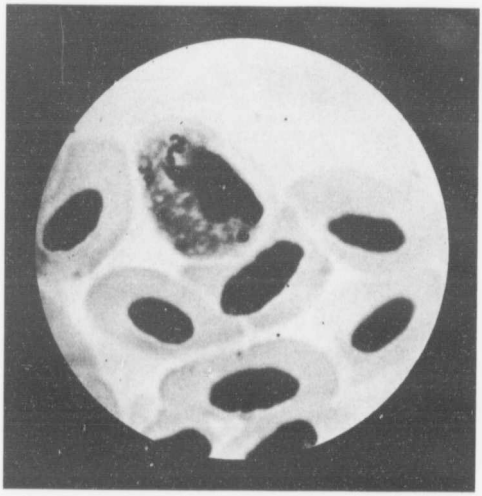
Infected individuals present the same symptoms, though in varying intensity. These are rigors, fever, headache, thirst, vomiting, delirium, followed by coma and death, in fatal cases. *Post mortem*, the bacillus has been obtained from the blood.

Prognosis is good in young people; unfavourable in adults.

Gilbert and Fournier believe that the disease is not so rare as one would suppose, being often mistaken for epidemic pneumonia. Dubief showed that the pneumonia was simply a complication of a disease, of an adynamic, typhoid type, with pronounced nervous, but no abdominal symptoms.

Bacillus ærogenes capsulatus.

Infection with *Bacillus ærogenes capsulatus* is being observed with some frequency. Bacteriological investigation shows the or-



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Hæmamœba relicta
(Proteosoma).

ganism to be of wide distribution, and apparently a frequent inhabitant of the air, soil, and intestinal tract.

Cases of gaseous phlegmon, in which the viscera, at autopsy, are found to be filled with gas bullæ, and the blood with gas bubbles, had been observed, but were looked upon as the result of putrefaction, or air embolism. E. Frænkel demonstrated the etiological relationship of *Bacillus phlegmones emphysematosæ*, to gaseous phlegmon.

Generally, the infection is mixed; the germs associated are the pyogenic, colon, typhoid, and putrefactive bacteria. In other cases, *B. ærogenes capsulatus* alone enters the organism, and produces the characteristic signs, with general infection and death.

Clinical and experimental evidence points to *B. ærogenes*, as the offending organism, in a very large proportion of the cases of gas production, in the tissues. Experimental inoculation, in animals, causes rapid development of gas in the blood vessels, and emphysema of the tissues and organs.

Puerperal infection, by the gas bacillus, may give rise to one or more of the following conditions:—

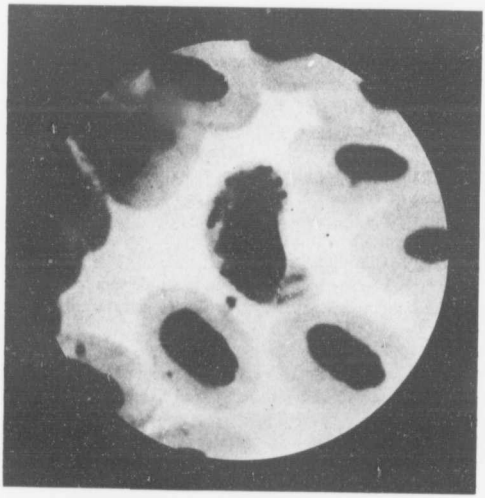
(1) Puerperal endometritis.
(2) Emphysema of uterine wall.
(3) Physometra.
(4) Emphysema of the fœtus.
(5) Gas sepsis.

All cases of gas sepsis have terminated fatally, in which the bacillus was isolated from the blood, during life.

Emphysematous gangrene results from infection, through wounds, or injuries, in any part of the body. Gas bacilli also obtain access, through the uterine cavity, urinary tract, gastro-intestinal canal, biliary apparatus, and respiratory tract. Ulcers of the stomach, intestine, or urinary tract, may be the portals of entry.

Cadaveric decomposition, accompanied by the production of gas in the body, and the formation of gas cysts in the viscera, may almost invariably be ascribed to the gas bacillus.

Post mortem, the blood contains bubbles of gas, and frothy blood exudes from the vessels. There is crepitation in organs and tissues.



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Hæmamœba relicta
(Proteosoma).

STAPHYLO-INFECTION.

Staphylococcus pyogenes is the organism, most commonly present in suppuration, being found in pure culture, in about 70 per cent.; the streptococcus, in 15 per cent.; the two organisms together, in 5 per cent.; and the remaining pyogenic bacteria, only occasionally.

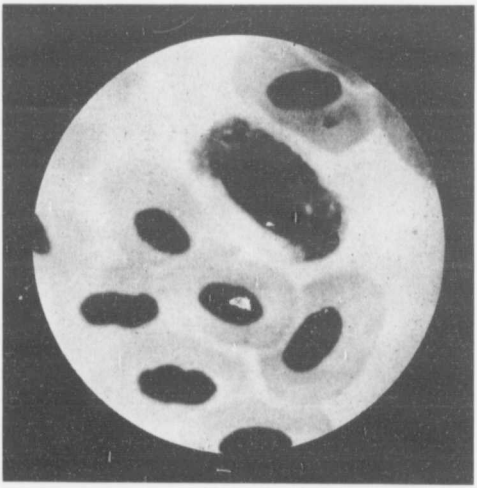
The points at which the organisms penetrate, in cutaneous infections, are the ducts of the sweat glands, the orifices of the sebaceous glands and hair follicles, and portions of the skin, where the protective epidermis has been scratched, or destroyed. After penetrating, by one or other of these paths, into the skin, they multiply either in the wall of the ducts of the sweat glands, and the adjacent part of the *rete mucosum*, or they penetrate into the external root-sheath, and into the *rete mucosum*, at the orifice of the hair follicles, or they develop at some part of the *rete mucosum*, which has been deprived of epidermis. The bacteria multiply rapidly at the seat of infection, gradually spreading in the wall of the ducts, until they reach the end of the sweat gland, or the sebaceous gland, or hair follicle.

There are marked differences in the pathogenic action of the streptococcus, and staphylococcus, in the tissues. The streptococcus is generally associated with erysipelatous, and phlegmonous processes, while the staphylococcus tends to cause more circumscribed suppurations.

In the determination of the morbid process, the number of the organisms inoculated, the anatomical arrangement of the part, and the vitality and absorptive power of the affected tissues, are most important factors. In the case of *Staphylococcus pyogenes aureus*, Watson Cheyne found that it was necessary to inject something like 1,000,000,000 into the muscles of rabbits, in order to cause a rapidly fatal result, while 250,000,000 produced a small circumscribed abscess. The same result was obtained with *Staphylococcus pyogenes albus*, only apparently fewer cocci were required.

Life duration of bacteria in the tissues.

An interesting instance of renewed virulence of staphylococcus, after a long period of latency, is given by Schnitzler. The patient had received an injury, resulting in a localised osteomyelitis of the tibia, which subsided, after discharge of pus and sequestra. The patient was attacked, 35 years later, by severe pain at the former seat



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Hæmamœba relicta
(Proteosoma).

of disease, attended by febrile disturbance. On chiseling through dense thickened bone, at the seat of disease, a closed cavity, the size of a walnut, containing granulations and pus, was found. In the granulations, *Staphylococcus pyogenes aureus* was present, in very virulent condition. Schnitzler points out, that the staphylococcus is capable of existing upon nutrient media, under unfavourable conditions, for a very long period, and argues that a cavity containing granulation tissue, well supplied with blood, such as was present in this case, offers a very favourable prospect, for the prolonged existence of micro-organisms. The case, in Schnitzler's opinion, shows that pyogenic cocci are capable of remaining latent, in the human body, for a great period of time, again becoming virulent, on some chance disturbance of the normal processes of metabolism.

Permeability of granulation tissue.

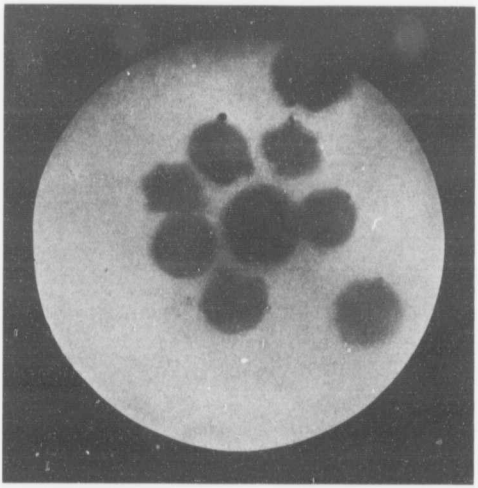
As a result of investigations, on the permeability of granulation tissue, for pathogenic micro-organisms, Jurgelunas arrived at the conclusion, that undamaged granulation tissue acts, in most cases, as a mechanical barrier, against the entrance of micro-organisms into the tissues, and the cells of this tissue forms also a second line of defence, owing to their phagocytic properties. Bacteria, taken from the granulation tissue of susceptible animals, show very slight structural changes, but those, recovered from the granulation tissue of immune animals, are profoundly altered.

Elimination of bacteria.

Infection of the blood by the staphylococcus, though traced to other sources, such as external wounds, otitis, etc., seems to have its most frequent origin in furuncles.

The localisation of secondary purulent deposits, in cases of staphylo-infection, is influenced by congestion, and vascular changes. The tendency of bacteria to be arrested, in the capillaries of the kidney, is indicated by their presence in the urine, and by the frequent occurrence of nephritis, as a complication of staphylo-infection.

A case of infection, reported by Tizzoni, affords some important information, on the means by which the organism endeavors to free itself from infective microbes. Although it is denied, by many pathologists, that bacteria can pass through healthy mem-



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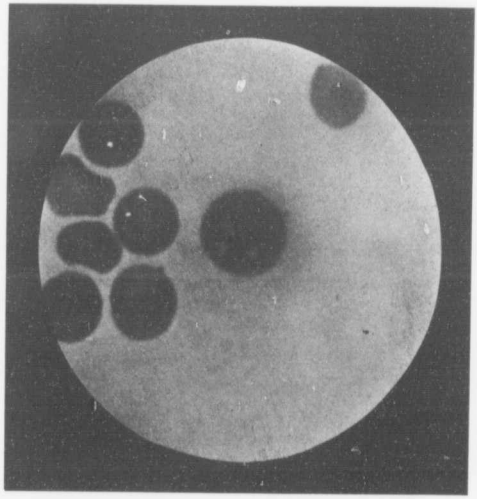
Piroplasma bigeminum.

branes, or be eliminated by healthy organs, it was clearly shown that in this case staphylococci could pass with the sweat into sudamina, and through the kidneys,—which, from the absence of albuminuria, were taken to be healthy,—into the bladder.

Passet and Longard found, in inoculated mice, that staphylococci passed into the conjunctival secretion, and Philipowicz and Maffucci frequently found anthrax bacilli, in the urine of infected animals.

Brunner was able to demonstrate bacteria in the urine, and also in the secretion, from the feet of animals inoculated with various pathogenic and non-pathogenic organisms, and subsequently treated with pilocarpin.

Pernice and Scagliosi record the results of an elaborate enquiry, into the excretion of bacteria by the organism. The main conclusions arrived at are—(1) *Staph. p. aureus, B. subtilis, B. pyocyaneus,* and *B. prodigiosus,* when injected into the body pass out in various ways. Almost always they are excreted with the bile and urine, but sometimes also through the different mucous membranes (of nose, mouth, trachea, stomach, vagina, etc.). They may further pass into the milk and semen, and into serous exudates. Transference of the hay bacillus from mother to fœtus has been observed by the authors. (2) The excretion of bacteria begins in from four to six hours after permeation of the organism, and continues until the animal dies, in the case of pathogenic bacteria. It is delayed for from twenty-four to forty-eight hours, when non-pathogenic bacteria are introduced. (3) *B. anthracis* and *B. pyocyaneus* retain their virulence when excreted. (4) The kidneys show changes in all cases in which the injected bacteria (whether pathogenic or not) appear in the urine. These consist chiefly in hyperæmia, blood extravasation, and degenerative states of the renal epithelium; they take place before the excretion of the organisms, for which they probably prepare the way. (5) Bacteria are found in the blood, in from four to six hours after subcutaneous inoculation. (6) Cultures are obtainable from various organs, before bacteria can be demonstrated in the blood. This is explicable on the supposition that many of the injected organisms are destroyed in the blood; those which escape settle in different organs, proliferate, and discharge fresh parasites into the blood, which has now lost its bactericidal property, and consequently permits their circulation.



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Piroplasma bigeminum.

STREPTOCOCCUS PYOGENES.

Of the many post-partum febrile disturbances, comprehended under the term puerperal fever, that of infection with the streptococcus, because of its frequency, and high mortality, is of vital importance.

In the majority of instances, puerperal fever means a wound infection of the genital canal, and ultimately of the whole system, with *Streptococcus pyogenes*. The type of infection, in which the streptococcus multiplies in the blood, and causes a rapidly fatal disease, is termed puerperal strepto-infection, or strepto-septicæmia.

The violent bruising, to which the parturient mucous tract is exposed, during labour, furnishes the primary infective focus. The primary infective focus may be situated in wounds of the perineum, vagina, cervix, and endometrium, may remain localised or may spread by continuity, or by metastatic infection. The bacteria enter through the smallest wound, and there seems to be no relation between the extent of the wounds received in parturition, and the severity of the infection.

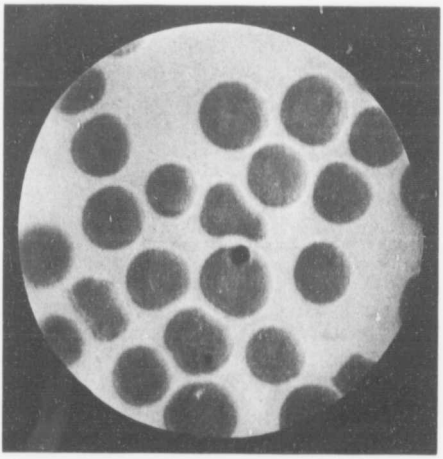
Sutured tears of the perineum,—when the suture includes but little more than the skin, while the rupture extends deep into the pelvic floor, forming a dead space in which the fluids stagnate,—are frequently the starting points of streptococcus invasion.

The majority of severe and fatal cases of puerperal infection, are due to streptococcus invasion of the endometrium, and placental site. The latter is the most favourable seat of infection, and from this the whole of the endometrium is invaded.

In some cases, the organisms cause few or no symptoms, remaining limited to the placental site, or surface of the decidua; in others, they penetrate deeply, and widely, along the blood vessels and lymphatics, and cause extensive thrombosis. Invasion of the uterine wall, by way of the lymph channels of the deeper layers of the mucosa (lymphatic type) appears to be more usual, than through the veins (thrombo-phlebitic type).

After penetrating between the muscular fasiculi of the uterine wall, the streptococci may enter the broad ligament, giving rise to diffuse cellulitis, or more frequently they invade the peritoneum, causing fatal peritonitis.

The rapidity of the invasion of the streptococcus varies according to its virulence. The variety of inflammation produced, whether purulent, serous, hæmorrhagic, or gangrenous, depends on (a) the



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Anaplasma marginale.

quantity, (b) the virulence, of the organism introduced, and (c) the resisting power of the individual.

The conditions of the genital canal are favourable to the development of streptococci, while the general disposition of the body, toward septic absorption, is increased during the parturient state.

By experiments on animals, Schimmelbusch and Bumm have shown that, after inoculation of the uterine mucosa, streptococci may penetrate 2 cm. in six hours, and can even earlier be detected in the blood.

When the infection is superficial, the uterine mucosa is covered with a layer of blood and fibrin, containing streptococci; the glandular epithelium is swollen and granular, and organisms are observed in the gland spaces. When the infection remains purely superficial, no organisms are found, in the deeper layers of the mucosa, which shows only round cell infiltration of the stroma.

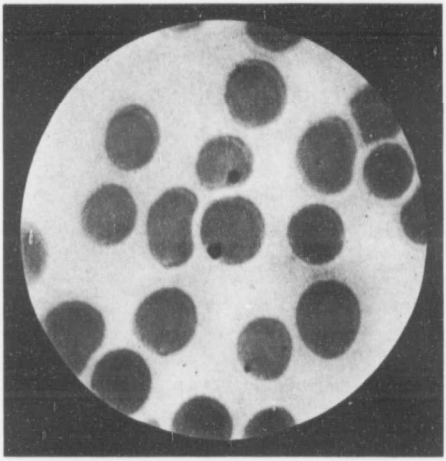
The infection may remain local for a short time, possibly only a few hours; at the time of the initial rigor, the organisms have probably penetrated the mucosa, and the uterine wall, and their complete removal by local measures is impossible.

If the organisms are very virulent, there may be little evidence of local reaction, the uterine mucosa being quite smooth, but often soft and swollen.

The streptococci, when accompanied by local reaction, can be recognised invading the whole thickness of the mucosa, and also occupying the small blood vessels. The connective tissue stroma shows abundant infiltration, with round cells, and the organism is present in the cellular spaces. The severer cases are attended with extensive superficial sloughing of the endometrium; ulceration sometimes occurs, with occasional deposit of that greyish pseudo-membranous material, which at one time suggested the relation of the process to diphtheria.

In the thrombo-phlebitic type, the infection follows the venous system, septic thrombosis extending from the uterine sinuses throughout the whole length of an ovarian vein, or, occupying the uterine, the internal, and external, iliac veins, may even extend to the lower part of the inferior vena cava. More frequently, the vessels are filled with purulent material.

In those cases which come to autopsy, it is found that the infection has extended, not in one only, but in several directions. Of the thrombo-phlebitic type, a proportion is connected with metastases in the organs.



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Anaplasma marginale.

Bacteriological examination.

The uterine secretion shows on coverslip preparations, and on culture, *Streptococcus pyogenes*. After the blood stream is invaded, streptococci are shown on culture, and may also be demonstrated on coverslip preparations.

The mere recognition of the streptococcus gives no information as to the virulence of that particular germ.

Symptomatology.

Symptoms of strepto-infection set in, within a few hours of labour, to the second or third week. In a pure strepto-infection, the uterine discharge may be suppressed; or, it may be profuse and sanguineous, but is never offensive. In mixed infection with *Bacillus coli*, or when putrefactive bacteria are present, the secretion is often very offensive.

Treatment.

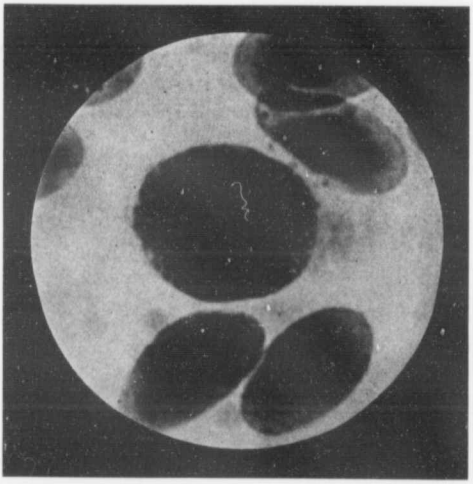
Since the days of Hippocrates, it has been known that portions of the placenta, or membranes, or clots retained within the uterus, will cause fever. Exploration of the uterus with the object of removing any contents such as clots, placental tissue, or decidua, is certainly indicated; but, at this point, opinion differs, as to the wisest course to pursue.

When the organisms have penetrated the mucosa, and uterine wall, their complete removal by local measures is impossible. The uterine douche is of very little value, in these cases. Bumm has shown that antiseptics, used in this way, have very little penetrating power. Kronig found that streptococci were just as abundant, and virulent, in the uterus, a few hours after a uterine douche, as before its use.

Early recognition of infection, and prompt treatment, will frequently avert grave infection. Find and remove, if possible, the focus of infection; to accomplish this, the removal of sutures, and cleansing of dead spaces, may be necessary.

Pinard advises that the curette should never be used, in the puerperal uterus, before the third day, owing to the risk of air embolism from opening up of venous sinuses.

The use of the curette, in puerperal infection, is mentioned only to be condemned; the curette does a vast amount of harm, in all cases



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Leucocytozoon.

of true septicæmia, by opening up new areas of absorption, and aiding in the dissemination, and distribution, of the infectious material. Owing to the hæmorrhage, the danger of perforation, and the opening up of new channels, by which the infection may spread, curettement of the puerperal uterus is a serious procedure.

As we have no clinical means of ascertaining the depth, or degree, of the septic invasion, local treatment should be restricted to swabbing out the uterus, with some non-toxic antiseptic.

Corroding antiseptics should never be used within the uterine cavity.

If there is evidence of infection, all sutures should be removed, and the vagina made aseptic. If the cervix is covered with grey exudation, and the uterus is bulky and tender, it is almost certain that the uterus is infected. The first rigor means, that the infection has spread to the pelvic veins.

The diagnosis and treatment is based on the bacteriological examination of the lochia. The lochia may be apparently normal, and yet contain streptococci.

To so conduct labour, as to lessen the amount of injury done, and thereby diminish the channels of infection, is of prime importance.

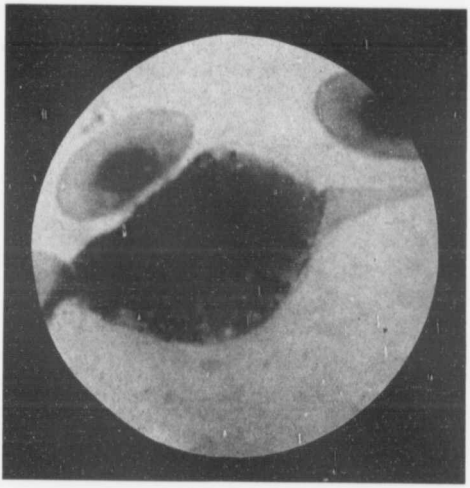
Puerperal strepto-infection is mostly a preventable disease, of high mortality, and spread by want of cleanliness.

Prognosis.

The uterus may be the seat of a septic endometritis, which remains superficial, the further progress of the infection being checked by the cellular protecting zone, developed in the deeper layers of the endometrium. Prognosis depends much upon the degree of the infection, and complications, of which the most essentially fatal is perforation of the uterine wall, in puerperal gangrene, due to streptococcus. The chronic form of strepto-infection is milder; most cases of recovery belong to this type.

Pharyngeal strepto-infection.

The tonsils are particularly likely to be the primary seat of infection, by virtue of the peculiar arrangement of their epithelial covering. Stœhr has drawn attention to the fact, that their epithelial covering shows gaps, large enough to allow the passage of leucocytes.



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Leucocytozoon.

Suppurative foci, in the tonsils, are a frequent source of general infection; they may be present in tonsils of normal appearance.

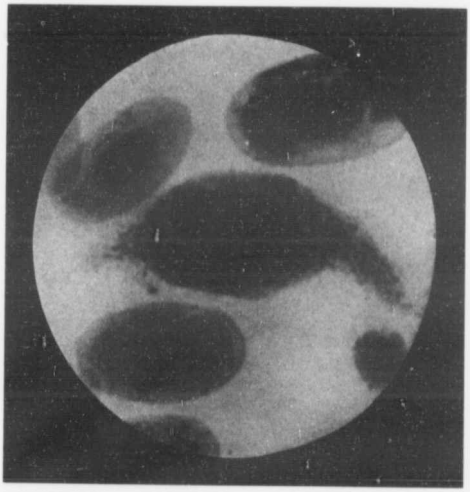
Pharyngeal strepto-infections are characterised by a violent exudation, into the tissues affected; serous, suppurative, and gangrenous inflammations represent various degrees of intensity of the infective process, caused by this organism.

The infection may remain localised, or may spread with incredible rapidity along contiguous mucous membranes, resulting in broncho-pneumonia, or along the blood paths causing endocarditis, pericarditis, pleuritis, meningitis, nephritis, and peritonitis. At the primary seat of infection, in the pharynx, a rapid œdematous swelling occurs; a pseudo-membranous exudation appears on the tonsils, or the crypts are filled with pus. An exudation on the tonsils, followed by small abscesses in the parenchyma, indicates the line of infection.

Hutinel and Claisse have published observations, on the nature of an acute strepto-infection, in young infants, which they believe to be due to rapid infection of the bronchial mucous membrane, by micro-organisms, derived from lesions in or about the mouth. The cases occur frequently, as complications of measles, but sometimes arise independently. They are particularly likely to arise in hospital wards, when an extensive epidemic of measles has led to overcrowding. The streptococcus, obtained from the blood, was in an extremely virulent state.

Goldscheider remarks, that the mode of action, of the streptococcus, depends on the accompanying conditions of invasion. It is a question whether severe streptococcus infections, as in puerperal strepto-infection, or in diphtheritic strepto-infection, are due to the invasion of a specially virulent streptococcus, or whether less harmful micro-organisms are able to develop more virulent properties. The experiments of Goldscheider and Brasch lead to the conclusion, that biological conditions of the animal body are of much importance in regard to the character of the disease produced.

The same micro-organism that produces erysipelas, in one individual, may give rise to a different type of infection, in another. Clinical observation shows that, where necrotic tissue is present, there is a special tendency to streptococcus infection. Strepto-infection is one of the principal causes of death, in those general diseases, which manifest themselves locally in the throat, such as diphtheria, scarlet fever, variola, etc. Experiments have shown, that



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Leucocytozoon.

the increase of virulence, of the streptococcus, is due to its association with other micro-organisms, especially the saprophytes.

Cutaneous strepto-infection.

Every wound, however trivial, exposes the recipient to the danger of infection.

The succession of changes, which take place in a living tissue, the result of infection by pathogenic micro-organisms, is the response—local and general—to the microbic invasion. Emigration of leucocytes which may be seen traveling along the connective tissue spaces, within a few minutes, and active proliferation of fixed tissue cells, which takes place around the seat of infection, within a few hours, are the barriers set up by the organism against microbic invasion. The bacteria pass from the centre of infection, into the surrounding tissues, and thence into the lymphatics, and general circulation.

That the streptococcus exists on the skin, and healthy mucous membranes, as a non-virulent saprophyte, is generally recognised. When the resistance of the tissues is diminished, the streptococcus becomes a most virulent organism.

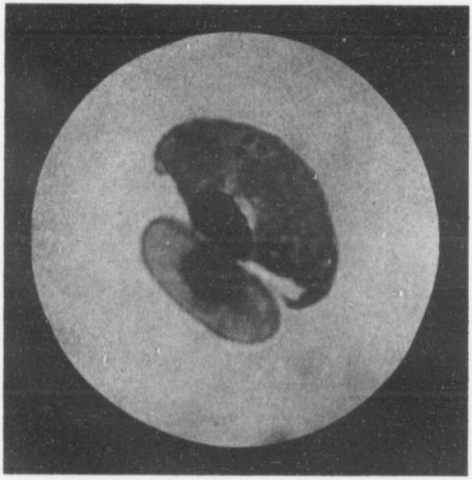
The pathogenic action of this organism commences at the surface, and spreads along the lymphatics, and is especially associated with phlegmonous, and erysipelatous, processes, where the pus occurs in the form of infiltrations of tissue, accompanied by death of portions of tissue. The fact that the same organism, that produces erysipelas in one individual, may give rise to a different type of infection in another, is not due to differences in biological characters, but simply to differences in the conditions under which they act.

No method, so far proposed, satisfactorily determines the virulence of a strain, inducing a given infection. The virulence of a particular strain, in an animal, is no criterion as to virulence in man; animal experimentation is therefore of no practical assistance.

It is quite probable, that bacteria reach the blood stream, in all infections. It would appear, that their pathogenicity depends upon the number present, and the resistance of the individual.

The streptococcus has been found in the blood, without apparently producing any pathogenic effect.

Bacteria disappear from the blood with remarkable rapidity; they are destroyed by phagocytes, or excreted by the various excre-



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Leucocytozoon.

tory glands, particularly the kidneys. The excretion of bacteria, in an active condition, by the kidneys, has been established by clinical and experimental observation.

The cases of descending infections, of the urinary tract, are explained on the supposition, that bacteria had entered the blood, were excreted in an active state, and found in the urinary tract suitable conditions, in which to act.

The experimental production of suppuration, by means of the injection of irritating chemical substances, and pyogenic bacteria, shows how the former place the tissues in a condition, which diminishes their resisting power, against the action of the bacteria. This fact contra-indicates the use of irritating, and corroding chemical substances, in suppurative affections. The rapid healing of a sluggish wound, or ulcer, when the use of strong antiseptics is replaced by normal salt solution, is a familiar experience in surgical practice. The use of antiseptics, strong enough to destroy bacteria, will also destroy granulation tissue, which acts as a barrier against infection, and creates just such a condition, as favours the development of pathogenic bacteria in the tissues.

Other chemical substances, which aid in enabling the bacteria to gain a foothold, are the products of the organisms themselves. Infection occurs, more certainly, and with less infective material, if there has been preliminary action on the tissues of the toxins of the bacteria, of chemical substances, or even of the toxins of other bacteria.

Streptococcus pyogenes is a most virulent organism, and apparently has the power of entering the tissues, spreading insidiously therein, and later setting up a violent reaction.

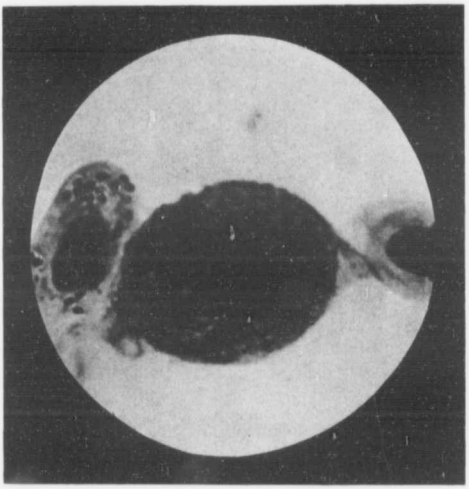
In the treatment of strepto-infection, the future belongs to serum-therapy.

Bacillus proteus vulgaris.

While, in a large number of cases, *Bacillus proteus vulgaris* has been found associated with other organisms, in very few cases has it been found in pure culture, and less frequently in the blood.

In health, the bactericidal power of the blood is sufficient to destroy the organism, if it should gain access to it, and it becomes pathogenic only, in conditions of lowered vitality.

Foa and Bonome have described a case of hæmorrhagic enteritis, with peritonitis and venous thrombosis, in which they found a very virulent culture of *B. proteus vulgaris*.



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Leucocytozoon and Halteridium.

Crogius and Schnitzler found a universal infection with the organism following proteus cystitis.

Pakes reports a case of thrombosis, of right and left iliac veins, associated with tuberculous enteritis, and phthisis. At the necropsy, *B. proteus vulgaris* was found in the thrombus.

Bacillus pyocyaneus.

Bacillus pyocyaneus has been found in pure culture, in general hæmic infections, but ordinarily the organism is harmless for human beings.

PYLEPHLEBITIS.

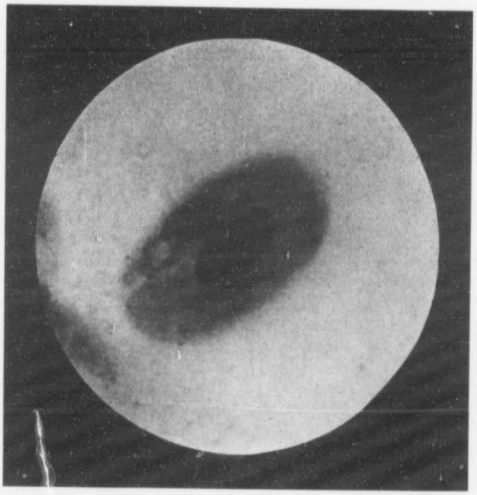
Pylephlebitis, or portal pyæmia, is a complication particularly rare but essentially formidable.

The main factor, in the production of pylephlebitis, is a septic focus in the portal area. Considering the varied nature of the organisms inhabiting the intestinal tract, and its liability to ulceration, it is a matter of surprise that portal pyæmia is not of more frequent occurrence. Statistics show that the great source of portal pyæmia is suppuration, in the neighborhood of the cæcum and its appendix. The sequence of events in such cases is about as follows:—

From a collection of pus around the appendix, thrombosed radicles of the mesenteric vein lead along the mesentery, and then into the trunk of the portal vein. Detachments of the venous thrombus are carried up to the capillaries of the liver, where they set up other septic foci. The embolus may be carried from the primary focus to the capillaries of the liver, producing portal pyæmia without phlebitis. The small pyæmic abscesses, with which the liver is riddled, are seen to be merely dilatations of the portal vein.

Thrombosis is the connecting link between suppuration and pyæmia, and pylethrombosis and pylephlebitis are incidents in the life of the septic process.

The septic process may lead only to portal thrombosis. Thus, from a suppurative focus, the mesenteric vein and its radicles, and the portal vein and its radicles, may all be occluded by thrombus, without suppurative pylephlebitis. The condition is one of portal



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Hæmogregarine infection of snake
(Naja nigricollis).

occlusion, in which the essential feature is the occlusion of the vein. A limited thrombosis of the venous radicles will produce symptoms of a comparatively mild and indefinite character, as compared with occlusion of the main venous trunks.

While typhoid fever is characterised by deep multiple ulcers of the small intestine, in which thrombosis of the portal radicles occurs, it rarely leads to portal pyæmia. Bryant, in a search through Guy's Hospital records, from 1828 to 1901, could not find a single case of pylephlebitis in typhoid fever. Dopper met with ten cases of liver abscess, out of 927 necropsies, on patients dying of enteric fever at Munich.

It is also rare for pyogenic organisms to invade the portal vein, from surfaces denuded by dysenteric ulceration. In explanation of this fact, Councilman and Lafleur have advanced the suggestion, that the *Amœba coli* does not usually reach the liver by the portal vein, but through the peritoneal cavity.

Of 64 cases of pylephlebitis, cited by Langdon Browne, the cause was attributed to appendicitis in 27. The stomach and intestines were the focus in six cases; gall stones were responsible in four instances.

It is stated that the operation for hæmorrhoids is followed by suppurative pylephlebitis, once in every 500 times.

Bristowe pointed out, in 1858, that abscess of the liver may arise from infection, by one of three routes—

(a) By the hepatic artery—general pyæmia.
(b) By the portal vein—portal pyæmia.
(c) In consequence of infection of the bile ducts.

Diagnosis.

Recognition of the condition remains exceptional. Von Schüppel lays stress on the following points in diagnosis:—

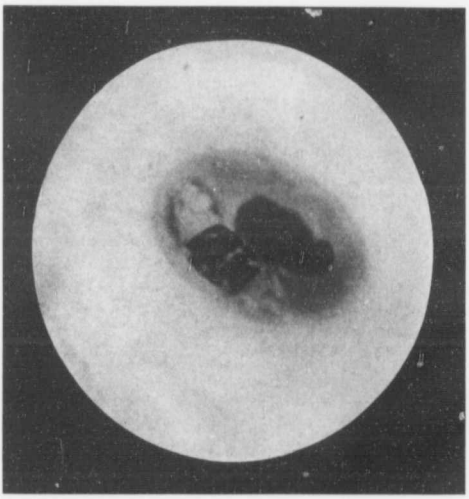
1. The presence of an affection, which we know will set up this disease, especially when accompanied by a chronic peritonitis.

2. Pain in the epigastrium, or right hypochondrium.

3. Violent rigors at irregular intervals, followed by a hot stage, and a remittent rather than an intermittent temperature.

4. Recent uniform painful enlargement of the liver; enlargement is not constant, but tenderness is.

5. Considerable enlargement of the spleen, especially when we can follow its development.



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Hæmogregarine infection of snake
(Naja nigricollis).

6. Icteric tinge of the skin, and urine; biliary diarrhœa.

7. Rapid emaciation, and profound loss of power.

8. Occasional development of diffuse peritonitis and typhoid symptoms.

9. Leucocytosis of 17,500 to 25,000 per c. mm.

A. E. Maylard (Glasgow) summarises the clinical signs of thrombosis as follows:—

1. Intra-abdominal pain is invariably present, sometimes commencing acutely, at other times gradually, and with no more discomfort than is manifested by a sense of uneasiness. In not a few instances, the pain has been colicky in character, sometimes located in the region of the umbilicus, at other times low down in the abdomen.

2. The passage of loose stools, sometimes containing blood. This symptom is an uncertain one, and seems to depend upon the extent of bowel involved, and the degree of its congestion. When present, it is a valuable diagnostic sign.

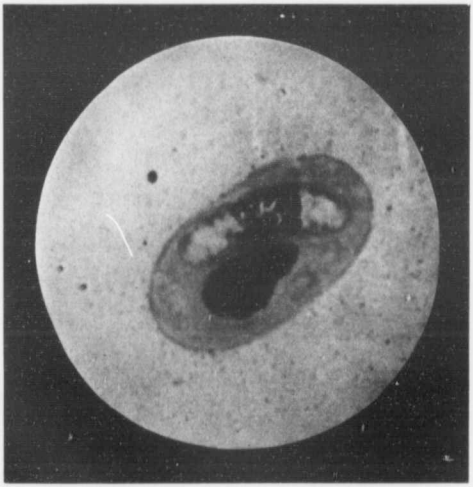
3. Vomiting is also a very inconstant symptom, and seems, in like manner, to be dependent upon the degree and extent to which the bowel is thrown out of action, by its impaired vascular supply. It is the presence of this symptom, which so frequently causes these cases to be taken as instances of acute intestinal obstruction, and which to a certain extent they are, although a wrong cause is usually ascribed to them.

4. The general condition of the abdomen is as a rule negative; there is neither rigidity, tenderness, nor distension, although, towards the close of the case, the latter may become more or less manifest.

5. The pulse, which has sometimes remained more or less normal in power and speed, is in most cases weakened and increased in rapidity.

6. The temperature presents no certain character, although in the severe cases it is usually reduced.

7. A symptom, which has been noted in not a few cases, is great excitability of the nervous system. In two cases it was present to a remarkable extent, and suggested that the patients were hysterical.



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Hæmogregarine infection of snake
(Naja nigricollis).

PNEUMOCOCCUS.

The *Pneumococcus* was discovered by Sternberg (1880), who obtained it by inoculating rabbits, with saliva, from a healthy individual, some years before its significance and life history, in connection with acute lobar pneumonia, were first demonstrated by Frænkel.

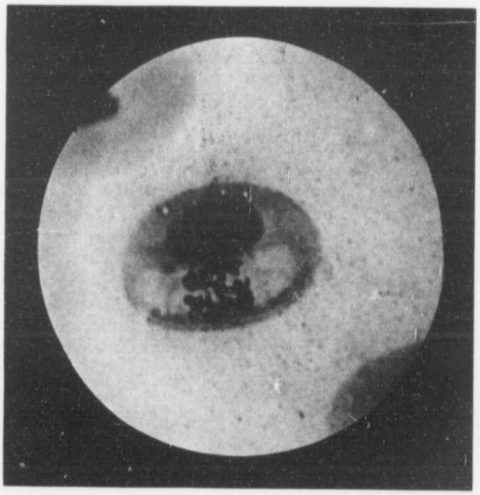
It appears that the *Pneumococcus* is frequently found in the respiratory tract of healthy individuals, and only exerts its pathogenic action in favourable conditions. Netter found the *Pneumococcus* in the saliva of 15 per cent. of healthy persons, Sternberg, in 20 per cent., Washbourne and Eyre, in 30 per cent. of hospital patients, suffering from other diseases. It has been found in the nose of healthy individuals, by Netter and Kurth, and by Gasperini, in 8 out of 10 healthy conjunctival sacs. Duerck examined the lungs of 13 children, who had died from other diseases; he found pneumococci 12 times, in most cases mixed with other bacteria; in the thirteenth case, other bacteria were found, but not the *Pneumococcus*. He also examined the lungs of dogs, and horses, and, out of 15 cases, he found pathogenic bacteria, only one being sterile; among these bacteria were pneumococci.

It is generally admitted that the *Pneumococcus* gains entrance to the organism, in all but exceptional cases, by the respiratory tract, and, that some tissue change is necessary, to determine the characteristic pathological activity.

Mme. N. Schultz, in a series of experiments, introduced the diplococcus into the jugular vein of rabbits, which are well known to be highly susceptible to this infection. Out of 14 animals thus inoculated, pneumonia resulted in 8, and microscopical examination showed the usual exudation of fibrin, hyperæmia, and leucocytosis, and the presence of diplococci in large numbers. The experiments show, that no antecedent alteration in the lungs is essential to the incidence of pneumonia, but that the disease may result from infection by the pneumococci, through the blood stream, these organisms finding here the most favourable site, for the multiplication, and for the development, of an active virulence.

That the *Pneumococcus* may actually enter through the lungs, and produce metastatic lesions, without leaving behind any trace of inflammation in the lung itself, has been established by animal experiments.

Presumably, the habitat of the *Pneumococcus* is the naso-



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Hæmogregarine infection of snake
(Naja nigricollis).

pharynx, and its vicinity, in healthy people. The life of the diplococcus, outside of the body of animals, is apparently only maintained with a struggle. That an organism of such virulence, as the *Pneumococcus* often proves to be, can live a non-pathogenic and innocent life, as a parasite, in healthy people, finds a parallel in the presence of the streptococcus, as a saprophyte, on the skin and mucous membranes.

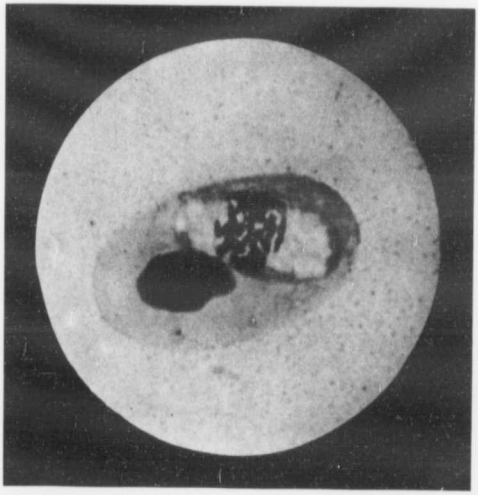
Tonsillar infection.

The two chief lines of defence, against the entrance of bacteria and particles, into the lungs, are the nose and larynx. The mucus, over the turbinate bones, retains an enormous amount of foreign matter.

The great importance of the tonsil, as a primary channel of infection, is again exemplified, in connection with *Pneumococcus* infection.

Darieu (Lyon) states that 3.7 per cent., of cases of acute tonsillitis, are due to the *Pneumococcus*. In the uncomplicated condition, this form of tonsillitis occurs in two forms, the erythematous, and the pseudo-membranous. The former usually sets in with a severe rigor, similar to that of pneumonia, with rapid elevation of temperature. The throat becomes painful; red, swollen, and yellow inspissated spots appear. Usually the condition subsides in 3 or 4 days, by crisis. The striking feature is the intensity of the febrile phenomena, which are out of proportion to the throat lesion. Darieu states, that the pseudo-membranous form begins in the same manner, and the general symptoms are similar. The difference consists in the presence of false membrane, closely resembling that of diphtheria. Both forms of infection terminate by sudden crisis, and rapid convalescence. The duration of the pseudo-membranous form is somewhat longer than the erythematous, extending from 5 to 10 days. Bacteriological examination alone renders diagnosis possible. Darieu points out the extreme importance of recognising such cases, as, in the event of their being mistaken for diphtheria, and brought in contact with patients suffering from the latter disease, diphtherial infection may be grafted on the pneumococcus infection.

Foulerton (London) reports a case, illustrating the possible effects of pneumococcus infection in the tonsil. The stomach was covered with a membrane, intimately attached to the under-



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Hæmogregarine infection of snake
(Naja nigricollis).

lying mucous membrane, giving the impression of poisoning by mineral acid. The *Pneumococcus* was obtained from culture tubes, inoculated from blood of femoral vein, from the mulberry spots on the face, from hæmorrhagic areas in the lung, and from the membrane in the stomach.

In a similar case, Dieulafoy (Paris) obtained the *Pneumococcus* from the lung, pericardium, peritoneum, and from small gastric ulcers, which implicated the whole thickness of the mucous membrane, down to the *muscularis mucosæ*, due to a rapid and localised necrosis of the areas affected.

Otitis media, which is not infrequently caused by this organism, results from the spreading of the pharyngeal infection along the eustachian tube.

Pulmonary infection.

The invasion of the lung tissue, and the multiplication therein of the *Pneumococcus*, is the cause of the anatomical lesions, in most cases of lobar pneumonia, and in about 67 per cent. of lobular or broncho-pneumonia. When invading the pleura, the *Pneumococcus* produces the same definite and fairly constant set of physical phenomena, as if the lung itself were involved.

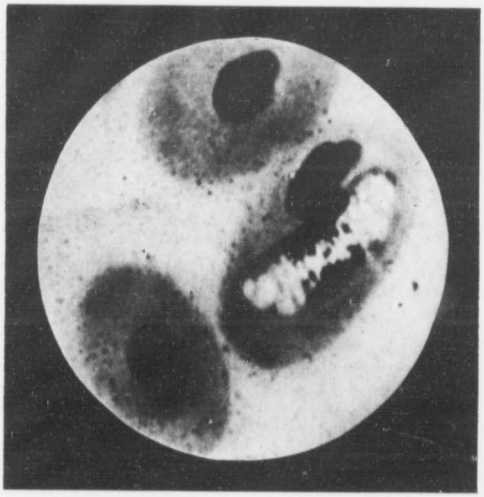
The many particles, both living and dead, present in the respired air, are entangled in the mucus, chiefly of the upper part of the respiratory tract, and are conveyed upwards by the ciliated epithelium. So effective is the filtering of the inspired air, that Tindall found the latter part of the expired air optically pure.

Straus counted the number of bacteria, in inspired and expired air, and found that in one experiment the inspired air contained 20,700 bacteria in the cubic metre, while the expired air only contained forty.

In spite of these provisions of nature, some particles and bacteria reach the alveoli, and their destination has an important bearing upon the question of infection through the lungs.

According to the experiments of Washbourn and Pembrey, it is the easiest matter for particles, which reach the alveoli of the lungs, to pass into its parenchyma, and thence to pass into the bronchial glands, there being no defence against the invasion of the lungs, when the particles have once reached the alveoli.

As a result of the experiments of Arnold, it has been definitely established that, after prolonged inhalation of air heavily laden



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Hæmogregarine infection of snake
(Naja nigricollis).

with fine particles, the latter are found in the peribronchial and perivascular lymphatics, in the adenoid tissue in connection with these lymphatics, and in the bronchial glands. The points in dispute are, the exact way in which the particles enter, and how far the mechanism of the lung facilitates or hinders the entrance of particles, from the alveoli, or tubes, into the lung. That no absorption takes place, through the trachea, or bronchi, is strongly supported.

The particles found in the lung, after inhalation, whether in the alveoli, or in the lymph spaces, and lymph vessels, are partly free, and partly enclosed in cells. Tchistovitch considers that these cells are derived from wandering cells, the smaller being *microphages* and the larger *macrophages*. One of the functions of these carrier cells is, to pick up fine particles from the alveoli, and to carry them along the bronchi, and trachea, to be extruded through the upper air passages.

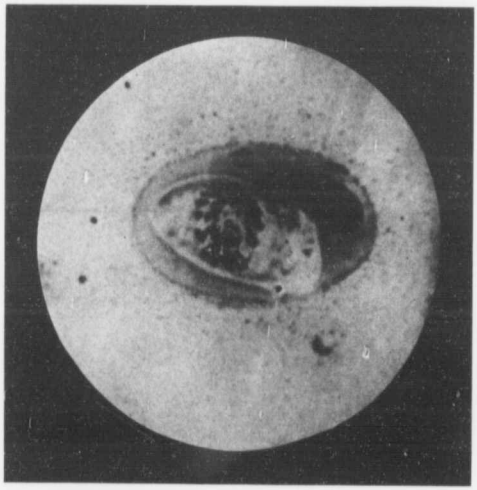
After particles have penetrated into the tissue of the lung, they are taken up by phagocytes. In the peribronchial and perivascular lymphatics, according to Arnold, the particles are chiefly free, while, in the peribronchial and perivascular lymphoid nodules, they are all enclosed in cells.

Tchistovitch states that, in his experiments, there was never any evidence of absorption by the alveolar walls. The particles, however, are taken up after a few hours, both in the alveoli, and in the lymph spaces, by phagocytes.

Grawitz, by blowing fine particles of dust into the trachea of rabbits, found isolated particles in the costal pleura, after twenty-four hours.

Baduel (Florence) found the diplococcus in the blood of 55 out of 57 cases of pneumonia, and that it was most virulent, in the acute stage of the disease. Its presence in the blood is not to be considered particularly dangerous, but it explains the localisations, wherever the bacterium may find a suitable nidus. It may find a suitable medium in the blood itself, and cause a pneumococcic septicæmia, of unfavourable prognosis.

Memmi gives a summary of results, derived from a study of 80 cases, which gave a positive result in 25 cases. Of the 56 cases which recovered, only six gave evidence of pneumococcæmia, whereas in the 24 fatal cases, the *Pneumococcus* was found in the blood, in 19. This corresponds with the generality of observations as showing that, *cæteris paribus*, the presence of pneumococcæmia



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Hæmogregarine infection of snake
(Naja nigricollis).

is a bad sign, but is not by any means necessarily fatal. In two cases, pneumococci were found in the blood, as early as the first day of the illness. A temporary and scarce pneumococcæmia is not reckoned, by Memmi, as a true pneumococcæmia; in true pneumococcæmia, the diplococci are very abundant, and easy to find by the ordinary methods. Memmi never found pneumococci in the blood, during the period of resolution, or in convalescence.

A number of observations have been made on the virulence of pneumococci, at different stages of pneumonia. Patella removed pneumococci daily, from the blood of the lung, and found a diminution in virulence; Banti made similar observations. Welch and Frænkel found the diplococci most virulent, at an early stage.

It would appear that there is a diminution of pneumococci, up to the crisis, which marks some critical event in the conflict, between the organism and the bacteria.

Endocardial infection.

Pneumonic endocarditis is by no means rare, as a complication of pneumonia, occurring in 16 per cent. of cases, reported by several observers.

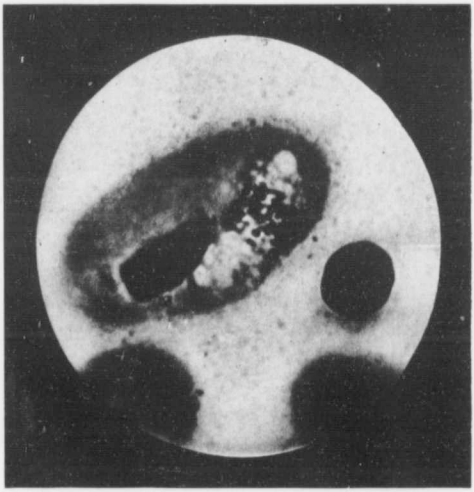
Netter (1886) demonstrated the possibility of a pneumonic pericarditis, without declared pneumonia. Pneumococcic pericarditis may occur as a primary manifestation; as a rule, it is secondary to pneumonia, by contagion through the pulmonary lymphatics.

Pneumonic endocarditis occurs in the later, rather than in the early, stage of the disease. The endocardial lesion is the localisation of a general, microbic invasion; it differs from that produced by the pyogenic bacteria, in the absence of infarcts, and metastatic abscesses.

As a complication of pneumonia, pneumococcic endocarditis is found in about 1 per cent. of all cases, and in 5 per cent. of fatal cases. It may develop before, during, or after, pulmonary involvement, and may be present, without there being at any time involvement of the lungs.

Arthritic infection.

The extremely grave nature of pneumococcic arthritis is indicated by the high mortality, which attends these cases. It is due to the fact that the arthritis is merely a local manifestation of a profound septicæmia.



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Hæmogregarine infection of snake
(Naja nigricollis).

Puerperal infection.

Primary infection of the puerperal uterus is a rare event. However, it occurs sufficiently often, to emphasize both the futility of the administration of anti-streptococcus serum, in all puerperal septicæmias, and the need of the most careful bacteriological examination of every case of puerperal fever, at its inception.

Peritoneal infection.

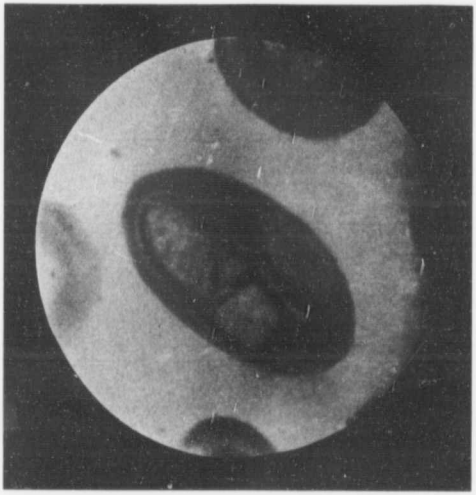
Barling, from a study of 28 cases of pneumococcal peritonitis, in children, recognises three clinical types, namely: (1) Very acute cases, with marked abdominal features from the outset, but with no other pneumococcal lesion, either in the lungs, or elsewhere; (2) cases which, simultaneously with the peritonitis, develop a pneumonia; and (3) cases, in which the septicæmia is more chronic in type, in which, some time previously, a pneumonia has been present, followed by general ill health and empyema, and finally peritoneal infection.

Pneumococcal peritonitis, in children, is from the outset widespread and diffuse; the infection of the peritoneal cavity is a septicæmic manifestation, rather than an invasion through any particular route, such as the Fallopian tubes, or the gastro-intestinal tract.

GONOCOCCUS.

From the date of its discovery by Neisser (1879), until quite recently, the *Gonococcus* had the reputation of being the only organism capable of penetrating healthy mucous membrane. It was formerly supposed that gonococci only invaded columnar epithelium, and did not penetrate deeper than the submucous layer. It is now known that they may invade squamous epithelium, and connective tissue, and even penetrate between the bundles of muscular fibres.

The *Gonococcus* rapidly invades the tissues, and spreads to the adjoining mucous membranes, either by direct cellular infection, or by means of the lymphatics. It has considerable powers of penetration, whereby it enters the vascular walls, and after producing



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Drepanidium magnum.
Hæmogregarine infection of frog
(Bufo regularis).

arteritis, phlebitis and lymphangitis, is disseminated through the circulation with metastases to the heart, pleura, joints, tendon sheaths, peritoneum, Fallopian tubes, uterus, iris, etc.

The local effects upon the mucous membrane may be the starting point of a grave septicæmia, with all its possible complications. Unlike other organisms, elsewhere referred to, no general infection by the *Gonococcus* has been reported, in which there was not present, at some time, specific inflammation at the point of inoculation. Local inflammatory and suppurative reaction, in the mucous membrane, precedes secondary lesions.

Of the metastases, arthritis is the first, in the order of frequency; it is present in 2 per cent. of the cases, and may occur a long time after the primary infection. Gonorrhœal arthritis is as liable to follow a mild attack, as a severe one. One attack predisposes to another, if there is a fresh infection of the urethra.

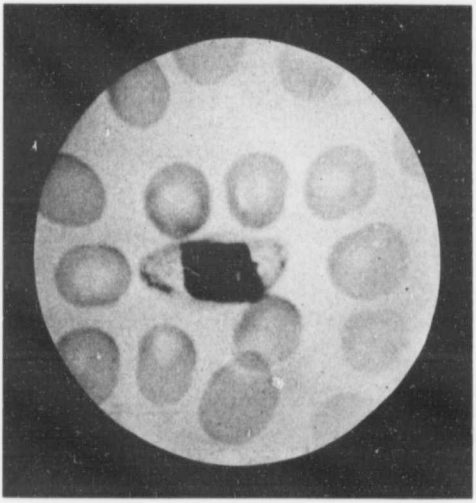
The metastases to the joints occur in the following order of frequency,—knees, heel and plantar fascia, ankles, hip, small joints of the feet, elbows, shoulders, wrists, and then the small joints of the hands.

Cases of blood infection, by the *Gonococcus*, become more numerous with the more general adoption of blood culture in diagnosis. The blood, peritoneum, endocardium, pleura, and joints, have been reached in a remarkably short period from the time of the patient's first contact with the infecting discharge, but, as a rule, the process takes weeks or months.

The virus of this disorder, once it has reached the tissues, may give rise to a series of pathological conditions, which equal in importance any other class of affections, with which we have to deal.

Observations have shown, that a large number of women, who are discharged as (clinically) cured, still carry virulent gonococci in their genito-urinary tracts, and so serve to spread the infection. The old view that gonorrhœa might be acquired from a woman, showing no clinical signs of the disease, still holds good. The frequency of serious sequelæ is, as Neisser has pointed out, largely due to the long persistence of its infectiousness, even in spite of apparently effectual treatment and cure, and to the fact that it so often occurs in women, without giving rise to marked or noticeable symptoms. Sænger states that, in his experience of women infected with gonorrhœa, 50 per cent. develop serious complications. Schültz puts the proportion at 33.3 per cent.

The frequency of gonorrhœal vaginitis has been shown to be



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Hæmogregarina balfouri.
Hæmogregarine infection of jerboa
(Jaculus gordoni).

minimal; in 483 cases of gonorrhœa, examined by Steinschneider, the vaginal form was present, as a primary affection, in 7 only.

The seats of election in the female are in order: the urethra, which is affected in 75 to 90 per cent., the cervix, which suffers in 40 to 50 per cent., and the Bartholin's glands, which are involved in 15 per cent.

The vitality of the *Gonococcus* in the tissues, and the obstinacy of the local infection, are well known. The tissues which it attacks are widely spread. It has been found in the urethra of both sexes, in the vagina, and cervical secretion, in the body of the uterus, in the pus of pyosalpynx, in the bladder and kidneys, in the cavity of the mouth and nose, in the ear, in the joints, in endocardial vegetations, and in the blood.

General infection, due to the *Gonococcus*, is now freely recognised, and the relation of gonorrhœa to endocarditis is established. The endocarditis may be transient, or may result in a chronic valvular lesion, or may pursue a rapidly fatal course, with symptoms of acute ulcerative endocarditis.

INFLUENZA.

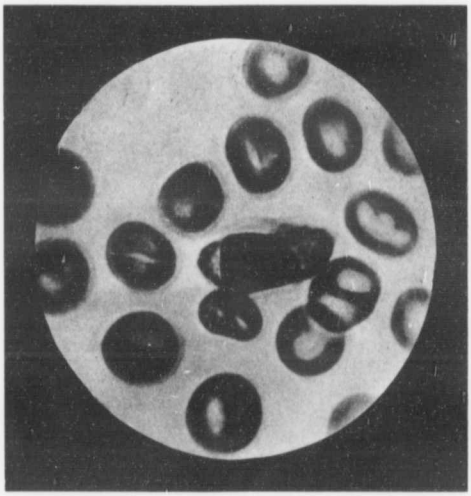
Pfeiffer's bacillus of influenza exerts its primary pathogenic action on the mucous membrane of the respiratory tract.

Influenza is, of all diseases, that which attacks the largest number of people, within a given short time. The rapidity with which the disease affects one great tract of country, after another, is the outstanding feature of the pandemics of the past.

The infection has shown a tendency to disappear for a time, and then break out afresh. One attack does not confer immunity.

The disease occurs in three forms, *viz.*, the gastric, nervous, and respiratory; the latter form predominates, in both epidemic and sporadic influenza. The prevalence of influenza, especially of the catarrhal type, is usually attended by an increase in the mortality, attributed to diseases of the respiratory organs.

Pfeiffer's bacillus is almost constantly found in the expectoration, in cases of influenza. It is found sometimes in pure culture, and, in doubtful cases, its recognition is of service in clearing up the diagnosis. There are cases of influenza, in which it is possible



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Hæmogregarina balfouri.
Hæmogregarine infection of jerboa
(Jaculus gordoni).

to make a diagnosis, only by the detection of the specific organisms in the sputum.

A number of instances are now on record, in which endocarditis was found associated with influenza, and in which Pfeiffer's bacillus was demonstrated in the endocardial lesions.

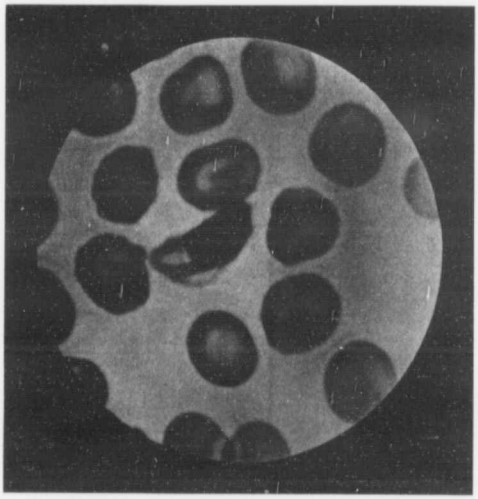
Bruschettini confirms Canon's observations as to the constant presence of Pfeiffer's bacillus, in the blood of patients, suffering from influenza in the acute stage. The blood was in every case drawn, to the amount of 5 to 10 cubic centimetres, from one of the veins in the bend of the arm, the time chosen being as near as possible to the maximum point of the fever. The blood was then placed in sterilised tubes in an incubator at 37° C., and after having been kept there for five or six days, a rich culture of the bacillus was obtained, which was then easily transferred to artificial nutrient media, where it grew very luxuriantly. Bruschettini states that, in the blood, Pfeiffer's bacillus is never accompanied by other micro-organisms, and it can therefore be obtained in pure cultures directly from that fluid. Human blood drawn from the veins is an excellent medium for the culture of these bacilli, which multiply abundantly therein.

MALTA FEVER.

Micrococcus melitensis is the cause of an endemic fever, resembling typhoid, of long duration, frequent relapses, and low mortality. Malta fever is not only widely distributed in the Mediterranean, but perhaps, more widely still, in tropical and subtropical regions.

Bruce (1887) isolated, and definitely ascertained, that the specific cause of the disease was due to the presence of a minute micrococcus, abundantly present in the spleen, both in the living and the dead.

Epidemics of the disease have been preceded by an epizootic amongst goats, which is also found to be associated with infection by the micrococcus. Malta fever was stamped out of Port Said, by destroying all dangerous goats in the town, and by laying an embargo on the importation of infected animals. As in the case of infected human beings, the micrococcus is found in the blood, urine, and milk.



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Hæmogregarina balfouri.
Hæmogregarine infection of jerboa
(Jaculus gordôni).

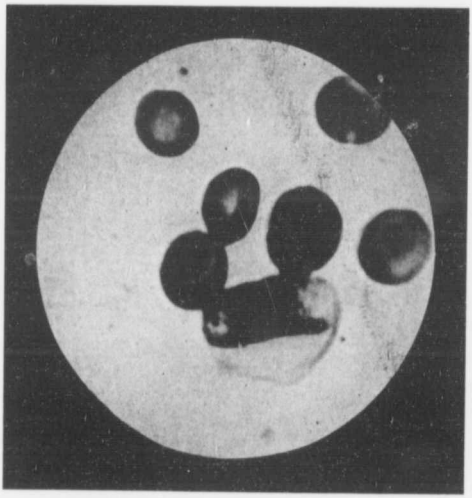
The milk of infected animals conveys the infection to man. The weight of evidence is against the spread of infection, by actual contact.

In *post-mortem* examinations, Kennedy found the micrococcus in the spleen, liver, kidneys, lymphatic glands, salivary glands, blood, and bile, but not in the intestines.

The micro-organism is not found in the saliva, expired air, sweat, or faeces. The urine seems to be one of the main channels by which the micrococcus leaves the body. Horrocks did not find it earlier than the fifteenth day, or later than the eighty-second day, of the disease. Kennedy recovered the micrococcus, from the twenty-first day to the two hundred and forty-ninth day, of the disease.

Micrococcus melitensis has been found in the blood by Gilmour, in 82 per cent., and, by Zammit, in 54 per cent., of the cases.

Villanova relates the history of an instructive case of Malta fever, which will serve to forcibly impress the clinical characteristics of the disease. The patient had been in the hospitals of Huesca, Lerida, Barcelona, and Zaragoza. The first diagnosis made was fever, a local term being used to describe the general attack. It was then discovered that the patient was suffering with orchitis, and pains in his shoulders and legs, and a diagnosis was made first of gonorrhœal arthritis, which was subsequently changed to subacute rheumatism. Subsequently, the patient suffered with sciatica, a coryza, a cough, and another diagnosis of la grippe was made. In Lerida, he had an infarct of the spleen, and nose bleed, and a diagnosis of typhoid was made, and the patient was treated with cold baths. Soon after, the diagnosis was changed to paratyphoid. The patient then went to Barcelona, where his trouble was diagnosticated malaria; he then left that hospital for another, where, after an examination by the r rays, he was said to have a pleuritic effusion on the right side, and his fever was thought to be due to septic absorption. When an attempt was made at paracentesis, the patient escaped, and made his way to Zaragoza, where the diagnosis of pulmonary tuberculosis was made, and finally he entered the hospital, where the correct diagnosis of Malta fever was established.



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Hæmogregarina balfouri.
Hæmogregarine infection of jerboa
(Jaculus gordoni).

BACILLUS DIPHTHERIÆ.

The escape of the Klebs-Læffler bacillus, into the organs, and into the circulation, is by no means uncommon, at least in fatal cases.

The primary infection, in diphtheria, occurs in the mucous membrane, and, by preference, in that of the throat. The primary lesion varies from a simple redness, or catarrhal condition, to a superficial, or deep necrosis, of the mucous membrane. Most frequently, the initial result of infection by *B. diphtheriæ* is an intense local inflammation, and the formation of a membranous deposit.

The fibrinous structure of the membranous deposit is the most prominent characteristic of the primary diphtheritic lesion. An acute exudative inflammation of mucous membranes, simulating very closely the primary lesion of diphtheria, occurs under a variety of bacterial infections, notably by *B. coli, Streptococcus pyogenes,* and *Pneumococcus.*

Streptococcus infection of the tonsils, associated with a fibrinous exudate, is frequently mistaken for diphtheria.

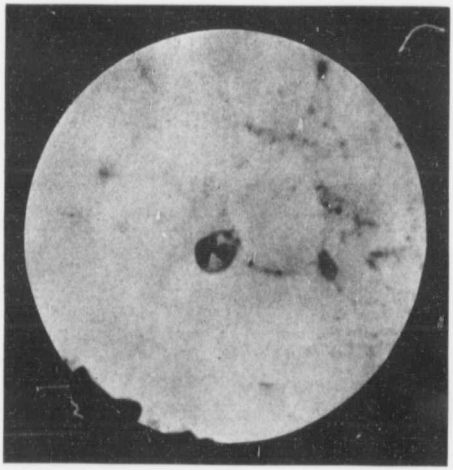
A remarkable formation of membranous exudate, on all the mucous surfaces, open to inspection, is reported by Cary and Lyons. The illness began with sore throat and pyrexia, followed by lobar pneumonia; an abundant white exudation membrane was noticed on the tonsils. The membrane spread to the general cavity of the mouth, and to the gums; it could be peeled off in shreds, leaving a granular bleeding surface. A fibrinous conjunctivitis developed, after which the glans penis became covered by a thick adherent membrane. Mucus was found in the stools, and a false membrane formed around the anus. The patient recovered. The *Pneumococcus* was present in all the various exudation membranes.

The dissemination of the diphtheria bacillus may occur in one of four ways:

1. By direct transference from one part of the body to another.
2. Along existing passages such as the nose, lachrymal duct, œsophagus, trachea, bronchi, etc.
3. Along the lymphatics.
4. By the blood stream.

Diphthero-septicæmia.

Frosch (1893) first demonstrated the escape of the bacilli into the blood and tissues. In ten examinations out of fifteen, he es-



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Leishmania donovani.

tablished the presence of the Klebs-Lœffler bacillus, with streptococci or staphylococci, in the internal organs and the blood.

Neisser has cultivated the bacillus from the blood during life.

Bardach, in his researches on diphtheria, notes that the bacillus, when particularly virulent, can be found very often in pure cultures, in the liver, the spleen, and the heart blood.

Councilman, Mallory, and Pearce found the diphtheria bacillus in the blood or internal organs, in 36 out of 59 cases of fatal diphtheria, complicated by other diseases, and in 83 out of 161 cases of uncomplicated diphtheria.

In most cases the malignant forms of diphtheria are due to the reciprocal exaltation of the diphtheria bacillus, and of the bacteria which are associated with it. According to the experiments of Roux and Yersin, the streptococcus plays the principal part.

The gravity of the combined infection is indicated by the following cases; according to Martin's statistics, 8 deaths in 10 cases; Chaillou and Martin give 13 deaths in 14 cases; Tézenas had 3 deaths in 3 cases.

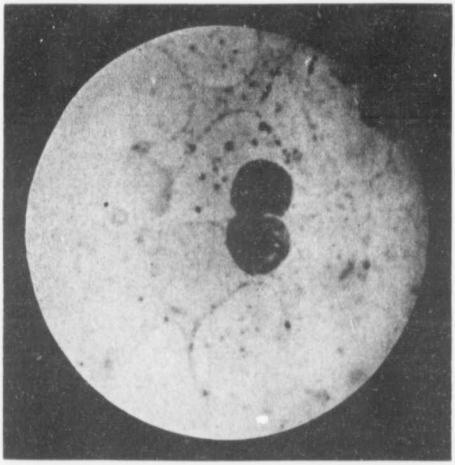
All observers agree that the most frequent form of general infection in diphtheria is strepto-infection.

It would appear that the onset of systemic bacterial infection, during the course of diphtheria, is signalised by the sudden appearance of alarming symptoms. Rapidly increasing weakness, compressible pulse, prostration, and tendency to syncope, which do not exist, or are only slight in uncomplicated diphtheritic infection, are a marked feature in these cases.

Braun and Thiry state that, in pure diphtheria of animals or man, the presence of Klebs-Lœffler bacillus in the organs is exceptional, while in strepto-diphtheria, or staphylo-diphtheria, the bacillus is frequently found in the blood, and in the organs. They conclude that:

1. At the autopsy, whether or not the bacillus is found in the membrane, it can be demonstrated in the blood and the internal organs. It has been found in purulent foci, in the middle ear, the trachea, the bronchi, the lungs, the liver, the spleen, the kidneys, the suprarenal capsules, the œsophagus, the brain, the pleuro-pericardiac exudates, the tracheo-bronchial, carotid, phrenic, and submaxillary glands.

2. According to recent observations, the presence of the bacillus in the organs is frequent: it is found there associated with streptococci and staphylococci.



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3. We are warranted in thinking, that it is a question of a true systemic infection, that is, of a diphtheritic septicæmia (strepto- or staphylo-diphtheritic septicæmia) and not of a simple dissemination or diffusion *Post Mortem*.

4. If the bacilli penetrate into the blood and the viscera, local treatment is insufficient, and cannot reach them.

PLAGUE.

Bacillus pestis was discovered during the Hong Kong epidemic, by Yersin and Kitasato, who isolated the bacillus from the buboes and blood of patients afflicted with bubonic plague, from the organs of rats and mice, which had died of plague, and from the dust and soil of houses, where patients had died of plague. In addition, they have shown that the bacillus could be easily cultivated outside the body, that the disease could be produced experimentally in animals, by inoculation and feeding, and that flies might be infected, and become a source of spread of the disease.

All cases of plague can be grouped under three main types, the bubonic, the pneumonic, and the septicæmic. The course of the disease depends on (1) the channel of entrance, (2) the virulence, (3) the quantity of the bacilli.

The rat is often, if not invariably, the intermediate host; the infection is carried from rat to rat, and from rat to man, by the flea.

The micro-organisms may gain entrance to the body, by any or all of the following channels:

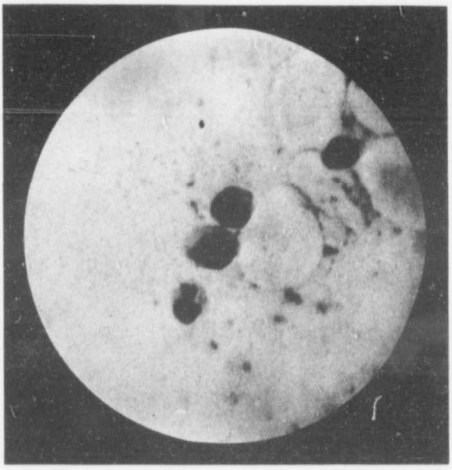
(1) By the skin or mucous membrane.

(2) By the respiratory tract.

(3) By the gastro-intestinal canal.

Cutaneous infection.

The skin is, at the present time, considered, by the majority of observers, to be the channel by which the plague bacillus most frequently finds entrance. Infection may take place through wounds, scratches, or insect bites. Flies, fleas, bugs, ants, and mosquitoes, are possible agents, in carrying the disease.



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The Austrian Commission succeeded in infecting rats, by rubbing a virulent culture into the intact skin. Infection by the skin is the commonest, and probably the only one, in bubonic cases.

The bubonic type is produced, experimentally, by inoculating slight cutaneous wounds with a virulent culture of the bacillus, or by injecting subcutaneously an attenuated culture.

In all cases, the lymphatic glands are liable to be affected, but typical inguinal and axillary buboes are produced chiefly in connection with cutaneous infection of the extremities. When the cervical glands are the seat of buboes, the virus is presumed to enter by way of the tonsil.

Respiratory infection.

Under ordinary conditions, the plague bacillus does not exist in the air, and infection seems to depend rather upon a prolonged and intimate contact. Pneumonic plague has been produced by applying the bacilli, with a small camel's hair brush, to the nostrils of guinea pigs. The bacillus may gain entrance to the respiratory tract, by inhalation from an infected person, coughing or sneezing in the face of a healthy individual. Batzaroff observed that pneumonic plague can be produced with bacilli, the virulence of which is so attenuated, that they do not produce the disease by subcutaneous inoculation.

In the sputum of pneumonic plague, the bacilli exist in almost a pure culture.

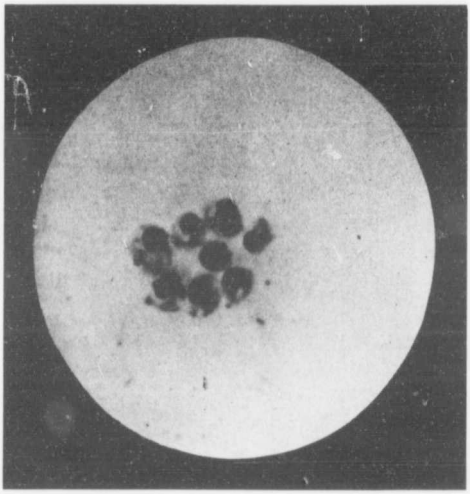
Pneumonic plague is a most rapidly fatal form of the disease, the patient usually dying on the third or fourth day.

Gastro-intestinal infection.

The experiments of Yersin and Kitasato showed, from the first, that the infection could be produced by ingestion of infectious products. Infection by way of the alimentary tract would seem possible, still, there is no direct proof, that either food or water serve to convey plague to human beings.

Septicæmic type.

While the pneumonic and bubonic types of plague are determined by the channel of infection, the septicæmic type results



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Leishmania donovani.

whenever the resistance of the tissues is considerably reduced, or the virulence or quantity of the virus very great.

The severity of the onset, in the septicæmic type, is such, that the patient seems struck down as if by some active poison. This type is described by Gibbon in his inimitable manner:

"The infection was sometimes announced by the visions of a distempered fancy, and the victim despaired, as soon as he had heard the menace and felt the stroke of an invisible spectre."

In the case of infection through the air passages, the bacillus is present in the bronchial and nasal discharges. In the septicæmic form, the blood contains a large number of bacilli, easily demonstrable by direct microscopical examination and cultivation.

Belleli has pointed out, that in cases of plague, in which buboes only are present, one can find large numbers of plague bacilli in the blood of the patient, if large quantities of this fluid be centrifugalised. Sometimes the bacilli can be found in the blood, before the appearance of the buboes, and even before the fever commences.

The bacilli have been shown, by Kitasato, to persist in the blood for three or four weeks after the onset of the disease, so that it can be diagnosed in convalescents, who may act as plague carriers.

Verjbitski, in a series of experiments, dealing with the part played by insects, in the epidemiology of plague, arrived at the following conclusions:—

(1) All fleas and bugs which have sucked the blood of animals dying from plague contain plague microbes.

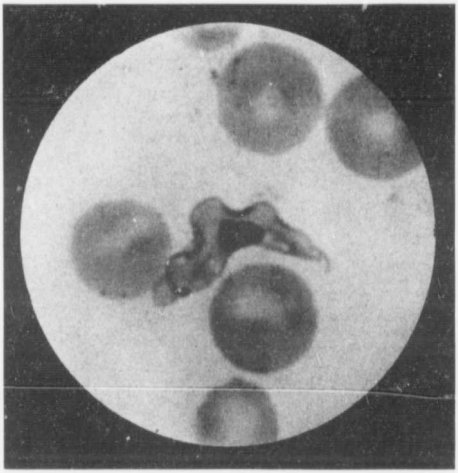
(2) Fleas and bugs, which have sucked the blood of animals suffering from plague, only contain plague microbes when the bites have been inflicted from 12 to 26 hours before the death of the animals—that is, during that period of their illness when their blood contains plague bacilli.

(3) The vitality and virulence of the plague microbes are preserved in these insects.

(4) Plague bacilli may be found in fleas, from four to six days after they have sucked the blood of an animal dying with plague. In bugs, not previously starved, or starved only for a short time (one to seven days), the plague microbes disappear on the third day; in those that have been starved for 4 to 4½ months, after 8 or 9 days.

(5) The numbers of plague microbes in the infected fleas and bugs increase during the first few days.

(6) The fæces of infected fleas and bugs contain virulent



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Trypanosoma gambiense.

plague microbes, as long as they persist in the alimentary canal of these insects.

(7) Animals could not be infected by the bites of fleas and bugs which had been infected by animals, whose own infection had been occasioned by a culture of small virulence, notwithstanding the fact that the insects may be found to contain abundant plague microbes.

(8) Fleas and bugs, that have fed upon animals which have been infected by cultures of high virulence, convey infection by means of bites, and the more certainly so the more virulent the culture with which the first animal was inoculated.

(9) The local inflammatory reaction in animals, which have died from plague occasioned by the bites of infected insects, is either very slight or absent. In the latter case, it is only by the situation of the primary bubo that one can approximately identify the area, through which the plague infection entered the organism.

(10) Infected fleas communicate the disease to healthy animals for three days after infection. Infected bugs have the power of doing so for five days.

(11) It was not found possible for more than two animals to be infected by the bites of the same bugs.

(12) The crushing of infected bugs *in situ*, during the process of biting, occasioned in the majority of cases the infection of the healthy animals with plague.

(13) The injury to the skin, occasioned by the bite of bugs or fleas, offers a channel through which plague microbes can easily enter the body and occasion death from plague.

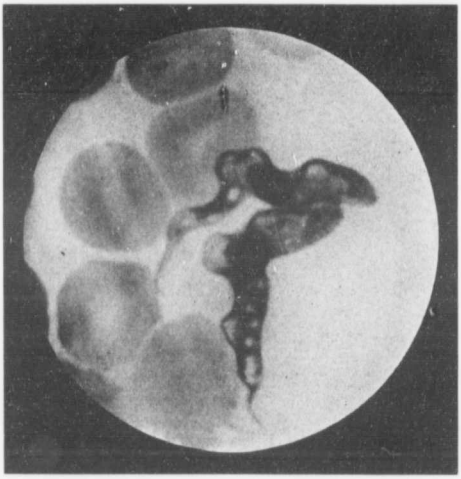
(14) Crushed infected bugs and fleas and their fæces, like other plague material, can infect through the small punctures of the skin caused by the bites of bugs and fleas, but only for a short time after the infliction of these bites.

(15) In the case of linen and other fabrics, soiled by crushing infected fleas and bugs on them, or by the fæces of these insects, the plague microbes can, under favourable conditions, remain alive and virulent for more than five months.

(16) Chemical disinfectants do not, in the ordinary course of application, kill plague microbes in infected fleas and bugs.

(17) The rat-flea, *Typhlopsylla musculi*, does not bite human beings.

(18) Human fleas do bite rats.



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Trypanosoma gambiense.

(19) Fleas found on dogs and cats bite both human beings and rats.

(20) Human fleas, and fleas found on cats and dogs, can live on rats as casual parasites, and therefore can, under certain conditions, play a part in the transmission of plague from rats to human beings, and *vice versa*.

The following are the conclusions which have been reached by the advisory committee, as the result of plague investigations in India:

(1) Considerable epidemics of human plague consist almost entirely of cases of bubonic plague, and are directly dependent on the occurrence of epidemic plague in rats. The development of the rat epidemic precedes the human epidemic, by an interval of about a fortnight. There is no evidence that any animals except rats play an important part in plague epidemics.

(2) *Epidemic plague in rats.*

(a) Rat-fleas, which have sucked the blood of a plague-infected rat, can transmit the disease to healthy rats to which they are transferred. The plague bacilli multiply in the stomach of the flea, and the flea may be still capable of conveying infection three weeks after having imbibed plague-infected blood.

(b) If plague-infected rats are kept in close confinement along with healthy rats, no epidemic of the disease occurs in the absence of fleas. In the presence of rat-fleas, the disease spreads from the infected to the healthy animals, and the rapidity and severity of the epidemic so produced is in proportion to the abundance of fleas.

(c) Rats may be infected by feeding them upon the bodies of other rats dead of plague. The distribution of the lesions, in the bodies of naturally infected rats, corresponds with that in rats experimentally infected by means of fleas, with that in rats infected by feeding.

The Committee, therefore, conclude that, *in nature, plague is spread among rats by the agency of rat-fleas.*

(3) *Epidemic plague in man.*

(a) Bubonic plague is not directly infectious from man to man, as is shown by the experience of plague hospitals, where there is no tendency for the disease to spread from the sick to the attendants.

(b) Material epidemics of plague in man are always associated with epidemic plague in rats. Epidemic plague among rats provides a large number of infected rat-fleas, and, owing to the mortality among the rats, brings these fleas on to human beings.

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Trypanosoma gambiense.

(c) Rat-fleas *(Pulex cheopis)* bite human beings, especially in the absence of their natural host.

(d) Rat-fleas, containing plague bacilli, and found capable of transmitting plague to animals, may be caught in plague-infected houses.

(e) Animals susceptible to plague (guinea-pigs, monkeys) placed in plague-infected houses, if unprotected from fleas, may contract the disease; whereas such animals, under the same circumstances, remain free from plague, if protected from fleas.

(f) The Commission have also performed numerous experiments with a view of testing other possible modes of infection, and have found that—

i. In the absence of fleas, no epidemic resulted when animals susceptible to plague (guinea-pigs) were kept in close contact with infected animals, although the animals took their food off floors grossly contaminated by the excreta of their infected companions.

ii. Susceptible animals (guinea-pigs) caused to live upon and feed off floors artificially saturated with plague cultures, failed to contract the disease.

iii. The excreta of plague-infected patients may contain plague bacilli, but the bedding, etc., of plague patients soiled with excreta containing plague bacilli was not found to be infective to highly susceptible animals, caused to live in and upon the bedding.

The Committee, therefore, consider that, *in the great majority of cases during an epidemic of plague, man contracts the disease* from plague-infected rats through the agency of plague-infected rat-fleas.

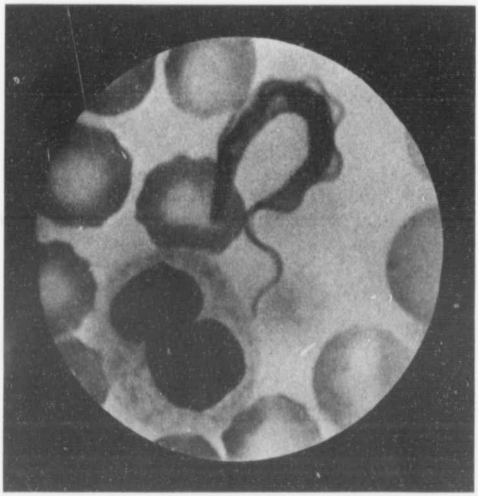
(4) *The seasonal recurrence and spread of plague.*

(a) The Committee has obtained no evidence that, under ordinary conditions, the plague bacillus survives for more than a few days outside the bodies of men, animals, or fleas.

(b) In large towns plague may persist throughout the year, since a few cases of acute plague, in men and rats, occur during the non-epidemic plague season.

(c) In villages there is no satisfactory evidence, that such persistence is of other than exceptional occurrence, and it seems probable that the recurring annual epidemics, in such places, are due in most cases to fresh importation of the infection.

(d) There is no evidence that plague infection is carried for more than short distances by the spontaneous movement of rats. Plague appears to be commonly imported into a fresh locality about



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Trypanosoma gambiense.

the persons of human beings, though the transference of infected rats and fleas in merchandise must be considered.

(e) In districts which suffer annual epidemics of plague, the rat epidemic, on which the human epidemic depends, occurs during some part of that season, when the prevalence of fleas is greatest.

SPIROCHÆTOSIS.

The various blood spirochætes which have so far been described are as follows:

1. *Spirochæta anserina*,—found in geese, by Sakharoff.

2. *Spirochæta gallinarum*,—found in fowls, in Brazil, by Marchoux and Salimbeni.

3. *Spirochæta granulosa*,—found in Sudanese fowls, by Balfour.

4. *Spirochæta theileri*,—from Transvaal cattle, by Theiler.

5. *Spirochæta obermeieri*,—European relapsing fever—by Obermeier.

6. *Spirochæta duttoni*,—African tick fever—by Ross, Milne, Dutton, and Todd.

7. *Spirochæta berbera*,—North African type—by Sergent and Foley.

8. *Spirochæta carteri*,—Asiatic type—by Carter.

9. *Spirochæta novyi*,—American type—by Novy and Knapp.

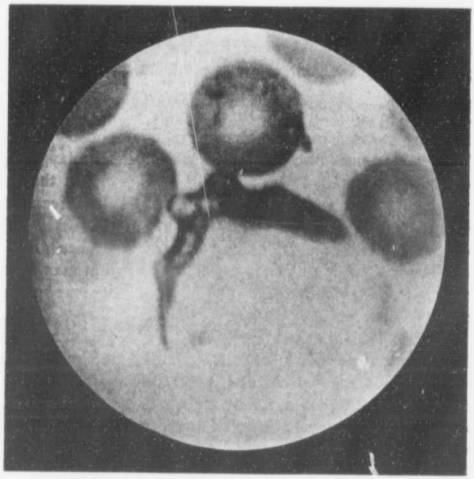
10. *Spirochæta pallida*,—by Schaudinn and Hoffmann.

Human spirochætosis.

The spirillar fevers form a group of hæmic infections, characterised by one or more febrile attacks, of varying duration and severity. Recent researches show that the range of human spirochætal fevers is much more extended than was thought to be the case.

The American, European, African, and Asiatic varieties of human spirillar fevers are caused by the presence in the blood of spirochætæ, which, in their morphological characteristics, closely resemble one another.

Various blood-sucking insects act as vectors of the disease.



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Trypanosoma gambiense.

Spirochæta obermeieri—the specific organism of European Relapsing fever—is conveyed chiefly, apparently, by the bedbug.

Spirochæta duttoni—the parasite of African Relapsing fever,—is transmitted mainly by ticks, hence the name—tick fever, by which it is mostly known.

Dr. Livingstone was the first to describe tick fever, which he met with on the Zambesi and its tributaries.

Two ticks, presenting life habits very similar to the common bedbug are responsible for the transmission of the African relapsing fever.

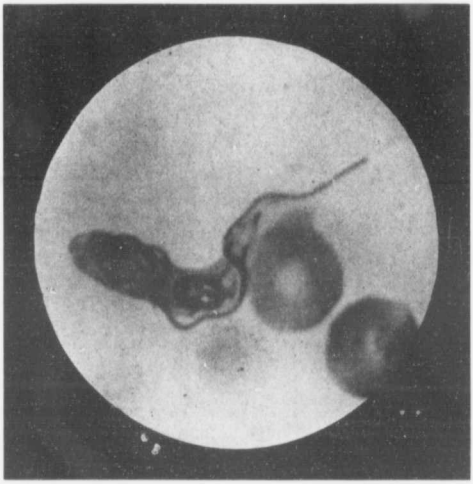
1. The Persian poison bug *(Argas persicus)* lives in cracks, in the ground, and walls of old houses. These bugs may become such a plague that all the inhabitants may be driven from a village by them.

2. The horse tick *(Ornithodoros moubata)* infests old camping grounds, along caravan routes. It comes out at night to seek food, when it attacks animals as well as human beings. By day, it hides in crevices in floors and walls. Ticks do their work in the night, and never travel far away from the dry earth of the infected huts where they breed.

Additional evidence corroborates the view that lice *(Pediculi vestimenti)*, and fleas, are carriers of the disease from man to man. In the Asiatic, Egyptian, and Algerian types, lice are probable vectors of the disease.

Dutton and Todd, in the Congo, showed by experiment that the spirochætæ were conveyed to a healthy subject by the bite of an *O. moubata*, which had fed on a patient suffering from tick fever, and that the larvæ hatched out from eggs, laid by an infected tick, could convey the infection. Mœllers has proved that the virus can be transmitted hereditarily to several generations of ticks.

Mackie, Dyson, and Jackson, acting under direction of the Bombay Government, investigated the prevalence of relapsing fever amongst the superior staff of the Motlibai Hospital, and unanimously came to the conclusion that the disease was spread, in the cases, by contact with fresh blood of women, who were admitted for abortion and miscarriage. Many of these cases were in a high state of fever, their blood containing spirilla, and the abortion was the direct result of the disease. During the performance of the necessary treatment, the medical officers and nurses contracted the disease, possibly through abrasions, or cracks, which were thus infected with spirillar blood.



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Trypanosoma gambiense.

After investigating an outbreak of relapsing fever, in the Nasik Mission Settlement, Mackie records the following summary of facts:—

1. An epidemic of relapsing fever broke out in a mixed settlement of boys and girls, living under similar conditions.

2. A very high percentage of boys fell victims to the disease in the course of a few weeks.

3. A much smaller percentage of girls fell ill, and at infrequent intervals extending over three months.

4. The most notable fact, in which the boys differed from the girls, was that they were infested with body lice, from which parasites the girls were almost free.

5. A well marked percentage of the lice, taken from the infected ward, contained living and multiplying spirilla.

6. The stomach of the louse was the chief seat of multiplication, and this was carried on in the face of active digestion, and after disappearance of other cellular elements.

7. With the increase of the epidemic amongst the girls, body lice became more in evidence.

8. With the subsidence of the epidemic amongst the boys, the percentage of infected lice fell.

9. An attempt to infect a monkey by means of lice, failed.

The facts reported by Mackie would seem to be sufficient to incriminate the body louse *(Pediculus corporis)* as a transmitter of Asiatic relapsing fever *(Spirochæta carteri)*.

Penetration of the skin.

Nattan-Larrier found that spirochætæ can easily and rapidly traverse the unbroken skin of the white rat, but only at points where the skin is fine and very vascular. The mucosa and the conjunctiva are very easily traversed, the male genital mucosa alone seeming to present any difficulty.

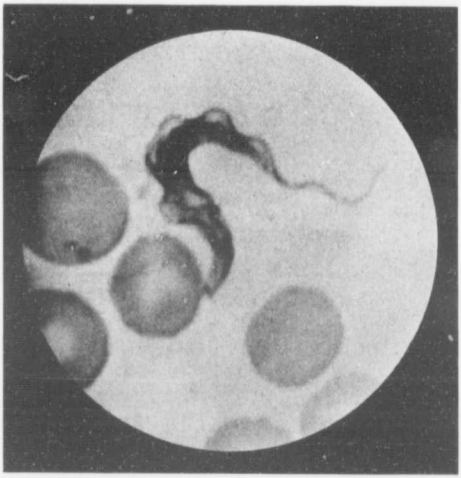
Gózony, working with *Spirochæta recurrentis*, came to the following conclusions:—

1. That infection by way of the skin is possible.

2. That the mucous membranes of the intestinal tract are not impassible by spirochætæ.

3. That spirochætæ can traverse the conjunctivæ of the mouse.

4. That the intact mucous membrane of the genital tract permits the passage of *Sp. recurrentis* through it.



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Trypanosoma gambiense.

Hereditary transmission.

Nattan-Larrier, in a contribution on hereditary transmission of *Sp. obermeieri* and *Sp. duttoni* in rats, finds as follows:—

1. Both *Sp. obermeieri* and *Sp. duttoni* can be transmitted from mother to fœtus. The number of spirochætæ penetrating the placental tissues is never great. This explains the long incubation, the small blood infection, and short persistence, of the parasites in the blood.

2. Spirochætes can pass from mother to fœtus, in the absence of any placental lesions.

Multiplication of spirochætæ.

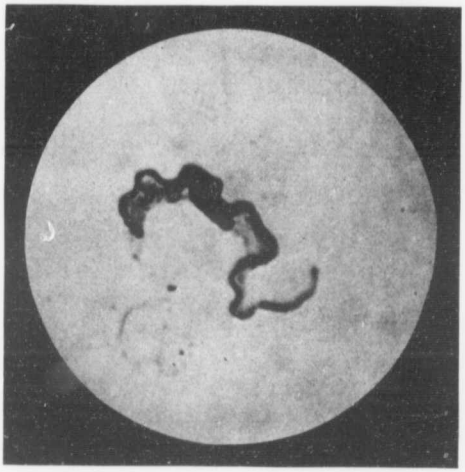
Fantham and Porter have described both longitudinal and transverse division of spirochætæ. In longitudinal division, rapid waves pass down the body of the spirochæte; at one end a split occurs which gradually widens. Waves pass down each of the diverging daughter forms, which then separate. Spirochætæ about to divide longitudinally, are slightly stouter than the others. Fantham and Porter state, that transverse division is initiated by waves passing from both ends towards the center of the organism. These waves meet and die out, and return waves pass rapidly from centre towards each end. The central nodal region becomes thinner, and finally divides. They observed longitudinal division at the onset of the infection, transverse division when the infection is at its height, and as the infection subsides, there is a reappearance of longitudinal division.

Mackie states, that in Indian spirillar fever *(Sp. carteri)*, division takes place transversely, and in deeply stained specimens, the dividing line between two daughter spirilla, is clearly seen as a gap or faintly stained area of endoplasm, reminding one of a node of Ranvier in a nerve fibril.

Mackinnon observed longitudinal and transverse division in *Sp. recurrentis*, and is inclined to think that both forms of division may take place, transverse being the more common. Breinl, Dutton, Todd, and Fantham have expressed the same opinion.

Diagnosis.

The diagnosis of spirochætosis is made by examination of peripheral blood, or by splenic or hepatic puncture.



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Trypanosoma gambiense.

The number of spirochætæ in the blood varies with the different varieties of the fever. Infection is heavy in the European type, but sparse in the African.

Spirochætæ are present in the blood, from the onset of the fever until the crisis, when they suddenly and totally disappear.

Choksy mentions one spirillum to every three or four red cells, in the grave form of Asiatic infection. Carter V. observed immense numbers, often incalculable, except by hundreds of millions. They were often so crowded, as to offer mechanical impediment to the circulation, and this was evinced by dusky lividity of the countenance.

The disappearance of spirochætæ from the blood, during the apyrexial interval, is supposed to be due to their congregation in the spleen. The blood is infective, in the apyrexial interval, as well as the pyrexial. This is due to the presence in the blood of infective granules, which are thrown off by the parasite, and which undergo transition into spirochætal forms. Leishman made the important discovery that in *Ornithodoros moubata*, the spirochæta of African tick fever breaks up into granules.

Avian spirochætosis.

Since the discovery by E. Marchoux (Brazil) of fowl spirillosis, several species of fowl spirochætosis have been found in different parts of the earth.

The disease is transmitted by ticks (*Argas persicus*), which have fed on infected fowls.

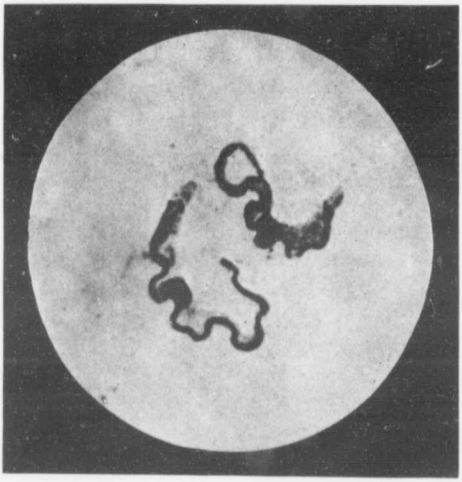
Schellack finds that *Argas miniatus*, *Argas reflexus*, and *Argas persicus* are all efficient as vectors, while *Ornithodoros moubata* can also transmit *Spirochæta gallinarum*.

Spirochætal infection, that follows the bite of an infected tick, results from the entrance of the infective material excreted by the tick whilst feeding, into the open wound caused by the tick's bite.

Gózony has shown that spirochætal infection can take place through the unbroken mucous membrane.

In infected fowl-runs, infection can take place by the ingestion, by fowls, of infected ticks.

Spirochæta gallinarum can pass into the immature ovum, so that it is possible that live chicks may be hatched, exhibiting a spirochætal infection.



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Trypanosoma gambiense.

There appears to be marked differences between the disease in chicks, and that in fowls. In chicks, the infection may be of great severity, death taking place often before spirochætes have time to appear in their blood.

Brumpt has pointed out, that, while chicks are easily inoculated with different species of spirochætes, certain adult birds exhibit a natural immunity conferred apparently by age.

Blaizot points out that, so far as we know at present, only a heavy acute infection is capable of conferring a permanent immunity. In this direction, the African fowl spirochætosis bears a close relationship to the spirochætal fevers of mammals.

In chicks, relapses are common, and in this the disease approaches mammalian spirochætosis in type.

Balfour (Khartoum), working with fowl spirochætæ of the Anglo-Egyptian Sudan, has observed certain corpuscular inclusions, which he has described as an "after-phase" of spirochætal infection.

The actual formation of the corpuscular bodies in the red cells has not been observed.

Balfour believes that the inclusions are not the direct result of spirochætes, invading the red blood cells, and breaking down therein, but are due to the entry of small granules derived from the chromatin cores of spirochætes, which have already disintegrated.

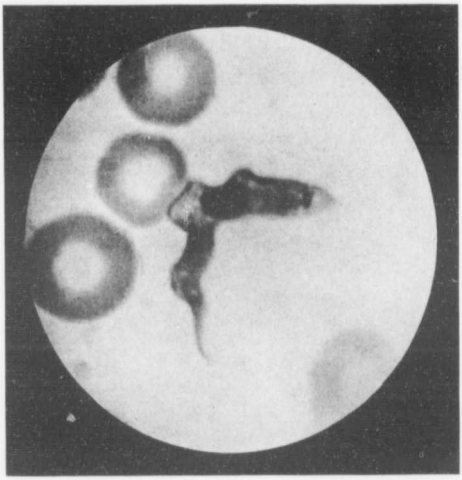
The peculiar tendency of the Sudan strain of spirochætes, to break up into "infective granules," in the internal organs, has led Balfour to look upon it as distinct from all other species hitherto described. He has proposed to name it *Spirochæta granulosa penetrans*.

Balfour states that fowl spirochætes, ingested by the tick, behave, in the contents of its alimentary diverticula, exactly as they do in the liver, spleen, lung, and, under certain conditions, in the peripheral blood of infected chicks. They shed granules, and continue to do so, until their periplastic sheaths, or cell membranes, are empty, or nearly so. The individual granules are small, usually coccal shaped, though frequently irregular in outline. Transition of granules into spirochætal forms has also been described.

The results of his work on the spirochætosis of fowls, in the Anglo-Egyptian Sudan, are tabulated by Balfour as follows:—

1. Ticks, either larvæ, nymphs, or adults, fed on chicks with acute spirochætosis, exhibit peculiar chromatin granules.

2. If ticks containing granules, are kept in the incubator, at



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Trypanosoma gambiense.

37° C. the granules may be seen to undergo a change and to assume a spirochætal form.

3. Chicks, inoculated with an emulsion of crushed larvæ, showing these granules, but no spirochætes, develop acute spirochætosis.

4. If batches of ticks, samples of which are found only to show granules in their tissues, be fed on clean chicks, such chicks, after from two to four days may exhibit, not spirochætes, but the corpuscular inclusions.

Syphilis.

The discovery of the *Spirochæta pallida*, and the proof of its position, as the specific organism of syphilis, are due to Schaudinn and Hoffmann.

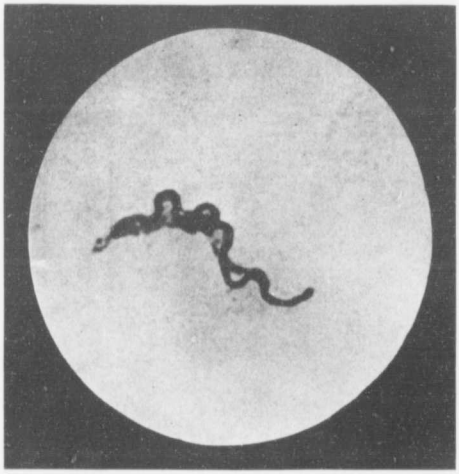
The spirochæta is an extremely delicate corkscrew like thread, showing numerous closely aggregated short, sharp, uniform turns, three to twelve in number. It is the smallest and finest of the spirochætæ, measuring from 4 to 10 μ in length. It is motile, either screw-like in either direction, or sinuous and whiplike.

Primary syphilitic infection is met with in all regions of the body. Clinical experience shows that *Spirochæta pallida* is conveyed (1) by the initial chancre and mucous patches; (2) by the blood and lymph.

Contamination by the chancre and mucous patch is undoubtedly the origin of the great majority of syphilitic contagions. The mucous patch is the cause of an infinitely greater number of contagions than the chancre. This is explained by the longer duration of the mucous patch, its liability to recurrence, and the multiple localisations.

The existence of cracks, abrasions, ulcers and skin lesions, favour the entrance of the specific virus, but are by no means essential. Chancres of the skin may be derived from any kind of contact with syphilitic matter. A skin provided with an epidermis in good condition may resist the introduction of contagious matter, but if the virus finds its way into a glandular orifice, or hair follicle, it will penetrate by setting up inflammation around it.

Infection may occur without any ascertainable point of entry of the virus. A case of undoubted syphilis came within the observation of the writer, in which absolutely no point of infection could be found, and in which the mode of origin of the disease is a complete mystery. The case referred to is that of a young lady



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Trypanosoma gambiense.

of undoubted virtue and veracity, in whom the first indication of illness was the appearance of secondary lesions. The secondary lesions were allowed to develop until they were quite characteristic. They disappeared promptly on the administration of antisyphilitics. The after history was marked by the recurrence of mucous patches.

When the primary lesion forms on a surface, at a distance from the point of contact, the secretions act as a vehicle of transmission of the virus. This explains the tonsillar location of the chancre in the recipient of an infection from mucous patches of the lips of the donor.

That the initial lesion is frequently insignificant, or greatly modified, by the tissue in which it appears, is well recognised.

The conditions, which are eminently favourable to transmission of contagion, are repeated and prolonged contact, moistening by body secretions, presence of fissures and excoriations, which form ports of entry for the virus. These conditions are found in extra-genital infection, the result of suckling. A syphilitic wet-nurse infects a child by lesions which develop on the breast during suckling. More often it is the nurse, who is infected by a syphilitic child, and develops a chancre on the breast.

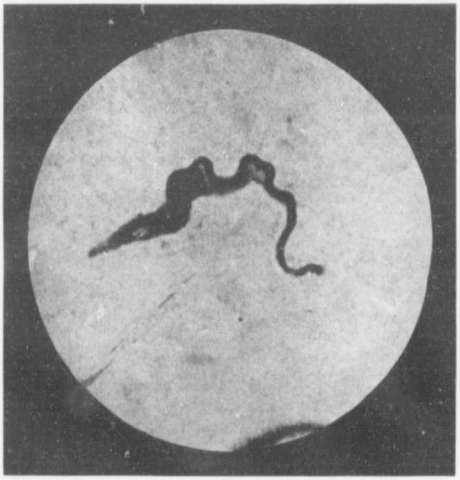
The mouth, by reason of the great frequency of syphilitic lesions within it, is responsible for the great proportion of unmerited contagion.

The chancre is the local lesion from which general infection spreads, and therefore the primary lesion should be immediately attacked and removed, notwithstanding the fact that, in preventing constitutional infection, excision of the infective focus rarely succeeds. Wide and free excision should be practised, when possible to do so without mutilation, and when the lesion is seen before other symptoms develop.

It certainly takes an appreciable interval of time for the organisms to travel from the site of inoculation, and the removal of the primary lesion can do no harm, and may do much good.

As the secretion from the chancre contains the spirochæta, every precaution should be taken to prevent specific contamination of the wound, during the course of the operation.

Matzenauer reports four cures in twenty-four cases of excision. Crivelli, in an analysis of 454 cases of excision, gives 339 failures. Ehlers, in an analysis of 584 cases, gives 447 failures. These statistics give 22 or 23 per cent. of successful excisions. It will be interesting to see if this encouraging success, in excision of syph-



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Trypanosoma gambiense.

ilitic chancre, is verified by future bacteriological examination. Excision is easily accomplished, when the nodule is of reasonable size and situated in redundant tissue.

From the point of inoculation, the lymphatics bear clinical and histological proof of the penetration into the body of the syphilitic virus. The lymphatics, running from the primary lesion to the glands, stand out at times as capillary or cord-like swellings. Involvement of the lymph glands, in the path of the infection, is a constant phenomenon.

The *Spirochæta pallida* is uniformly present in the primary and early secondary lesions.

The blood is infective, but the precise time it becomes so is uncertain. It has been proved to be infective before the advent of the secondary lesions.

While the infection is mostly rapid through the tissues, prolonged periods of secondary incubation are recorded. Napp has reported an interval of 328 days between the chancre and the secondary symptoms,—the longest on record.

The *Spirochæta pallida* is associated with every syphilitic lesion, except the gumma, in which it is not regularly found. The organism has been found in the most varied lesions of syphilis, in almost all its stages, in the eruptive lesions, in the glands, in the ulcerated tissues, blood, bullæ, internal organs, papules, condylomata, and mucous patches.

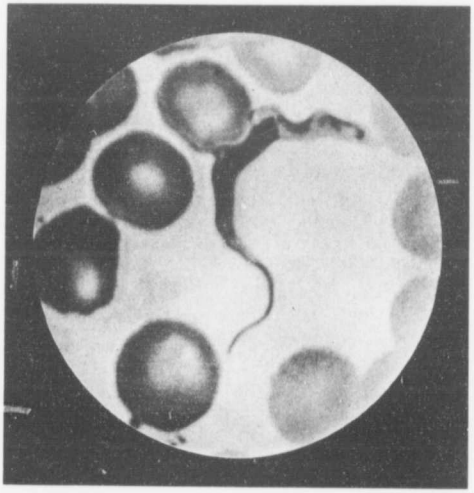
It is a striking fact that the symptoms of syphilis, during the eruptive stage, are so slight, yet the blood and tissues are contaminated by hordes of spirochætæ.

During the early stages, the blood, lymph, and all the products of inflammation are infective. Every individual in the infective stage is a menace to the community. Ricordi mentions cases, where one syphilitic gave origin to sixteen, eighteen, and twenty-three cases of syphilis, creating a sort of local epidemic.

The detection of the *Spirochæta pallida*, in very late lesions, has shown how long the specific organism may linger in the tissues, and that the disease is transmissible in all its stages.

The specific organism is found in practically all the lesions and affected organs in acquired, and in the organs and placenta of heredo-syphilis.

In the consideration of syphilitic heredity and propagation, the following propositions have been pretty well substantiated:—



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Trypanosoma gambiense.

1. The blood transmits syphilis from the mother to the fœtus.

2. The semen transmits syphilis from the father to the fœtus.

3. Syphilis can be transmitted from the father to the mother through the fœtus.

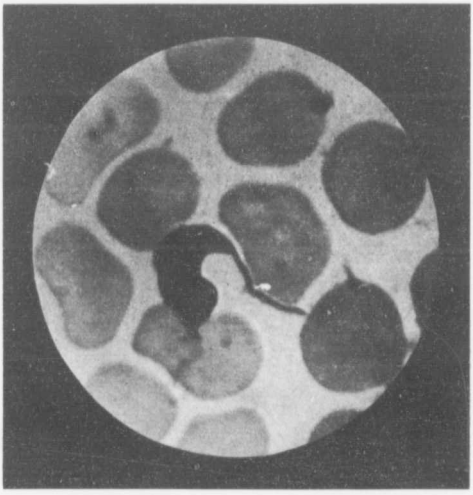
MALARIA.

The intermediate host, responsible for the transmission of all known kinds of malaria from man to man, is the Anopheles. Given the presence of this insect and malarious subjects, infection and reinfection continue indefinitely. The insects infected from malarious patients live for weeks in the dark corners of houses, infecting or reinfecting whomsoever they may bite,—each of whom becomes in turn a focus, from which the disease spreads further.

The habits and geographical distribution of mosquitoes and other insects, engaged in the transmission of disease, are of enormous importance to the human race. Very numerous investigations into the question of malarial transmission seem to have proved, that so far as human malaria is concerned, Anopheles alone have to be considered. No species of Culex has as yet been incriminated, in regard to human malaria. Wherever malaria develops, Anopheles is found. The insects can be transported long distances from malarial centres, consequently the geographical distribution of Anopheles does not coincide with the map of malaria.

A few years ago, comparatively few species of mosquitoes were known. About 580 species have so far been described; of these, about 150 are classified as Culex, and about 50 species as Anopheles.

The genus Anopheles differs much from genus Culex, in the adult, in the larva, and in habits. In the female Anopheles, the palpi are long, whereas in the female Culex they are short. The genus Culex is smaller, Anopheles larger. The two genera may be differentiated, by their difference in size, and their manner of resting. In Anopheles, the proboscis is directed toward the surface on which the insect is resting; in Culex it is directed parallel to the surface. In other words Culex holds the abdomen parallel to, or at an acute angle to, the resting surface; whereas Anopheles carries the abdomen directed upwards (at an angle of about 145°) and holds



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Trypanosoma cruzi.

the head down. Culex larvæ live everywhere in warm countries,—in almost every receptacle where a little water lodges. Culex is a pot-breeding mosquito; Anopheles a puddle-breeding mosquito, dependent on rainfall. Anopheles larvæ live where conditions are most suitable to their existence. The larvæ obtain their food from algæ, and are generally found in small slow runnels, containing green flocculent water-weed, in small puddles frequently replenished, and in stagnant collections of water, not capable of being scoured out during rain.

The places where Anopheles larvæ are not found are:

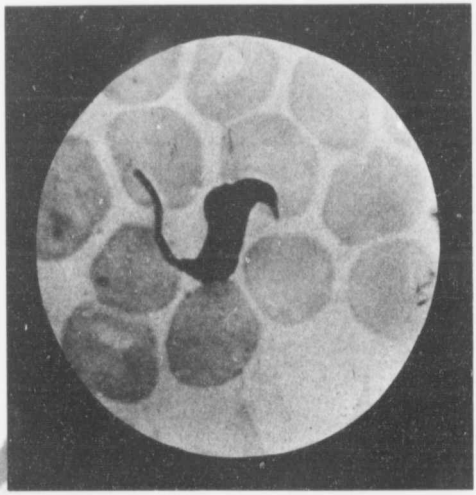
1. Very evanescent rain water puddles;
2. Puddles free of green weed, fungus, or algæ;
3. Puddles which are apt to be scoured out by rain;
4. Large pools which contain minnows;
5. Rapid streams, or drains;
6. Domestic receptacles.

The practical solution of the malaria problem lies in:

1. Avoiding infected localities;
2. Destruction of Anopheles breeding places;
3. Protection from mosquito bite.

Hæmamœba malariæ.

The discovery was made in 1880, by Laveran, of living organisms in the red corpuscles of malarious patients. This discovery was the first great step in the etiology of malaria. Nine years after Laveran's discovery, Golgi of Pavia announced that he had observed differences in the parasites of tertian and quartan fevers, so great and so constant, as to make him satisfied that they were two distinct species of organism. Marchiafava and Celli, in studying Roman fevers, discovered that there was at least one other species to which the special characteristics of the so-called summer-autumn fevers of Rome were due. It was recognised that some of the individuals of the third organism, instead of being of rounded form, were of crescentic shape. This species received the name "æstivo-autumnal," on account of the season in which it showed itself. The more dangerous crescent form is commonest in the tropics, and hence has been termed "tropical malaria." The quartan has proved the mildest of the three fevers.



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Trypanosoma cruzi.

The genus *Hæmamœba* is characterised by the development of pigment and includes the following:

	Host-
Hæmamœba subtertiana	Man
Hæmamœba tertiana	Man
Hæmamœba quartana	Man
Hæmamœba relicta (*Proteosoma*)	Birds
Hæmamœba danilewskyi (*Halteridium*)	Birds

Hæmamœba quartana.

This species is the cause of quartan fever, and is termed the quartan parasite. In infections with a single group of quartan parasites, the paroxysms occur at intervals of approximately seventy-two hours.

The different stages of development of the parasite, in quartan fever, are about as follows:—

Twelve hours after the paroxysm.—A nucleated spore, which has been set free in the blood, after segmentation of the mother parasite, comes in contact with a red blood-corpuscle, to which it adheres.

Twelve to twenty-four hours after paroxysm.—The spore has penetrated into the substance of the corpuscle, where it undergoes development at the expense of the cell. The organism develops into a small ring, enclosing a central clear area. The size is now one-sixth to one-fifth of the red blood-corpuscle.

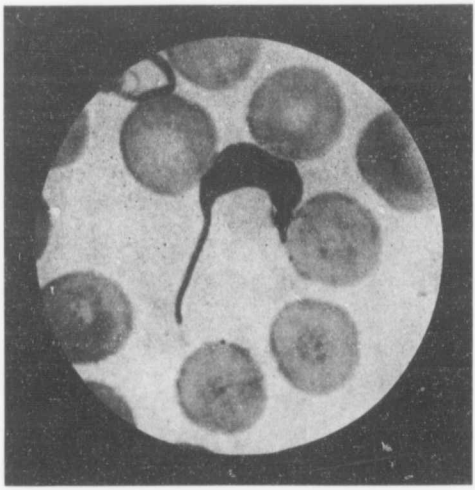
Twenty-four to thirty-six hours.—The parasite forms the first granules of melanin, or pigment, which appear first at the periphery. The organism has increased but little in size.

Thirty-six to forty-eight hours.—The parasite occupies from one-half to two-thirds of the body of the corpuscle; it is markedly pigmented, usually round; amœboid movements sluggish.

Forty-eight to sixty hours.—Amœboid movements are arrested; the parasite almost fills the corpuscle, leaving only a small rim recognised by its colour.

At sixty hours.—The margin of red blood-corpuscle has disappeared; the granules of melanin are arranged radially. The pigment granules remain mostly peripheral, till before sporulation, when they begin to congregate in the centre, this being the indication that sporulation is about to take place.

At sixty-nine hours.—The grains of melanin are crowded



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Trypanosoma cruzi.

toward the centre of the disk; segmentation, or formation of from six to twelve spores, is in progress.

At seventy-two hours.—The parasite has attained full development, and sporulation is completed; the spores separate from the central heap of pigment, and from each other; the remains of the corpuscle disintegrate, the new brood of spores is set free and fever results. The pigment granules, stored-up in the body of the parasite, escape into the blood-plasma, where they are taken up by phagocytes.

The task of ridding the body of pigment, and of defunct parasites, devolves on the phagocytes; the pigment granules are taken up by the leucocytes, and are mostly deposited in the spleen and the liver, though also sometimes in the bone-marrow; this accounts for the well known pigmentation of the spleen, in persons who have suffered from malaria.

The pigment carried by the quartan parasite is large in amount, and coarse in grain, sometimes forming short rods. The granules are refractile, even glistening, which makes the photographic reproduction of quartan parasites exceedingly difficult.

The blood-corpuscles, invaded by quartan parasites, become neither enlarged nor pale; they are often somewhat diminished in size, and more deeply coloured.

The sporulating form, or quartan rosette, is made up of six to twelve pear-shaped bodies, arranged symmetrically around the centrally placed mass of black pigment.

Simple quartan fever results from the development, in the blood, of one generation of the parasites, which come to maturity every three days. The blood may be infected by several generations of one kind of parasite. Infection by three generations of quartan parasites, with twenty-four hours interval, would produce quotidian fever. The blood may be infected by several kinds of malarial parasites simultaneously, resulting in mixed infections. Examination of the blood, from these types, reveals the presence of parasites of different ages.

Single quartan infection.—In infection with a single generation of quartan parasites, the paroxysms occur at intervals of seventy-two hours. Between two paroxysmal days, there are two days free of paroxysm, thus—

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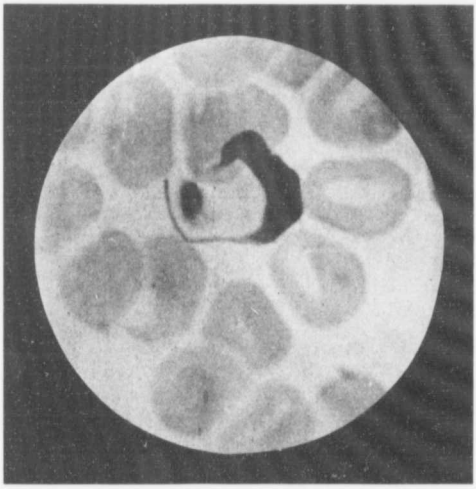

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Trypanosoma cruzi.

Hæmamœba tertiana.

The tertian parasite is the cause of tertian fever; it completes its cycle of development in forty-eight hours.

Development of tertian parasite.

The development of *Hæmamœba tertiana* is about as follows:—

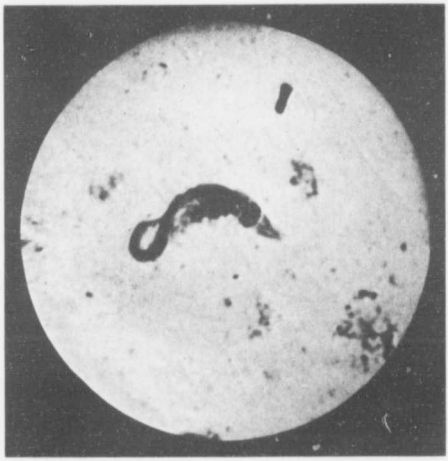
First quarter of the cycle.—If the blood of a patient, suffering from tertian fever, be examined, shortly after a chill, a number of the red blood-cells will be found to contain small actively amœboid bodies, which are the early forms of tertian parasites. These small bodies are found to be made up of a deeply stained nucleus, which lies eccentrically in a larger circular unstained area; the whole is surrounded by a narrow rim of lightly stained protoplasm. The increase in size of the infected cell, which is characteristic of corpuscles, infected by tertian parasites, may often be observed, even at this early stage. In this respect, the infected cells differ from those containing quartan, and subtertian parasites, which are diminished in size. With the growth of the parasite, there is often loss of hæmoglobin. The swelling and decolorization of the red blood-corpuscles, though very frequent, are not constant.

Second quarter.—After twenty hours growth, the parasite fills about one-third of the corpuscle. The ring shape, assumed by the organism, in the early stage, is maintained and increased in size. The organisms are still actively amœboid; they contain very fine pigment granules. The infected cells are pale and enlarged. During this stage, the number of amœboid figures seen is very great.

Third quarter.—The organism fills two-thirds to four-fifths of the corpuscle. There is abundant pigmentation; the chromatin is subdivided. In this stage the nucleus occupies the entire ring, and the parasite is full grown.

Fourth quarter.—The presegmenting body, and the tertian rosette, are the features of this period of development.

During the growth of the parasite, more and more pigment, in the form of fine granules, and lines, develops, particularly at the periphery. The greater the amount of pigment, the older the parasite, and the less actively amœboid. In the formation of the tertian rosette, the pigment is concentrated in the centre of the organism, in a thick clump; glistening dots, representing the chromatin of the individual segments, begin to appear, and finally the



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Trypanosoma cruzi.

outlines of fifteen to twenty spores become distinct. The spores sometimes arrange themselves regularly in two concentric rows, but usually there is no symmetrical arrangement, as seen in the quartan type. The tertian sporulating body is almost, or quite, the size of a normal red blood-corpuscle; the containing cell is enlarged and almost decolorised. The spores of the tertian parasite, or tertian amœbulæ, are spheroidal, or slightly oval, and smaller than quartan amœbulæ. After the host-cell disintegrates, and the spores separate from one another, the pigment escapes into the blood-plasma, to be taken up by the phagocytes.

Schüffner's granules.

Red blood-corpuscles, invaded by tertian parasites, frequently present a mottled appearance. The appearance in infected cells of granules, or points, was first described by the observer, whose name they bear. The origin and nature of these granules are not quite clear. They appear as fine, more or less rounded, particles, scattered irregularly throughout the whole of the red corpuscle. The fact that their staining reaction is identical with that of the nuclear chromatin of the parasites, might point to their being of a similar nature. The granules are probably the result of changes in the corpuscle, brought about by the invading parasite, and are not directly connected with the parasite itself. Schüffner's granules are commonly but not invariably present, and occur only in red blood-corpuscles, infected by the tertian parasite.

Single tertian infection.—In infection with a single generation of tertian parasites, the paroxysms occur at intervals of forty-eight hours. Between two paroxysmal days, there occurs one day free of paroxysm, thus—

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Examination of the blood in single tertian infection, at the time of a paroxysm, reveals the presence of one group of parasites, represented by full grown organisms, segmenting forms, and early spore invasions.

Double tertian infection.—This type occurs in infection by two groups of tertian parasites, with a twenty-four hour age interval.

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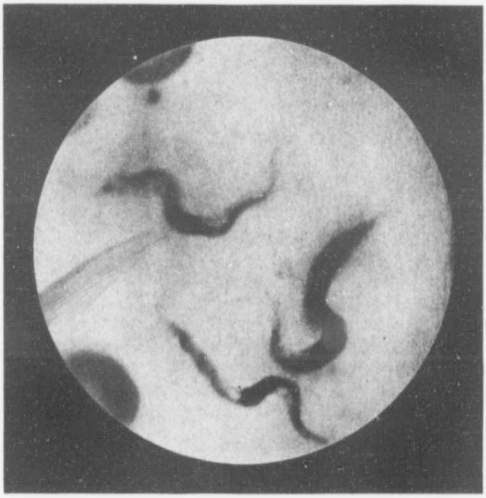

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Trypanosoma brucei.

In double tertian infection, segmentation of a generation of parasites occurs daily, resulting in quotidian intermittent fever. Examination of the blood reveals the presence of two groups of tertian parasites, at different stages of development. Thus, at the time of a paroxysm, while one group is represented by full grown parasites, the second group is represented by half grown organisms.

Hæmamœba subtertiana.

This parasite is the cause of æstivo-autumnal or tropical fever. Irregularity of the fever, as well as the tendency toward the development of "pernicious" symptoms, are the clinical characteristics of æstivo-autumnal infections. A striking feature of this fever is the great length of the paroxysms, which are often of over twenty-four hours duration, differing from the tertian and quartan fevers. Ordinarily, the cycle of development of the subtertian parasite occupies about forty-eight hours; the intermittent fever of æstivo-autumnal malaria is of the tertian type. Paroxysms may occur at intervals, greater or less than forty-eight hours. Marchiafava and Bignami describe a quotidian parasite, the cycle of development being twenty-four hours.

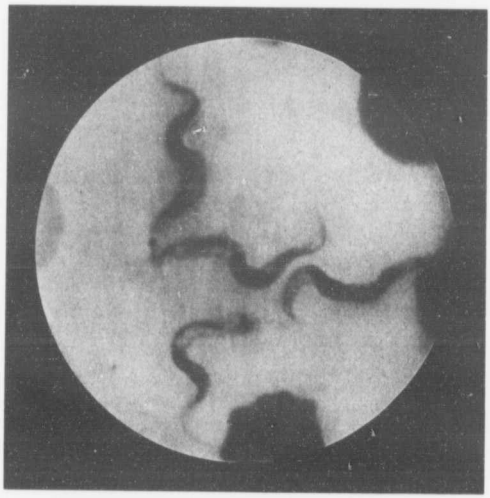
According to Mannaberg, the principal reasons for the irregular manifestations of the fever are found in the following facts:

1. The generations of parasites are less uniform than in fevers of the first group, as a consequence of which sporulation is completed, not in the short period of a few hours, but continues to take place for twenty-four to thirty-six hours. The fever paroxysm is, therefore, prolonged.

2. The evolution of the parasites is not confined within any strict limits, as is the case in parasites of the first group; on the contrary, there is a marked inclination to hastening of the maturation, in other words, to anticipation.

3. Multiple generations, although seldom more than two, as well as mixed infections, are frequent.

The symptoms of subtertian infection present an extraordinary variety. There is scarcely a symptom, that can be described as of constant occurrence. In many instances, the irregularity of the fever is due to a number, more or less great, of successive generations of the parasite, at different stages, developing in the blood simultaneously. A continued type of fever, which we now know is the result of the segmenting forms of one group of subtertian



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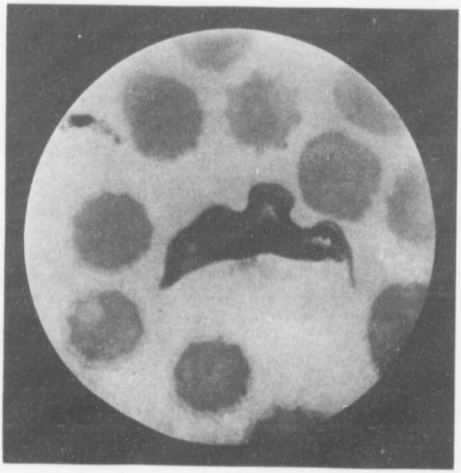
Trypanosoma brucei.

parasites, over-lapping those of another, was recognised even by Hippocrates (460-377 B. C.), who divided the fevers into continued, quotidian, tertian, and quartan. Celsus (first century A. D.), described the various forms of ague, and mentioned a condition, which is identical with the malignant type of æstivo-autumnal fever.

The minute study of malarial diseases commenced, after the introduction of cinchona bark, from Peru into Spain, by the Viceroy Del Cinchon, and his physician, Juan del Vego; the latter used the bark as a therapeutic test, to distinguish malaria from other fevers. Torti (1712) published the first classical description of pernicious malarial fevers; Andourd (1803-1823) called attention to the constant enlargement of the spleen. The discovery of melanæmia by Merckel, Virchow, and Heschl (1847-1850), was the next landmark in the history of malaria. The discovery of the specific parasites, by Laveran (1880), was the first great step in the etiology of malaria. Golgi of Pavia, in 1889, announced that he had observed differences between the rosettes of the tertian and quartan forms of the fever, so great and so constant, as to make him satisfied, that they were two distinct species of organism. At the same time, he made the important observation, that the periods of occurrence of the fever corresponded with the times of maturation of the parasites. These, coming to maturity about the same time, shed their sporules into the blood, and this determined the febrile attack.

Golgi's observations explained the periodicity of the intermittent fevers. Grassi and Feletti (1890) recognised a third species of the parasite, having the peculiarity, that some of its individuals, instead of being of rounded form, were of crescentic shape. This species bears the title "æstivo-autumnal," on account of the season in which it showed itself in Italy. It was also noted, that æstivo-autumnal was not so regular in its periods, as the others, and was much more dangerous. These discoveries explained the sporulation, and propagation of the parasites, within the human body. Apparently, the whole life history of the organism was passed in the human body, but the question as to the mode of entrance of the parasite still awaited an explanation.

This problem was solved by Manson and Ross, who demonstrated the sexual cycle of the malarial parasite, in the body of the mosquito. Manson, observing that the flagellated organisms were never met with in the blood, when first drawn, conceived that their function must be that of spores, for spreading the parasite in the



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Trypanosoma pecaudi.

external world, and some suctorial insect seemed to him the probable agency of their diffusion.

Manson had previously observed the cycle of development, passed by filarial embryos in the mosquito, and became impressed that a similar series of events occurred with malaria.

Ross proved, by direct observation, that the stomach of a mosquito was a suitable medium for the flagellated phase of the malarial parasite to develop in, and that different species of malarial parasites require different kinds of mosquito, as their alternative hosts.

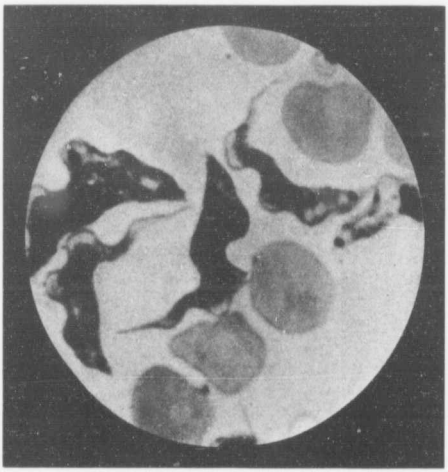
The æstivo-autumnal parasite.

The early intracorpuscular forms of this parasite, differ in no way from similar bodies of tertian and quartan infection. In fresh blood, it appears as a small, round, pale body, adhering to the red corpuscle; later, it is found within the corpuscle. In prepared specimens, it appears as a small, round, clearly defined, and darkly stained body. Corpuscles containing two or more spores, or amœbulæ, are frequent. Whilst it is not uncommon for two or more spores to invade one blood cell, usually only one goes on to full development.

As the parasite develops, it assumes a ring shape, surrounding a central clear area. The ring may be of uniform calibre throughout, but frequently develops a thickening of one segment. The organism presents one nuclear body, two nuclear bodies close together, two nuclear bodies at opposite poles, or more than two nuclear bodies, placed equidistant, or scattered irregularly around the periphery.

A red mottling of the infected corpuscles is frequently seen, similar to that described in tertian malaria, as Schüffner's dots. These are Maurer's granules. In colour, the infected cells often present a greenish-yellow tinge, contrasting with the pale-yellow of the normal ones.

Pigment usually forms when the organism occupies more than half of the corpuscle. The pigment takes the form of fine, or coarse, black granules, distributed around the periphery, or heaped up at one or more points. The granules are not numerous; they increase in size with age. The organism now has the appearance of a limiting membrane, containing a strongly basophile medium, holding granules in suspension. In this form, it increases, until it occupies most or all of the blood-cell.



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Trypanosoma pecaudi.

Development of the crescent.

It has been established, that the parasites of malaria are present in human blood, in two distinct forms, one sporulating asexually in the human body, and causing the attacks of fever, the other undergoing sexual development in the body of the mosquito. Both forms are developed from spores, introduced by the mosquito. The stage, at which they begin to develop their respective peculiarities, is uncertain. Instead of carrying out the process of sporulation, some of the plasmodia become crescent-shaped, and remain quiescent in the human body.

The crescents are of two different natures, male and female. In the female crescent, the pigment granules are generally grouped in the form of a ring, or compact mass, and in the centre of the crescent body; (2) the protoplasm stains a deep blue; (3) the shape is long, narrow, and typically crescentic; (4) nuclear chromatin is massed in centre of pigment.

In the male crescent, the pigment is more scattered, and, as a rule, placed eccentrically, being nearer to one end than the other; (2) the nuclear chromatin is arranged in an extensive loose network, or in four or five masses; (3) the protoplasm stains more faintly; (4) the shape is shorter and broader than the female.

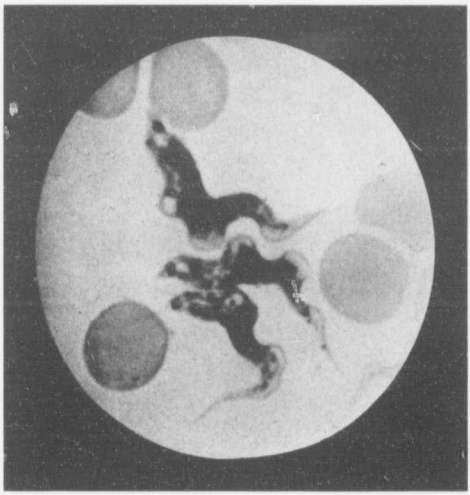
The discovery has only recently been made, that the crescents are bodies with sexual capabilities, whose function is the prolongation of the species, in a cycle outside of the human body. It had long been known, that certain large pigmented, intracorpuscular forms, of tertian and quartan parasites, and the crescents of æstivo-autumnal infection, did not undergo sporulation, but remained circulating in the blood.

The crescentic body lies inside the red blood-corpuscle, the hæmoglobin of which it has absorbed. A delicate bow may be seen running from the extremities, or horns, of the crescent. This bow, or halter, which crosses the concavity of the crescent, is the outer border of the corpuscle, the shell of which is still closely applied to the convex surface.

As a rule, crescents only appear in the blood, after the fever has been present some time, and are still met with, long after the patient has recovered from the immediate effects of malaria.

The formation of flagellated organisms.

The formation of flagellated organisms does not take place



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Trypanosoma pecaudi.

in the circulating blood; it begins after the blood remains on a slide for a few minutes, or has remained for some time, in the body of a mosquito. The flagellated body has been observed to be evolved from certain of the large intracorpuscular amœboid bodies of tertian and quartan parasites, and from the crescentic body of the æstivo-autumnal parasite.

As viewed under the microscope, the crescentic body can be seen to develop into the flagellated organism, by passing through the following successive stages:—

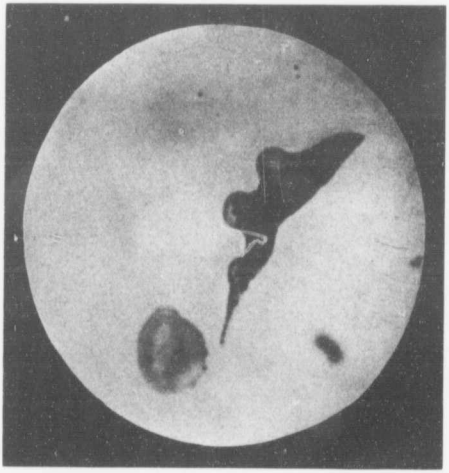
(1) Crescents;
(2) Oval bodies;
(3) Spheres;
(4) Flagellated bodies.

The crescent becomes straight, next it becomes oval, then spherical, after which the centrally collected pigment becomes arranged as a capsulated ring, before being scattered through the sphere. Finally, flagella, usually about four in number, burst through the periphery of the sphere, and grow to a length of three to five times the diameter of a red corpuscle.

Shortly after the appearance of the flagella, they become detached from the body of the organism, and move about as free parasites in the blood. The free flagellum represents that form of the malarial parasite, which is destined to propagate the species outside the human body. The free flagellum,—a true spermatozoon in form, appearance, and mode of development,—penetrates the female, crescent-derived sphere, which is fertilised thereby, completing the sexual developmental cycle of the parasite.

The asexual cycle.

Sporulation.—Segmentation, in æstivo-autumnal infection, does not take place in the peripheral blood, but in the internal organs, particularly the spleen, bone-marrow, and cerebral capillaries. The sporulating body, of the subtertian parasite, differs from that observed in tertian and quartan fevers, both in size and in number of spores. Whilst the quartan body quite fills the corpuscle, and the tertian, fully developed body exceeds the red corpuscle in size, the subtertian rosette, or sporulating body, is considerably smaller than the red cell. The number of spores varies from eight to fifteen.



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Trypanosoma pecaudi.

Pathogenesis of subtertian infection.

The disparity between the number of subtertian parasites, found in the peripheral circulation, and the severity of the illness, is a subject to which many writers have drawn attention. As a rule, the number of parasites increases with the severity, and duration, of the disease. In some infections, they are remarkably numerous,—so numerous that, in certain fields, almost every corpuscle harbours a parasite.

Külz reports malaria, without the finding of parasites in the blood, and the finding of parasites without malaria. He points out that malaria may be present, even when no parasites can be detected in the spleen.

In rare instances, and at certain times, the parasite, or its product melanin, even in severe infections, might not be detectable in the peripheral blood. In these cases, invaded corpuscles accumulate in the capillaries of certain organs of the body, whilst only stray ones are found in the peripheral circulation.

Irregularity and persistence, with a tendency to develop pernicious symptoms, are the clinical features of æstivo-autumnal infection. These features are explained by the physical characteristics of the specific parasite.

Among the features which distinguish this parasite, from tertian and quartan forms, are: (1) the short cycle of development; (2) the resistance to quinine; (3) accumulation of parasites in various internal organs.

The degree of anæmia depends, on the one hand, on the destruction of blood by the parasites, and on the other, on the activity of the blood-making organs. The short cycle of development enables the subtertian parasite to increase with great rapidity. Blood regeneration is never sufficient, to make good the loss, with the rapidity of its occurrence, particularly in the enormous blood infection, so often seen in this form of malaria. A considerable degree of anæmia, therefore, is never lacking.

While the average duration of a tertian paroxysm is between eleven and twelve hours, the length of the æstivo-autumnal is more nearly twenty-four hours, with a striking tendency to become remittent.

The subtertian parasite may cause a continuous as well as a remittent fever, the rapidity of its multiplication masking the periodicity.

× 3000 diam.

Trypanosoma pecaudi.

The pernicious type of æstivo-autumnal fever may be due to an enormous blood infection, or to the localisation of the parasites in one organ. In this case, the symptoms would depend on the localisation, which might be almost entirely limited to the brain, the stomach, or the intestines.

Cerebral type.

The possibility of sudden death, from cerebral localisation of æstivo-autumnal parasites, is well worth remembering. A patient, with no subjective symptoms of illness, may expire with such suddenness as to simulate heat-apoplexy.

A malarial fever, of a mild, irregular type, which does not yield promptly to quinine, should be kept under constant observation.

It is noteworthy, that pernicious attacks are, as a rule, preceded by attacks of milder form; they are not generally observed as primary illnesses.

The earlier observers had remarked the presence of pigment, in the cerebral capillaries of such cases, and attributed the associated symptoms to thrombosis by the pigment.

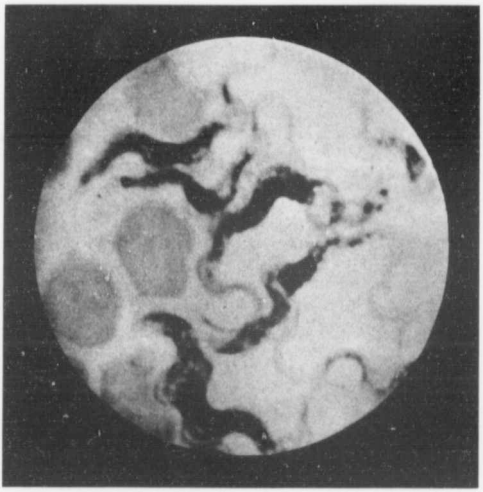
Schellong explains the different symptoms of malaria, as occurring through capillary stasis, which ensues as a result of the disintegration of the red corpuscles, in the various organs, by the influence of the malarial parasites.

It was shown, by observations made by Bignami, in these cases, that, in pernicious fevers, the brain is usually found so full of parasites, that, in some areas, it is impossible to find a red corpuscle presenting a normal appearance. The arterioles, and smaller veins, have fewer parasites than the capillaries.

The rapidity of the symptoms is associated with the short cycle of the parasite, and the interference with the cerebral circulation sufficiently explains the predominance of the cerebral symptoms.

In connection with the special selection of the brain by this parasite, G. Thin called attention to the comparatively small size of the cerebral capillaries, their calibre not being much more than half that of the capillaries of the other parts of the body, and being scarcely equal to that of a red corpuscle. It was known that the infected corpuscle adhered to the vascular wall.

This tendency to adhere to the capillary endothelium, in con-



× 3000 diam.

Trypanosoma evansi.

junction with the small calibre of the cerebral capillaries, favours thrombosis by the infected corpuscles.

Thin suggested, that the arrest of the infected corpuscles, in these fevers, in the brain capillaries, while the infected corpuscles, in tertian and quartan fevers, were not arrested in them, might be due to the greater toxicity of the parasite in these fevers, which affected the corpuscles more severely, and rendered them more adherent to the endothelium. The blocking, once begun, would be furthered by the short cycle of development of the parasite.

In many of the smaller capillaries, the lumen of the vessel is filled with red corpuscles, each containing one or more parasites. The veins contain a smaller number of infected cells. The intracorpuscular forms are present, in every stage of development.

The delirium, convulsions, aphasia, coma, and other cerebral symptoms, are a consequence of occlusion,—by the malaria parasites, of the capillaries of the various nerve centres involved.

Intestinal type.

This form, which, according to Martin, has a course without any attendant rise in temperature, bears a great similarity to Asiatic cholera, and mostly ends in death.

Severe diarrhœa, vomiting, and thirst, are the most prominent symptoms. Collapse supervenes, but consciousness is often maintained until the last moment.

The possibility of a suddenly developed dysentery, being of malarial origin, must be kept in view.

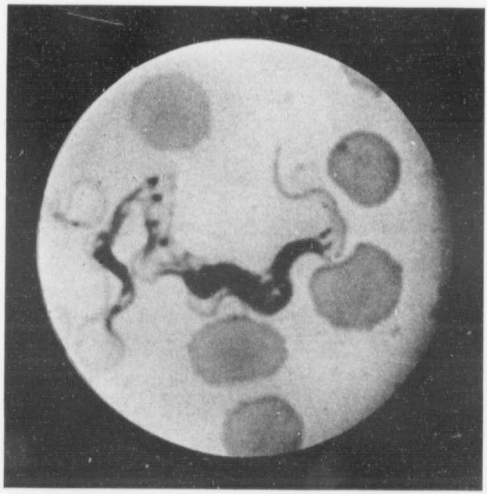
A blood examination will clear up the diagnosis between ordinary and malarial dysentery.

In the intestinal type of malaria there is probably an accumulation of plasmodia, in the vessels of the intestinal tract. These accumulations may lead, as in the brain, to thrombosis, to capillary hæmorrhages, and to necrosis.

What determines the swarming of plasmodia to the different organs, in the various types of malaria, is unknown.

Among the factors, which are at present considered as especially responsible for the development of the pernicious type of fever, are the following:—

(1) The number of parasites;
(2) Their toxicity;
(3) Their resistance to antimalarial measures.



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Trypanosoma evansi
(dividing).

Severity of the infection.

The number of parasites, in æstivo-autumnal infection, is frequently extraordinary. Fields may be seen in which every corpuscle harbours a parasite.

As the cycle of development, of the subtertian variety, is completed in the internal organs, therefore, nothing can be concluded from the ordinary blood examination, as to the number of parasites that may be present. Graham gives records of three cases, one cerebral, one with symptoms like peritonitis, and one dysenteric, in none of which were any parasites found in the blood.

The enormous destruction of blood-corpuscles, incident to a high grade of malarial infection, is productive of malarial cachexia. The brunt of the disturbance falls on the bone-marrow and the liver; the former to repair the blood-destruction, and the latter to remove the débris. So long as the bone-marrow is able to repair the blood-loss, and the other organs to meet the demands made upon them, there will be no cachexia.

The mere accumulation of parasites may be sufficient to terminate life.

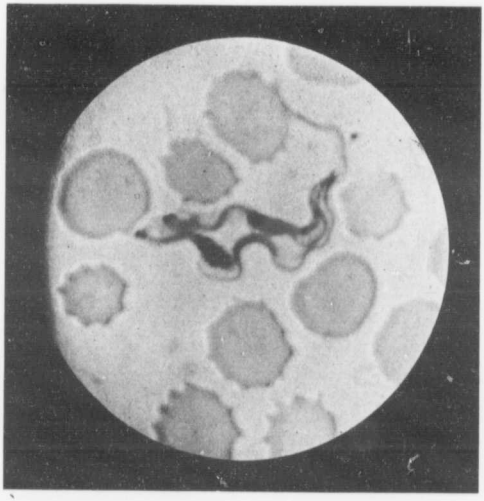
With respect to the blood-loss, the effect is the same, as in oft repeated hæmorrhages. In malaria, there is always blood destruction, in proportion to the grade of infection. There is, therefore, no malaria without loss of corpuscles.

While in benign tertian, and quartan infections, the blood may differ but little from the normal; in subtertian infections, a blood condition, passing through all the phases of anæmia, is repeatedly observed.

In one patient, before the paroxysm, Boisson found 1,700,000 corpuscles per c. cm.; after the paroxysm, 670,000; in another case, before the paroxysm, 2,400,000; after, 1,600,000.

The excretion, by the kidneys, of hæmoglobin set free in the circulation, by reason of the solution of corpuscles, is only a symptom of the blood destruction. Ponfick is the author of the postulate, that hæmoglobinuria only occurs after the destruction, in a paroxysm, of one-sixth of the corpuscles.

In addition to the periodic destruction of blood-corpuscles, there are by-products which must be removed from the circulation. The work of removing débris falls principally on the liver, but also on the spleen, the lymph glands, the kidneys, and the intestinal mucous membrane.



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Trypanosoma evansi
(dividing).

Melanæmia.—The presence of melanin in the blood is peculiar to malaria, and of diagnostic importance. Melanin is a product of digestion of the hæmoglobin, and is formed in the body of the parasite. After the destruction of the corpuscles, the pigment is set free, after which it is taken up by the leucocytes, and deposited in internal organs, where it acts as a foreign body.

As long as malaria parasites continue to develop, melanin may be found; it disappears from the blood, usually within forty-eight hours of the termination of an infection. In the absence of malaria parasites, from the peripheral circulation, the detection of pigment-bearing leucocytes, in the circulation, is of great diagnostic importance, as an indication of the continued activity of the parasites in the internal organs.

The melanin, which is carried to, and deposited in, the liver, where it acts as an irritating, foreign body, lays the foundation for progressive hepatic disease. That malaria may be one of the exciting causes of cirrhosis, most authorities agree.

During severe malarial infection, large quantities of débris, consisting in part of corpuscles destroyed by parasites, as well as corpuscles destroyed by toxins, are brought to the liver. Bile is the product of this reduction of hæmoglobin. The flooding of the duodenum, with bile, results in bilious vomiting, and bilious evacuations.

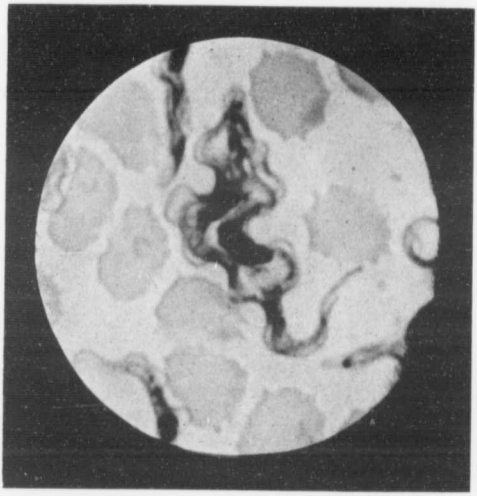
Toxicity of the parasite.

That malaria parasites produce a toxin was suggested by Golgi, whose demonstration of the coincidence of the fever paroxysm, with the segmentation of tertian and quartan parasites, did much to clear up the mysticism surrounding these fevers. Marchiafava, Bignami, and Celli, demonstrated the same for the subtertian parasite.

The severity of the paroxysm is, according to Golgi, in exact proportion to the number of parasites.

A greater toxicity is attributed to the subtertian, than to the tertian, and the quartan parasites. It would appear that the perniciousness of a malaria parasite depends, to a great extent, upon the susceptibility of the individual, and the proliferative activity of the parasite.

Tertian and quartan infections usually pursue a favourable course, terminating in spontaneous recovery. Even when severe



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Trypanosoma evansi
(dividing).

relapses bring about grave cachexia, dangerous symptoms are comparatively rare.

Of an altogether different character is the æstivo-autumnal infection, which, if untreated, gives rise, in many instances, to the gravest manifestations. The rapidity of the multiplication of the parasites, and their special malignancy, combine to make a subtertian infection one of uncertainty, and of grave apprehension.

Resistance to medication.

The effect of quinine, on malaria, depends on its power of destroying the plasmodia in the circulation. The object of the administration of quinine is the destruction of the parasites; a certain concentration of solution is therefore necessary, to attain the object for which it is used.

Of all the developmental forms of the malaria parasite, the spores are the most susceptible to quinine. Quinine exercises its action rapidly on the youngest parasites, when they are free in the plasma.

In the administration of the drug, *per os*, several hours before the expected paroxysm, the greater portion would then be in the circulation at the time of segmentation ready to act on the newly formed spores.

If quinine be exhibited in large doses, four to six hours before a paroxysm, sporulation may be delayed, but not prevented.

The young, endoglobular parasite, is protected by the corpuscle, and is less sensitive to quinine.

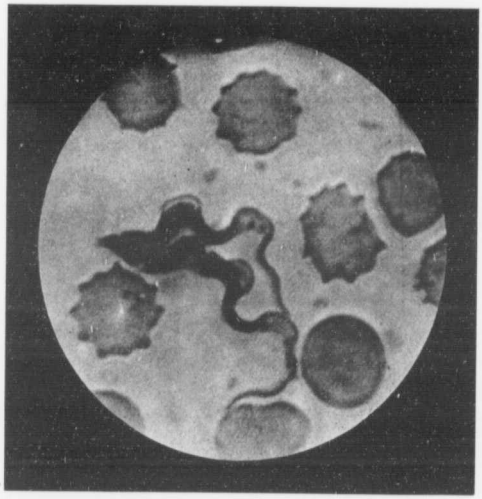
The crescents successfully resist the action of quinine.

Halteridium and Proteosoma.

The members of the genus *Hæmamœba* show such remarkable analogies in the processes of their development, that the laws which govern the development of one variety may safely be assumed to hold good in that of the others.

Birds, particularly in warm climates, suffer from a plasmodial infection, of which the parasites are strictly analogous to human malaria.

Since Danilewsky discovered the occurrence of disease producing endoglobular parasites in birds, two important species of bird malaria have been studied, each of which bears a marked re-



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Trypanosoma evansi
(dividing).

semblance to human plasmodia. They are both endoglobular, and both are composed of pale protoplasm carrying a large number of grains of black pigment. Like the human parasites, they sporulate and form flagellated bodies.

Koch gives a summary of the development of both *Halteridium* and *Proteosoma:*

1. Young parasite, composed of chromatin, nucleus and very scanty plasma, no pigment. Lives in or on red blood corpuscles.

2. Adult parasite, composed of chromatin, pigment, and considerable increase in plasma.

From this point development may proceed in two ways.

3. Endogenous, that is, a sexual form of development, in body of principal host (bird). Simple division into numerous small spores which commence their cycle afresh, abandoning the pigment in the mother cell.

3. Exogenous, that is, sexual form in body of intermediate host (mosquito). Parasite leaves the blood corpuscle, and can be differentiated into male and female.

4. Formation of spermatozoa and impregnation of female.

5. Conversion into vermiform bodies which

6. Pass through the stomach walls, and form coccidia-like spheres, in which

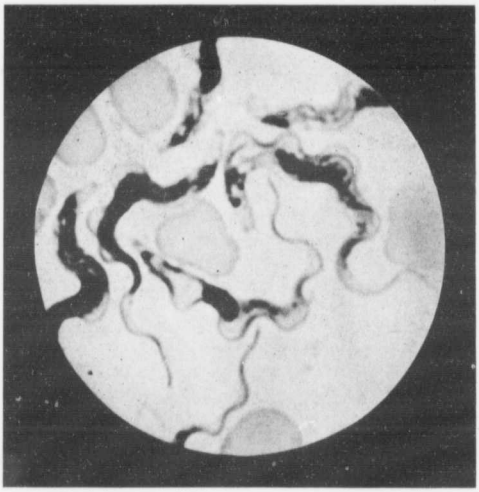
7. Sickle-shaped bodies develop.

8. Passage of these into the poison glands, and possibly into other organs.

9. Infection of principal host.

In the adult stage, the *Proteosoma* is easily distinguished from *Halteridium*, by the fact that the latter does not alter the position of the nucleus of the red corpuscle, while the former pushes it to one side.

Halteridium does not displace the nucleus, but spreads along one side of the corpuscle, and expands over both ends of the nucleus.



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Trypanosoma evansi.

Halteridium.

Hæmamœba danilewskyi, or *Halteridium*, is found in sparrows, finches, jays, pigeons both tame and wild, and in small birds of prey.

The adult parasites contain many coarse, dark pigment granules, and exhibit marked sexual characters. The cytoplasm of the female forms is very dark. The male parasite is recognised by the paler cytoplasm, and considerable amount of nuclear material.

The intermediate host is as yet unknown; Koch and Ross failed to communicate it by mosquitoes.

Infection by this plasmodium, which apparently is not pathogenic, persists for months.

Hæmamœba relicta
(Proteosoma).

Proteosoma infection is found in sparrows, larks, weavers, and finches. Canaries are very susceptible, and in these the disease runs a more acute course, ending somewhat abruptly between the tenth and fourteenth days. One attack of *Proteosoma* infection confers a certain amount of immunity.

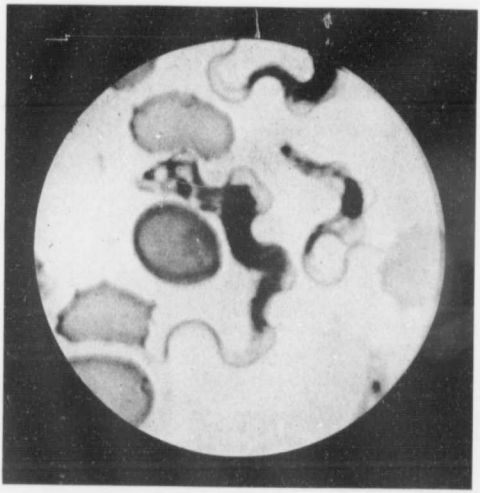
The intermediate host is the grey mosquito *(Culex)*.

The flagellated malarial body was for a long time a puzzle to observers. Manson considered it to be the form of the parasite, by which it is able to survive in water, from which, subsequently, man was infected by drinking the water containing these forms. Manson concluded, that the mosquito was the liberating agent of the malaria parasite, as well as of the filaria, and that the flagellated body, sucked in its latent form into the mosquito stomach, developed therein; that the flagella broke free from the central sphere, as they do on ordinary blood slides, and that, in virtue of their locomotive faculty, they traversed the blood in the mosquito's stomach, penetrated the wall in the mosquito's stomach, entered some cell, and there started the extracorporeal life of the parasite.

Manson considered that his theory was justified by certain facts, which he had discovered in connection with filaria, and by analogies from the life-histories of sporozoa.

Manson's theory was the starting point of mosquito-malarial work.

Ronald Ross took up the investigation, and proved, by direct



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Trypanosoma evansi.

observation, that the stomach of the mosquito is a suitable medium for the flagellated phase of the *Plasmodium malariæ* to develop in.

In this connection, Ross showed that the *Proteosoma* of birds, and the crescent-forming malarial parasite of man, were capable of development in grey *(Culex)* and in dapple-winged *(Anophelinæ)* mosquitoes respectively.

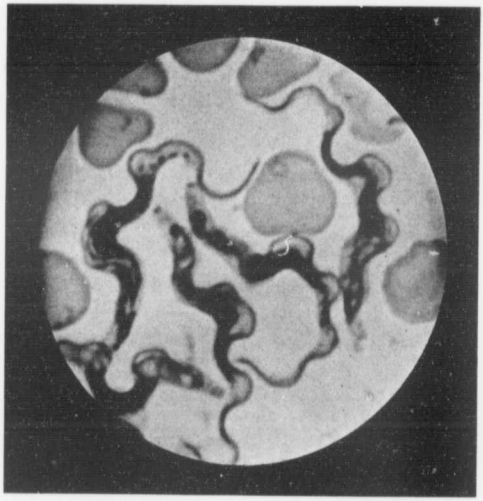
The examination of grey mosquitoes *(Culex)*, fed on sparrows infected with *Proteosoma*, showed that the *Proteosoma* formed two different kinds of reproductive elements, namely (1) a body from which, when ruptured, escaped vast numbers of filaments: these floated away in the surrounding fluid; and (2) a smaller number of bodies containing large black spores.

Ross very easily accomplished the infection of healthy birds. Sparrows and weaver birds, whose blood on several examinations had been found to be entirely free from infection, were subjected nightly to the bites of numerous grey mosquitoes, fed more than a week previously on a sparrow containing *Proteosoma*.

The birds became infected with swarms of parasites. All of them died very soon, and the liver was profusely charged with the black pigment of malaria. The invasion of the blood by the parasites presented such constant and unmistakable characters, that no possible room for doubt was left as to the infection being due to the mosquitoes.

Ross found the course of events was as follows: The blood would remain entirely free from *Proteosoma* until the fifth, sixth, seventh, or eighth day after the experiment, when one or two parasites only would be found in an entire specimen. Next day, it would invariably be seen that the number of parasites had largely increased; and this increase would continue until, in a few days, in almost every case, the parasites became so exceedingly numerous, that from ten to sixty would be counted in a field. Most of the birds then died, and showed the characteristic features of malarial infection.

MacCallum, while investigating the *Halteridium*, distinguished differences between the spherical bodies, seen in the shed blood of a bird infected with that parasite. Though alike in size, some had a more granular protoplasm than the others, which had a more hyaline aspect; and he had observed that the more hyaline ones alone formed flagella. These, after wriggling themselves free from the parent cell, swam away until they approached the more granular bodies, into which they plunged and disappeared. Here was wit-



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Trypanosoma evansi.

nessed the process of fertilisation. The flagella were neither more nor less than spermatozoa, and the more granular cells were ova. As a result of fertilisation, the female cell altered its shape, and assumed an elongated form, to which the term vermiculus was applied.

Manson connected this observation with the previous one of Ross: The pigmented bodies seen in the stomach of the mosquito were fertilised female cells.

This at last explained the function of the flagella.

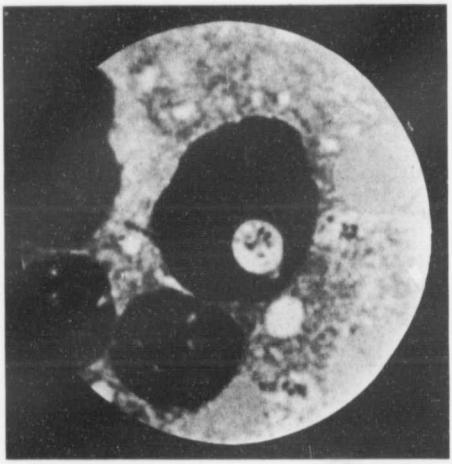
Following out these observations, Grassi, Bastianelli, and Bignami succeeded in tracing out the complete development of æstivo-autumnal parasites in *Anopheles maculipennis*.

PIROPLASMA.

Piroplasma comprises a number of species, parasitic in the blood of various mammals. The parasites bear a striking resemblance to malarial organisms, but are devoid of pigment.

The following species are recognised:—

	Geographical distribution.
Bovine—	
Piroplasma bigeminum ..... Smith and Kilborne	Europe America Australia Asia Africa
Piroplasma bovis ..... Babes	
Piroplasma annulatum ... D-chunkowsky	Transcaucasia Japan South Africa Madras Annam Portugal
Piroplasma mutans ..... Theiler	Gold Coast
Piroplasma bacilliforme ..... Miyajima and Shibayama	Dutch Indies China German East Africa Sudan Congo New Guinea Australia
Piroplasma parvum ..... Theiler	South Africa East Africa Egypt Tunis



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Development of trypanosomata in internal organs.
Intracystic form of Trypanosoma pecaudi in splenic pulp.

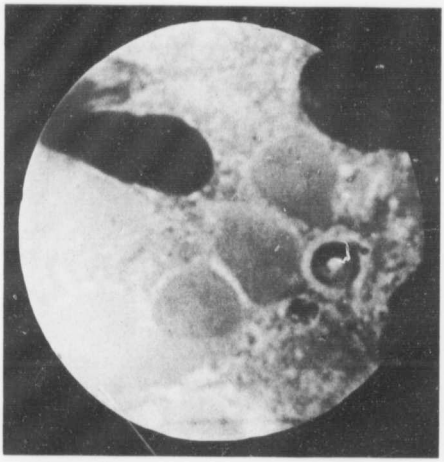
Sheep—	
Piroplasma ovis .....Starcovici	Roumania, Italy, France, West Indies, U. S. of America, South Africa
Canine—	
Piroplasma canis ..... Piana and Galli-Valerio	India, Africa, France
Piroplasma gibsoni .....Patton	Italy
Equine—	
Piroplasma equi .....Laveran	Germany, South Africa
Piroplasma caballi .....Marzinowsky	Madagascar, Venezuela
Human—	
Piroplasma hominis ..... Wilson and Chowning	Idaho, Montana, Wyoming, Utah, Nevada, Oregon, Washington, Alaska
Rat—	
Piroplasma muris .....Fantham	
Monkey—	
Piroplasma pitheci .....Ross	
Hedgehog—	
Piroplasma ninense .....Yakimoff	

Symptomology.

The clinical account of piroplasmosis consists principally of the appearance of high fever, anæmia, enlarged spleen, and bloody urine.

The clinical characters of piroplasmosis, together with the characteristics of the parasite, and the *post-mortem* appearances, bear a striking resemblance to malaria.

Red-water fever—the name by which it is known in infected districts—sufficiently indicates the most prominent symptoms, hæmoglobinuria and pyrexia. The sanguineous, dark red or black colour of the urine is a sequel of the destruction of red blood corpuscles, and the mixture of the urine with the dissolved hæmoglobin. Although, in severe infections, the disease is accompanied by hæmo-



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Development of trypanosomata in internal organs.
Endoglobular form of Trypanosoma pecaudi in the spleen.

globinuria, this is not a constant concomitant, nor even a frequent one.

According to Theiler, there are three different piroplasmoses known to exist in Transvaal cattle: (1) one due to *Piroplasma bigeminum*, and commonly called "red-water," (2) one due to *Piroplasma parvum*, and known by the name of East Coast fever, and (3) one due to *Piroplasma mutans*, for which a specific term does not exist, but it probably ranges under the name of "gall sickness."

An acute and chronic form of piroplasmosis is seen in dogs. In the former, anorexia, fever, anæmia, jaundice, weakness, and paresis of the hind legs, make up the clinical picture. The chronic form is associated with intense anæmia and emaciation, but rarely with jaundice or hæmoglobinuria.

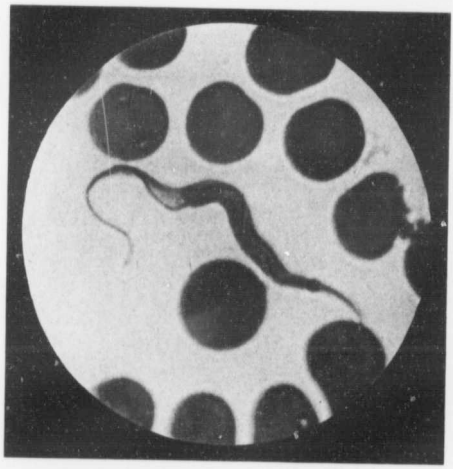
Transmission of piroplasma.

Piroplasma infection is conveyed through the agency of ticks. Infection is transmitted hereditarily through the egg; young ticks—the progeny of infected mothers—carry the infection. The female tick drops off the animal and deposits her eggs on the ground; the young crawl on to animals, soon after their liberation, and they carry with them the infection. *Piroplasma parvum*, the parasite of East Coast fever, is an exception, as it does not pass through the egg; infection taken in by the larva is transmitted by the nymph, and that taken in by the nymph is transmitted by the adult. The adult tick lives a long time, and the contained piroplasma lives as long as its host, having been found after the tick has been starved for many months.

Immunity.—An attack of piroplasmosis confers immunity for that particular strain, but the animal may still be susceptible to an attack by another strain of piroplasm.

Blood lesions.

The various phases of anæmia are found associated with piroplasmosis. As in malaria, the grade of anæmia varies with the type and severity of the infection. From simple diminution in hæmoglobin, the blood in severe infections may be seen in poikilocytic, normoblastic, and even in megalocytic and megaloblastic phases of anæmia.



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Trypanosoma lewisi.

Morphology of piroplasmata.

All the known species of *Piroplasma* exhibit great similarity in morphological characters. Spherical, bacillary, and pyriform are the forms assumed by the endoglobular parasites. The pear-shaped forms are the most characteristic.

A common arrangement in *P. bigeminum* is for two such bodies, with their narrow ends concurrent, to be present in a blood corpuscle.

The occurrence in corpuscles of piroplasms in pairs, fours, eights, and sixteens, suggests their multiplication by binary fission.

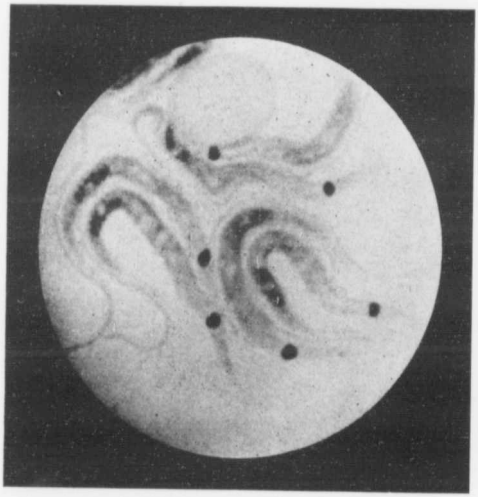
In the pear-shaped forms, the nucleus is lodged at the broad end of the organism, and appears as a compact mass of chromatin. They sometimes show amœboid movements within the corpuscle, becoming irregular in form, and also throwing out pseudopodia from various parts of the body. *P. bovis* and *bigeminum* are the parasites which present the form of a pear.

Bacillary form.—*Piroplasma annulatum, mutans, parvum,* and *bacilliforme,* present the rod or bacillary form in endoglobular development. This form is bacillus-like, with the chromatin at one end of the rod. Often the rods are somewhat thicker in the middle, and between this form and the pear shape all transitions take place.

Spherical form.—This form, in which the centre appears vacuolated, with the chromatin at the periphery, resembles the early rings of tropical malaria.

Smith found, in Texas fever, that the percentage of infected corpuscles is seldom higher than 1 to 2 per cent., in the circulating blood. On the contrary, when the animal dies or is killed during the febrile stage, a very large number of blood corpuscles is found to be infected in the capillary tracts of the various tissues.

Nuttal and Fantham, working with *Piroplasma parvum,* observed that the percentage of infected corpuscles in the peripheral circulation rises steadily as the disease progresses, and, at the same time, there is a progressive increase in the number of infected corpuscles, which contain two, three, and four or more parasites. The percentage of infected corpuscles, observed in smears from various internal organs, immediately after death, and the percentage of corpuscles containing more than one parasite, coincide with those obtained in the case of the peripheral blood. In other words, there does not appear to be a heavier infection of the corpuscles in any of the internal organs, than there is in the general circulation.



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Trypanosoma lewisi.

In cattle that recover from the disease, a general decrease of parasites is noted in the blood after the crisis.

The animal is completely protected against relapses, and recovery apparently leaves a complete immunity.

Anaplasma marginale.

Anaplasma marginale is a specific protozoal parasite of cattle, which Theiler proved to be the cause of gall sickness in South Africa. The endoglobular bodies were considered to be a phase in the life-cycle of *Piroplasma bigeminum*, until Theiler determined their exact significance.

The parasite appears as a spherical body, which consists wholly of chromatin substance. The situation of the "marginal points" varies. Some are marginal, others are central, but the majority are a short distance from the edge of the corpuscle. They may occur free in the plasma. They range in size from minute points to bodies as large as eosinophile granules.

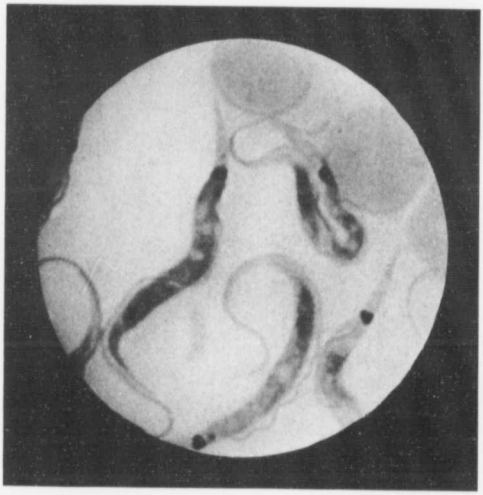
In South Africa, the blue tick *(Boophilus decoloratus)* is supposed to act as vector of the disease. Theiler states that *Anaplasma marginale* and *Piroplasma bigeminum* can be transmitted, not only by the same species of ticks, but by one and the same individual. Balfour has noted the existence of anaplasmosis and piroplasmosis, occurring together in equines in the Sudan, where the blue tick does not exist. He considers that *Rhipicephalus evertsi* is the tick implicated in transmitting the disease in the Sudan.

HÆMOGREGARINA.

The genus *Hæmogregarina* forms one of the most widely distributed groups of Hæmatozoa, appearing in all three classes of cold blooded animals. While isolated hæmogregarine infection occurs in mammalia, it exists as a natural infection in the blood of fish, amphibia, and reptiles.

The method of development, of the hæmogregarine, corresponds closely to that of the malaria parasites, the intermediate host being the leech.

Hæmogregarina stepanowi, discovered by Danilewsky (1885), is



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Trypanosoma lewisi.

the first hæmogregarine, of which the whole development has been observed. This hæmogregarine is a parasite of the marsh tortoise; the belief that the intermediate host was the proboscis-leech originated with Schaudinn, who instigated Siegel's investigation, on the process of development of the hæmogregarine, afterwards fully worked out by Reichenow (1910).

When harboured by the blood corpuscles, the hæmogregarine takes the form of a bean; it is differentiated into male and female forms.

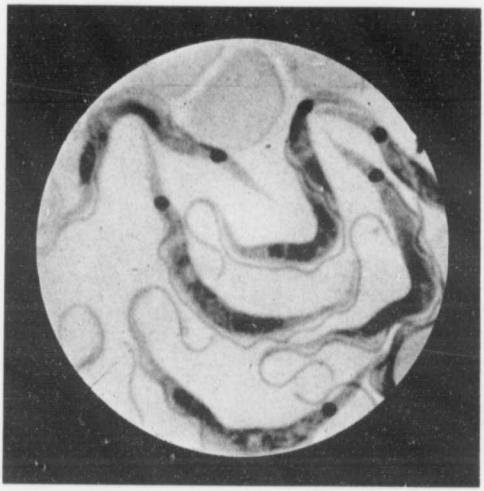
Billet describes, in the Gecko *(Platydactylus)*, two kinds of bean-shaped parasites, which he regards as male and female. Some are more slender, and longer, and have an oval, strongly staining nucleus; others have a shorter, and thicker shape, and their rectangular nucleus stains only slightly, and consists of separate chromatin granules, and shows in the middle an entirely uncoloured space.

Sambon observes, in *Hæmogregarina rarefaciens*, bean-shaped parasites, in which he conjectures a sexual difference; first, some with strongly staining granular protoplasm and scarcely visible nuclei, second, those with pale plasma, and deeply stained nuclei.

Conjugation and fertilization.

As soon as the male has found a female, they place themselves side by side, and surround themselves with a common membrane, very thin, and hence not always visible (Reichenow).

The conjugation of the sexual forms, in the leech, is thus described by Reichenow: On contact with the male form, the female prepares for fertilisation. The chromatin granules of its nucleus arrange themselves, in a number of separate heaps, about ten in number. The female form is now ready for conception. Meanwhile, the nucleus of the male form has also changed. The amount of chromatin has further increased; a thick, impenetrable heap of large specks takes the place of chromatin granules, arranged in rows. The nucleus forms four nuclear divisions. While the relative size of the sexual cells, at conjugation, was about the same, the female, in the meantime, has grown considerably, and the male has shrunk. As soon as the male form has entered the female, it spreads out, after which takes place the union of the male with the female nucleus. Both nuclei proceed to form a "fertilisation spindle." Segmentation of the nucleus follows, with the formation of two daughter nuclei. A



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Trypanosoma lewisi.

second segmentation results in the formation of four daughter nuclei. After the second division follows a third; regularly, eight nuclei are formed.

The nuclei develop into narrow, vermiform cells, which escape from the mother-cyst, by rupture, penetrate the intestinal epithelium, and reach the surrounding blood spaces.

Asexual development in the tortoise.

The method of multiplication of the hæmogregarines, in the tortoise, is by segmentation. The stages of division occur exclusively in the internal organs; the growing forms, on the other hand, are found everywhere in the blood.

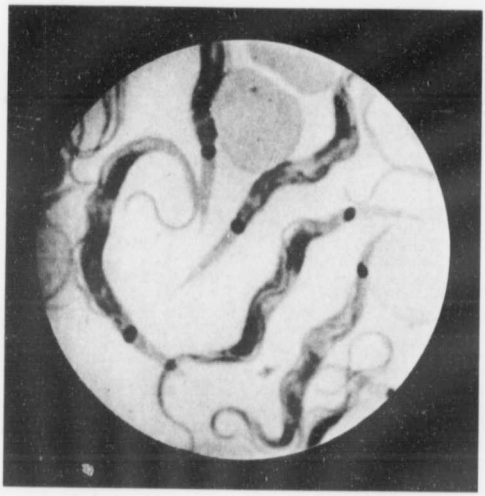
The number of nuclei, resulting from segmentation, varies from 4 to 24. The large numbers occur at the beginning of infection, and small ones at the end. Segmenting forms, which, at the beginning of the infection, contain numerous nuclei (up to 24), gradually decrease in size as the infection proceeds, till only a small number (6 or less) of nuclei develop.

The slender young parasite escapes from the mother-cyst, and propels itself, in the blood, by a vermicular movement. This movement is continued, until the parasite comes in contact with a blood corpuscle, into which it penetrates. Reichenow has remarked the great ease, with which the entrance of the parasite is effected. It takes place with the same gliding movement, as the journey through the serum, only much more slowly.

After penetration of the corpuscle, the hæmogregarine assumes a shorter and broader shape, equally rounded at both ends, and, at the same time, the nucleus takes a spherical form.

The intra-globular parasite has a bean-shaped appearance, which Minchin explains by the idea, that the hæmogregarine has to accommodate itself to the space, narrowed by the cell nucleus which is often found lying close to the concave side of the parasite. On the contrary, Reichenow observes, that the nucleus lies as often on the convex side, or at any other place, and that the curved shape of the parasites depends upon an adaptation to the protoplasmic structure of the blood corpuscle.

As the parasite grows in the corpuscle, it changes its shape, by bending its end, into a little hook-shaped continuation. When the parasite happens to get into a cell, of sufficient length to permit



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Trypanosoma lewisi.

of full development, without crowding, the curvature does not take place.

Through the movements of the parasite, the containing membrane frequently ruptures, and the hæmogregarine escapes, as a long thin worm. On preparing for segmentation, the parasite, formerly worm-like, now assumes an oval shape.

In the tortoise, the asexual multiplication goes on for about 4 months, before the development of the sexually differentiated forms begins.

Effect on host-cells.

The hæmogregarine has no injurious effect on the blood corpuscle. No change of a degenerative nature, caused by the parasite, can be seen, either in the protoplasm, or in the nucleus. It is occasionally seen that an infected corpuscle has lost its hæmoglobin.

Transmission of hæmogregarine infection.

Leeches are the transmitting agents of hæmogregarine infection of fish, amphibia, and water tortoises. Ticks are supposed to act as intermediary hosts for saurians, snakes, and land tortoises.

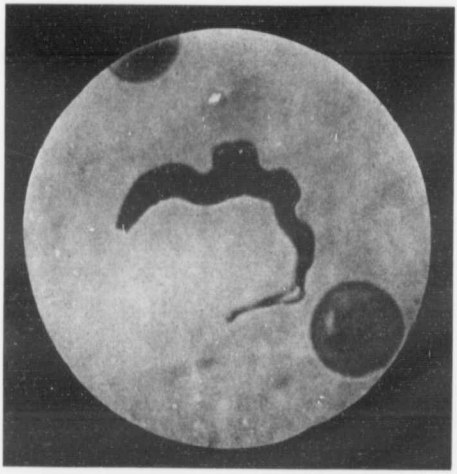
Leucocytogregarina.

The genus *Leucocytogregarina* is parasitic in the blood of mammals. Since the discovery by Bentley in India of the leucocyte parasite of dogs, similar parasites have been described from the rat, mouse, cat, palm-squirrel, and hare.

Leucocytogregarina develops in the host-cell, as a cylindrical body. The parasites do not alter, to any extent, the shape of the host-cells, which seem to be normal. They are usually within large mononuclear leucocytes, but also occur within eosinophile, and neutrophile leucocytes.

The nucleus of the parasite resembles that of *Hæmogregarina*, and is quite unlike the nucleus of *Leucocytozoon*.

Leucocytogregarina is frequently, though not invariably, contained within a cytocyst. The parasites are intracellular, but they may leave the host-cell and move about in the plasma.



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Trypanosoma equiperdum.

Leucocytozoon.

The genus *Leucocytozoon* was established by Danilewsky, who applied the term to parasites which he found in the tawny owl.

Leucocytozoa are found exclusively in avian blood, and inhabit leucocytes, although some doubt has arisen as to the exact nature of the host-cell. Sakharoff considers the enclosing elements to be leucocytes, and, on account of the marked alteration which takes place in the nucleus of corpuscles, invaded by *Leucocytozoa* of the raven, believes that this parasite destroys the nucleus, and thereby annihilates the phagocytic action of the leucocyte. Berestneff agrees with Sakharoff, in believing that the phagocytic action of the host-cell is overcome by karyophagy.

The presence in the peripheral circulation of two well-marked and distinct forms, which represent male and female parasites, often recognisable in fairly young individuals, is one of the chief characteristics of this group of parasites.

The adult female forms are very conspicuous, on account of their granular cytoplasm, which stains a deep blue. They contain, as a rule, many small, circular, unstained areas (vacuoles), and, frequently, large numbers of coarse, or fine, chromatophile granules. The nucleus, which is arranged in a compact mass, is usually indistinct.

The smaller, pale staining parasites, with chromatin granules scattered about the centre, are male forms. The cytoplasm of the male forms is finer in texture, and rarely contains vacuoles.

The contour of the host-cell is unchanged, or it may assume a characteristic form, in which each extremity is prolonged into a triangular tag.

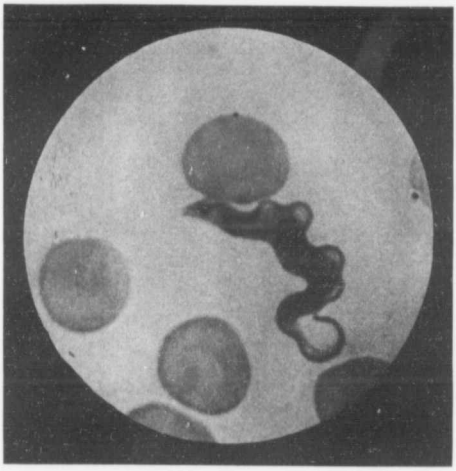
The parasite surrounds, and is invariably closely connected with, the nucleus of the host-cell, which is found at the centre of the spindle, or the nucleus is pushed aside, and flattened, by the parasite.

Leucocytozoon differs from *Hæmamœba*, in being larger, and in possessing no black pigment granules.

KALA-AZAR.

Kala-azar is a chronic, and extremely fatal fever, which, since 1882, has existed in epidemic form in Assam.

It was first seen in 1869, in the district of the Garo Hills,



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Trypanosoma equiperdum.

thence gradually spreading up the Pramaputra, keeping, however, mostly to the southern bank.

While the progress of the disease was slow, it is estimated that, during the succeeding thirty years, one-fifth of the population perished from its ravages. Bentley's figures for Assam give the extraordinarily high mortality of 96 per cent.

Recent reports show that the disease is of wide distribution. It is now known to occur in Assam, Bengal, Southern India, Ceylon, Burmah, China, Arabia, Egypt, Sudan, Tunis, Algeria, South Africa, and Crete. Nearly every country of the Mediterranean littoral has been found to harbour cases of the infantile form.

The insect, which acts as the transmitting agent of Kala-azar, is as yet undetermined. It is probable that the parasites are withdrawn from the blood by blood-sucking insects, such as fleas, bugs, and ticks, and that one of these may prove to be the vector.

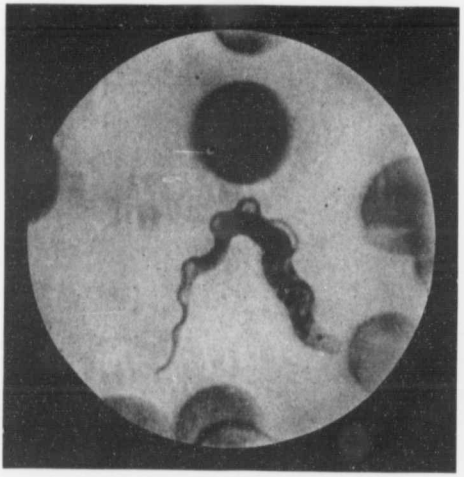
Basile was able to infect three young dogs, by keeping them beside cases of infantile Kala-azar, and believes that the flea is the most likely vector. Cortesi and Levi remark that, in Tunis, the majority of cases are encountered during the two or three months following the spring season, when dog ticks are most common. The occurrence of the disease, in the spring, and early part of the year, has also been noticed by others.

The spread of the disease through members of a household, or community, and the tendency to linger in certain houses, suggested that it may be conveyed by the bedbug. In India, however, the disease appears to cling to river banks, and yet bedbugs are equally common at a distance from rivers.

Leishmania donovani.

The parasites of Kala-azar, known as Leishman-Donovan bodies, are minute round, or oval bodies, measuring usually about 2.5 to 3.5 microns in the longest diameter.

The cytoplasm contains two characteristic chromatin-masses, situated usually opposite to each other, on the shorter axis of the body. The nucleus, or larger chromatin body, is excentrically situated, nearly always compact, and sometimes has a central vacuole; it is more or less spherical, and stains more faintly than the smaller chromatin body. The smaller chromatin body, or blepharoplast, is not always visible, but, when present, is round or rod shaped, and stains more deeply than the nucleus.



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Trypanosoma equiperdum.

The parasites multiply by one of two methods. The most common method is by simple longitudinal fission; in an individual slightly larger than normal, there is a division, first of the nucleus, then of the blepharoplast, and then the body divides longitudinally. A less common method is by multiple fission, in which the body forms as many parasites as there are nuclear segments.

The flagellate form of the organism has never been found in the human system; Rogers (Calcutta) records its development into a flagellate, outside the body, in citrated blood, at low temperatures.

The histological lesions of Leishmania-donovani.

Makkas (Athens) summarizes the histological lesions of Kala-azar as follows:—

1. The spleen, the liver, and the bone marrow are, during the course of the disease, and prior to the terminal cachectic stage, the only organs infected with leishmania.

2. The occurrence of leishmania, in other organs, before the final stage, is thus rather of the nature of an accident.

3. The organ first infected with parasites is the spleen, and it is only later that they instal themselves in the liver and bone marrow.

4. The more serious lesions of the liver are only produced, after the lapse of some time from the commencement of the disease.

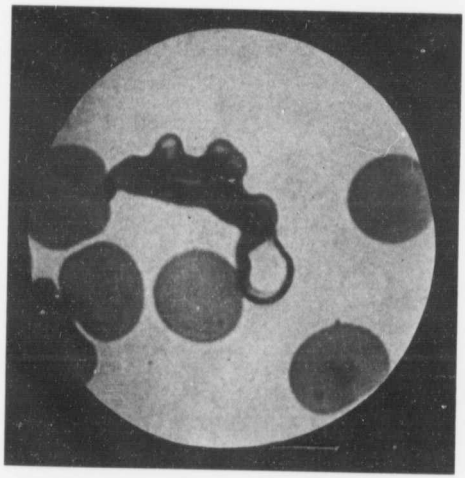
5. The fact that the parasites, whether in the spleen, liver, or bone marrow, are always in one kind of cell, which is phagocytic in nature, shows the degree to which the organism combats the disease.

6. The chief lesions of the spleen are due directly to the organisms themselves.

7. The lesions in the liver are due rather to toxins, generated, in all probability, by the leishmania.

8. It is the same toxins that bring about the enormous destruction of red corpuscles, which takes place in this disease.

9. The alterations in the bone marrow are merely an exaggeration of the normal physiological function of this organ.



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Trypanosoma equiperdum
(dividing).

Leishmania infantum.

It has been clearly demonstrated that a type of the disease, chiefly, though not exclusively, confined to young children, has a wide distribution along the shores of the Mediterranean.

Observers differ as to the exact relation of the Mediterranean disease to the Indian Kala-azar. Pianese and Nicolle consider the Indian and the Mediterranean diseases to be distinct, while Feletti, Jemma, Di Cristina, Gabbi, and others, regard them as identical. There is this difference, that a spontaneous infection of dogs has been found in the endemic areas of the Mediterranean disease, but no such infection has been encountered in India.

Nicolle and Comte state that the children, whom they found infected, had been in habitual contact with dogs. They are inclined to think that infection may be derived from the dog, and that in this animal the disease runs a benign course.

Laveran and Pettit, working with the Tunisian strain, have shown that, in monkeys and dogs, the infection may be of such a mild nature, that parasites can only be detected in the organs by the cultural method.

Basile has described two different forms of natural infection in dogs, the acute and the chronic. He thinks that the former, which affects young dogs, and lasts from three to four months, plays the more important part in the spread of the disease.

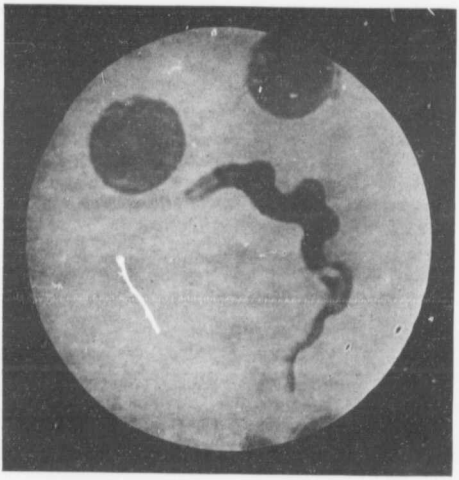
Nicolle concludes that the Mediterranean type is a natural infection of the dog, transmissible to the child. The absence of clinical symptoms, in the animal, makes it difficult of recognition.

Infantile Kala-azar, or Leishmania infantum, is essentially a disease of early childhood. The great majority of cases occur in children of two or three years of age.

The disease is found, almost exclusively, amongst children of the poorer classes, especially those engaged in agricultural labor.

Many observers have noticed its frequent occurrence in more than one member of the same family. In Malta, the communicability of the disease is so firmly rooted in the mind of the people, that all articles of clothing and bedding, used by the patients, are destroyed.

The duration of Leishmania infantum may extend over several months, or years. Its progress may be broken by remissions. Though nearly every case is fatal, Nicolle believes that a sponta-



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Trypanosoma equiperdum.

neous cure is possible. Spagnolio has recorded spontaneous recoveries.

In Palermo, according to Longo, the disease occurs in a comparatively mild form, and is of long duration, extending into years, and possibly ending in recovery in some cases. This has led to the idea that the Mediterranean disease is of less virulence than the Indian Kala-azar. In Catania, however, the disease, as observed by Longo, Feletti, and others, is of a severe type, and rarely is there a history of over a year's illness. The progress is more rapid, and there is a greater frequency of serious complications, than in the cases recorded from Palermo.

Leishmania canis.

Since the discovery, by Nicolle and Comte, of canine leishmania, which resulted in the advance of the theory of the canine origin of Kala-azar, dogs have been found to be liable to this disease, in nearly all the endemic centres of Kala-azar, except in India and Sicily. Basile undertook the examination of the dogs in a village, which was discovered to be an endemic centre for Kala-azar. In all of the houses where the disease had been found, Basile discovered infected dogs. He has found the dog flea (*Pulex serraticeps*) in the bed clothes, and mattresses of families, who are accustomed to keep dogs in the house. Basile also finds that the human flea (*Pulex irritans*) is a frequent ecto-parasite of the dog.

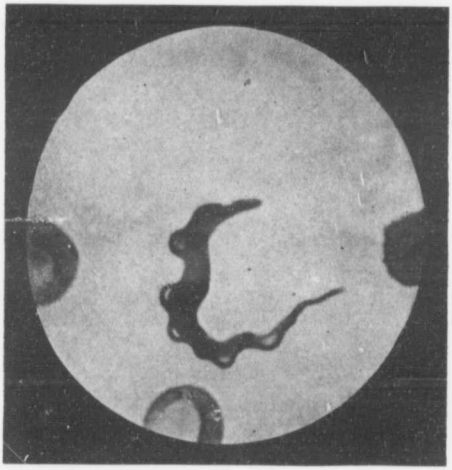
Death of healthy dogs resulted from bites of the fleas, coming from houses, where existed both canine and human leishmania.

Basile states that there is no doubt, that the dog flea becomes infected with leishmania, directly from the dog, and that it is proved, by his experiments, to be capable of transmitting the infection, at least in the districts of the Mediterranean.

In the intestine of *Pulex irritans*, caught in the bed of a child suffering from Kala-azar, parasites were found, identical with those found previously by Basile in *Pulex serraticeps*.

From his observations, Basile believes the disease in man and dog to be identical, and that, by means of fleas, it is transmitted from dog to dog, man to man, dog to man, and man to dog.

Patton (Madras) undertook experiments with biting insects and ticks. Only in bedbugs were positive results obtained. The bugs were fed, a varying number of times, on cases in which parasites were in the peripheral blood. From the results, Patton con-



× 3000 diam.

Trypanosoma equiperdum.

cludes that the parasite can be recovered from the midgut of the bugs, fed on cases of Kala-azar; the parasites have in a few cases shown considerable development. Donovan was unable to confirm Patton's observations.

The blood in Leishmania-donovani.

The anæmia associated with Kala-azar varies with the degree of infection.

The reduction in the red blood corpuscles is moderate.

The hæmoglobin is reduced, but nearly always in proportion to the reduction in the red cells; the colour index deviates but little from normal.

Poikilocytosis and polychromatophilia are observed; normoblasts and megaloblasts are present in severe conditions.

The number of leucocytes varies; in some cases, the number is normal, in others there is leucopenia.

There is great relative increase of lymphocytes, which may reach seventy or eighty per cent.

The differential lymphocyte percentage varies, from time to time, in the same individual.

As the polynuclears decrease, the prognosis is said to become progressively worse.

Diagnosis.

The diagnosis of Kala-azar is made by the discovery of the parasite. The parasites are found in the peripheral blood, in the early stages, but are most abundant towards the end of the disease. Donovan (India) found parasites, in the peripheral blood, in 93.2 per cent. of his cases. Marshall (Sudan) states that, out of fifteen cases in which the blood was examined, the parasites were present in thirteen cases, or 86.6 per cent.

The experience of those who have investigated Leishmania infantum, of the Mediterranean districts, is that the presence of parasites in the blood is so inconstant, that, as a means of diagnosing the malady, examination of the peripheral blood is of little service.

Culture method.—This method is always useful, where parasites are scanty, and will sometimes reveal an infection undetectable by other means. The parasite is easily cultivated on blood-agar.

× 3000 diam.

Trypanosoma equiperdum.

Spleen puncture.—Practically, all observers are agreed that the surest means of diagnosis is by spleen puncture. In the chronic cases, presenting wasting, prominent abdomens, large livers and spleens, the operation is comparatively easy. The thin and lax abdominal wall allows the spleen to be fixed against the lower ribs, by inserting the hand under its edge, and pressing firmly upwards and outwards. To obtain parenchyma cells, the spleen pulp may be broken up, by moving the needle point laterally.

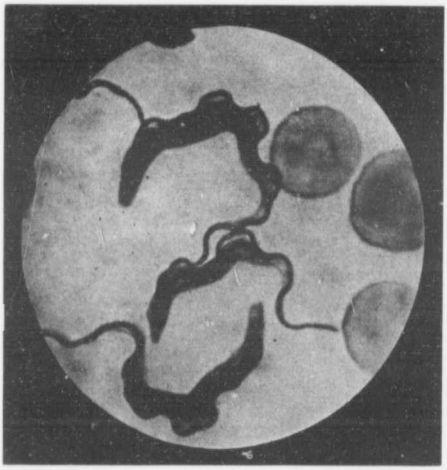
Liver puncture.—Puncture of the liver is a valuable diagnostic procedure, but inferior to spleen puncture. In mild infections, and early in the disease, a negative result may be obtained. Liver puncture is the method of choice in animals, since it is difficult to locate the spleen by palpation.

Examination of bone marrow.—Pianese, believing that the bone marrow is earlier infected, and contains a greater number of parasites than the spleen, advocates perforating the head of the tibia, or lower end of the femur, and removal of marrow as a diagnostic method. He states that one drop of bone marrow is more useful for diagnostic purposes, than a cubic centimeter of spleen juice. The removal of marrow is done by means of a trocar, and canula, to which is attached a strong aspirating pump. The quantity of material obtained is small, and the procedure is more difficult than spleen puncture.

Vesication.—The production of artificial blisters on the skin, as a method of diagnosis, was suggested by Cummins. The leishmania have been found within mononuclear cells, contained in fluid from blisters.

Lumbar puncture.—La Cava carried out lumbar puncture, in one case, in which there were meningeal symptoms, in the form of eclamptic convulsions, severe frontal headache, and torpor. The parasites were found in the spinal fluid.

Examination of superficial lymph glands.—Cochran has found this method of use in China, and advocates its use as a means of diagnosis. He has found that the post-cervical, and the superficial inguinal glands, contain leishmania. He recommends removal of a superficial gland, under local anæsthesia. The gland is cut, and a smear is made from the cut surface. In such smears, the parasites were present in large numbers. The parasites were found easily in a smear from a gland, when they were present in small numbers only in spleen puncture. Puncture of the gland *in situ* was negative in two cases, while smears from the excised glands were positive.



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Trypanosoma equiperdum.

Localisation of the parasites.

The number of the parasites, and their distribution in the tissues, depend on the duration and degree of the infection. The spleen is probably the organ first infected; it is always the organ most infected. The parasites are included in hypertrophied, endothelial cells, of the blood lacunæ. They are contained in the mononuclear cells, up to fifty or eighty in each, or in the débris of the cells. The parasites may be extracellular, in groups or single, but are never in the red corpuscles. In heavy infections, they are contained in polymorphonuclears, where many are undergoing digestion.

Liver.—Usually this organ is heavily infected, sometimes to the same extent as the spleen; at other times, the parasites are scanty. Parasites are found in the liver cells, and in the vascular endothelium.

Bone marrow.—The parasites are found in the vascular endothelium, and in mononuclear cells.

Leishmania are exceptionally encountered within the endothelium of kidneys, lungs, suprarenals, and mesenteric glands.

TRYPANOSOMATA.

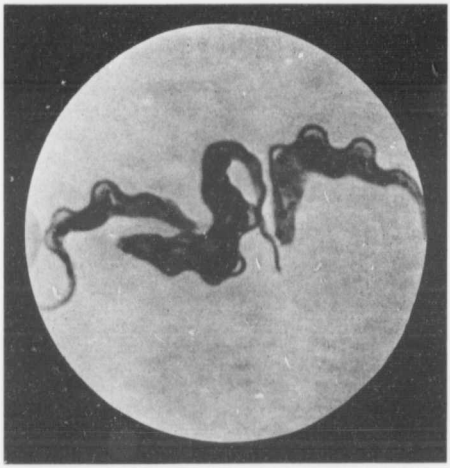
The observation of trypanosomes in the blood, by Dutton, and in the cerebro-spinal fluid, by Castellani, in 1902, and their positive identification by these investigators, as the specific organisms of African lethargy, or sleeping sickness, has given great pathological importance to the genus *Trypanosoma*.

Species of the genus *Trypanosoma* are the cause of enormous loss of human life, and also of most important diseases in animals, such as the dreaded tsetse-fly disease in South Africa, Dourine, Mal de Caderas, and the fatal Indian horse sickness "Surra."

The history of sleeping sickness, like that of Kala-azar, is one of gradual extension of infected areas.

The trypanosoma.

The species of this genus are identified by morphological and biological characters.



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Trypanosoma equiperdum.

The *trypanosoma* is an elongated, unicellular organism.

The nucleus is usually large, and situated about the middle of the body.

The blepharoplast is a small mass of chromatin, placed near the anterior extremity. It is also called the centrosome, and the micronucleus.

The undulating membrane is a fin-fold, which runs along the dorsal edge of the body, forming frill-like folds, and terminates at the posterior extremity.

The flagellum arises from the blepharoplast, and is continued beyond the posterior extremity in a whip-like filament. The free flagellum may vary greatly in length; sometimes there is no free flagellum. Sometimes, in the same species, there are long forms with a free flagellum, and short forms without.

The anterior extremity varies in shape, in different trypanosomes, and at different stages of development; it may be pointed, or obtuse.

The posterior extremity is pointed, and is continued by the free end of the flagellum.

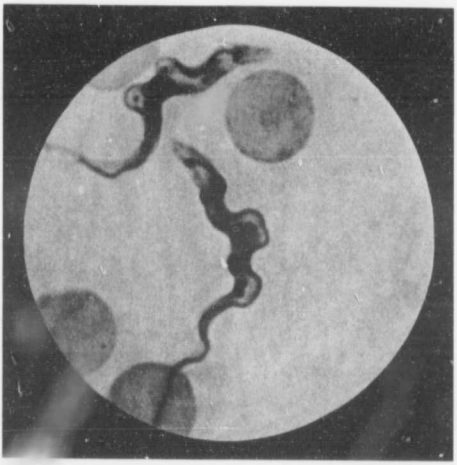
The vacuole is a clear area, adjoining or surrounding the blepharoplast.

The chromatophores are a variable number of dark-staining granules, contained in the cytoplasm.

Measurements.

Trypanosomes vary considerably, in size and shape; *Trypanosoma theileri* and *ingens* are recognised by their large size. Many trypanosomes have small forms, and large forms, and it is important to know within what limits the dimensions vary.

Lingard measures the distance from the anterior extremity to the blepharoplast, from the blepharoplast to the anterior end of the nucleus, the length of the nucleus, the distance of its posterior end to posterior end of the protoplasmic body, and the free portion of the flagellum. For each species, he makes a large number of measurements, and from the value per cent. of the mean of each of these, is calculated the mean total length per cent. Laveran says that this method of measurement would be excellent, if the trypanosomes of the same species always appeared under the same aspect,



3000 diam.

Trypanosoma equiperdum.

and with dimensions approximate to the type dimensions, which one established with Lingard's rules. Unfortunately, this is not the case.

Under Bruce's system of measurement, the trypanosomes are drawn at a given magnification (2000 diameters), and they are measured in a uniform way from films fixed and prepared in a uniform fashion. From trypanosomes thus measured, the average size is obtained, and a maximum and minimum is stated.

The fact that the same strain of trypanosomes, taken from different animal sources, is productive of differences in measurement, must be taken into account. Errors of measurement are avoided, by using strains inoculated into the same laboratory animal.

Multiplication of trypanosomata.

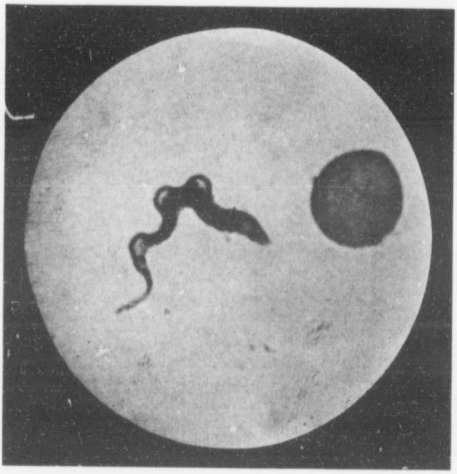
Trypanosomata multiply in the blood, by simple longitudinal division. The process begins most frequently with the division of the blepharoplast, which elongates and divides. The nucleus divides almost simultaneously. Division of the flagellum follows division of the blepharoplast, which, in turn, is followed by division of the whole body. Duplication of the flagellum begins at the blepharoplast, and terminates at the free end. When the newly formed flagellum has entirely separated from the old one, division of the body proceeds from the tail end forwards.

Dividing parasites are frequently seen, still adhering by their anterior extremities. The young forms are about equal in size, and are slightly smaller than the parent form.

Multiplication is extraordinarily rapid. Trypanosomes seem capable of dividing in man, three to four times in twenty-four hours, and in rats, as many as ten times. The rate of multiplication depends on the suitability of the medium, which appears to vary from time to time in the same animal.

Trypanosoma gambiense.

The group of pathogenic trypanosomes, having forms with free flagellum, and forms without free flagellum, contains four species—*Tr. gambiense, rhodesiense, pecaudi,* and *brucei.*



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Trypanosoma equiperdum.

Morphology of Tr. gambiense.

Trypanosoma gambiense is markedly pleomorphic. It is found in three forms:

(a) Short and stumpy (up to 20 μ)
(b) Intermediate (over 20 μ to 25 μ)
(c) Long and slender (over 25 μ)

The nucleus is oval in the long forms, and round in the short and stumpy. The blepharoplast is small and round; it is situated about 1.1 μ from the anterior extremity, in the short and stumpy forms, 1.8 μ in the long and slender.

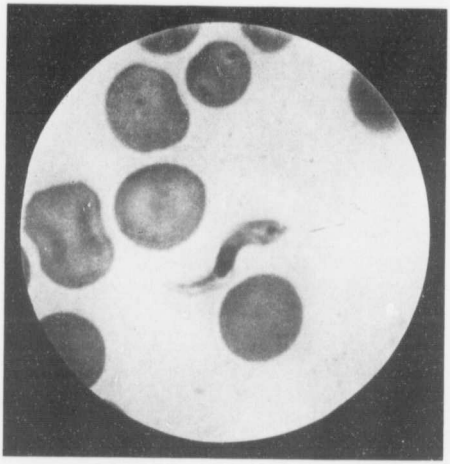
The flagellum in the long and intermediate forms, is free; in the short and stumpy forms, there is no free flagellum. The undulating membrane is well developed.

Tr. gambiense has little or no translatory power, in the field of the microscope.

Bruce has pointed out that great differences are sometimes found in the average length of *Tr. gambiense*, in the same individual. For instance, the trypanosomes of a European, at the beginning of his illness, averaged only 17 μ, whereas at a later date they averaged 25 μ.

As a result of investigation on *Trypanosoma leptodactyli*, which is the trypanosome of the common frog, in Brazil, Carini thinks that one can differentiate trypanosome forms into sexes. The narrow forms, with large compact nucleus, slightly developed, undulating membrane, and clear protoplasm, appear to be the males. The broader trypanosomes, with small loose nucleus, well developed membrane, and dark blue protoplasm, Carini regards as females.

The significance of the different forms of *T. gambiense* is unknown. According to Swellengrebel the stout forms (not longer than 24μ, broader than 2μ) are more resistant to unfavourable influences, than the long forms. Bevan and MacGregor are inclined to the opinion, that the long forms occur when conditions are favourable to the parasite, while the smaller types appear when adverse conditions arise. Such circumstances as the production of anti-bodies by the host, or the unsuitability of the medium for the existence of the parasite, in the host about to die, give rise to the smaller forms.



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Trypanosoma nanum.

The parasites in the peripheral blood.

The number of parasites in the circulation, in sleeping sickness, is subject to considerable fluctuation. A regular periodicity has been noted in the rise and fall, in the number of parasites in the blood. The periodical increase of trypanosomes is revealed by careful daily enumeration. Observers have noted the irregularity of the appearance of *T. gambiense* in the blood of the African native, and state that the parasites are present for two to five days, and absent for two to three weeks.

It is a matter of frequent observation, that trypanosomes may be absent for long periods (although no treatment has been given), from the peripheral blood of an animal, or person, suffering from trypanosome infection. It also frequently happens, that the parasites reappear, after a more or less long absence, in the blood of persons, who have apparently been cured by appropriate treatment. Persons afflicted with sleeping sickness may, under treatment, enjoy long periods of apparent good health.

A rise in temperature is concurrent with an increase in the number of parasites, or a reappearance of the parasites in the blood.

Diagnosis.

In the microscopic diagnosis of *Trypanosoma gambiense*, the following procedure is recommended:—

Firstly—Examine the peripheral blood, if negative; then,

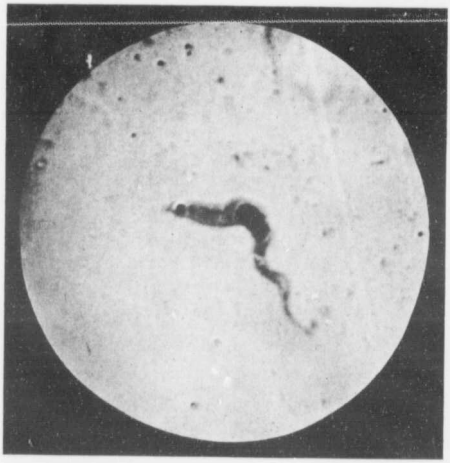
Secondly—Perform gland puncture, if negative; then,

Thirdly—Take 10 c. c. of blood, centrifuge, and examine the leucocyte layer, making a number of films; if negative, then,

Fourthly—Proceed to lumbar puncture, removing 10 c. c. of cerebro-spinal fluid-centrifuge, and examine. If the result be still negative, the patient is probably healthy; or,

Fifthly—In cases in which the glands have sclerosed, and parasites cannot be found, blood may be inoculated into monkeys, or guinea pigs.

Ten c. c. of cerebro-spinal fluid, or 20 to 60 c. c. of defibrinated blood, is inoculated into the peritoneum of a monkey. If the blood still contains parasites, the monkey becomes infected in 7 to 30 days. Thiroux and de la Salle (Senegal), employing this method, obtained positive results in 18 out of 38 cases, in which parasites were not discoverable in the blood by direct microscopical examination.



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Trypanosoma nanum.

Thiroux and de la Salle have used this method to verify cures. After the completion of treatment, each patient undergoes this test once a month. The test has shown blood relapses in patients, apparently in good health. If the test shows that the blood has been free for three months, a blood relapse is improbable.

In cases in which the clinical symptoms do not clearly indicate implication of the central nervous system, lumbar puncture should be avoided until it is established that the blood is not infected; otherwise trypanosomes may be introduced into an uninfected cerebro-spinal fluid.

Trypanosoma rhodesiense.

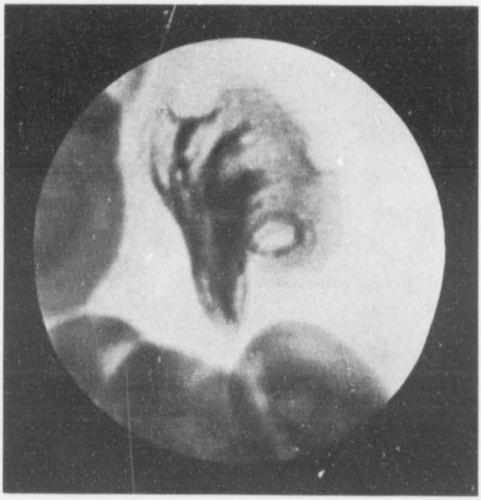
The peculiar features of this trypanosome were first noticed by Stephens and Fantham, in the blood of a rat infected from a patient, who had contracted the disease in Rhodesia, where Glossina palpalis is not found. This species was originally described almost entirely on the ground of morphology.

Morphology.—There is no essential difference between *T. rhodesiense* and *T. gambiense*, except, that in a certain number of parasites of the former, the nucleus is situated near the blepharoplast. There are transitions between forms, in which the nucleus is in the middle, to forms in which it is terminal and anterior to the blepharoplast. In rats infected with the strain, according to Stephens and Fantham, a few trypanosomes appear in the blood after about three days. The stumpy forms, with the nucleus anterior, appear about the fifth or sixth day, and increase somewhat in number to the seventh or eleventh. They form about six per cent. of the trypanosomes present. *T. rhodesiense* are 17 μ to 21 μ long, 2 μ to 3 μ broad. There is a well marked blepharoplast and a very short free flagellum.

The strain can be distinguished by the long anterior end, or snout, in many of the long forms.

Apart from its morphology, *T. rhodesiense* differs from *T. gambiense* in its greater virulence for most animal species. The parasite, when inoculated under the skin, kills rats in nine days, and mice in five. The ordinary gambiense strain, under the same conditions, kills a rat in eleven days, and mice in nine. *T. gambiense* kills *Macacus* in about a month, while *T. rhodesiense* does so in less than fifteen days.

Mesnil and Leger cured mice of *T. gambiense* infection, and



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Trypanosoma rotatorium.
Trypanosome infection of frog (Bufo regularis).

then inoculated with *T. rhodesiense*. These became infected, whereas others reinoculated with *T. gambiense* did not. They point to the case of the *Macacus*, which was quite immune to *T. gambiense*, and had an attenuated receptivity to *Trypanosoma rhodesiense*.

The claim, that there are two strains of trypanosomes, producing sleeping sickness in man, namely *T. gambiense* and *T. rhodesiense*, is based mainly on morphology and pathogenicity.

The blood in sleeping sickness.

The blood shows a constant lymphocytosis, at all stages of the disease.

Nattan-Larrier and Allain give the following leucocyte count for sleeping sickness:—

Polymorphonuclears	40.52 per cent.
Large mononuclears	7.91 per cent.
Lymphocytes	38.37 per cent.
Eosinophiles	11.79 per cent.
Basophiles	0.38 per cent.
Myelocytes	1.22 per cent.

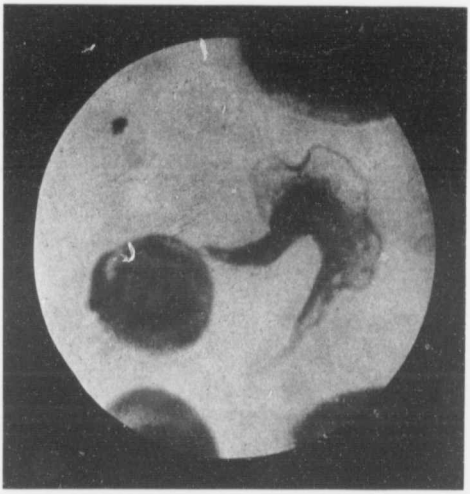
Martin and Lebœuf give:

Polymorphonuclears	49.04 per cent.
Large mononuclears	6.36 per cent.
Lymphocytes	37.60 per cent.
Eosinophiles	6.24 per cent.
Transitionals	0.76 per cent.

Newham (H. B.), reports the presence of eosinophilia, without obvious cause, in a case of trypanosomiasis in a European; it was observed, that with the appearance of trypanosomes in the blood, the proportion of eosinophiles fell, and when the trypanosomes were banished, by the administration of a drug, the proportion rose, reaching on one occasion twenty-six per cent. He concluded that there was an interaction between the eosinophiles and the invading parasites.

Transmission of human trypanosomes.

The organism of sleeping sickness is conveyed, from the sick to the healthy, by the bite of a species of *Glossina* (Tsetse), a genus of blood-sucking flies, peculiar to South and Tropical Africa, and the southwest corner of Arabia.



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Trypanosoma costatum.
Trypanosome infection of frog (Bufo regularis).

Proof of the rôle of *Glossina*, as a carrier, is found in the geographical distribution of the fly, and the disease.

Glossina palpalis has been found to be a true host of *Trypanosoma gambiense*, that is to say, one in which a definite cyclical development of the parasites is undergone, or one in which the parasite establishes itself, and maintains the existence of its species.

This development takes a period of at least twenty days, from the time when the fly fed on infective blood. After this interval has elapsed, a fly may become permanently infective, and liable to produce the disease in any human being, or susceptible animal, on which it feeds. It is quite likely that a fly, once infective, remains infective for the rest of its life. No case of hereditary transmission of trypanosomes, by tsetse flies to their offspring, has ever been observed.

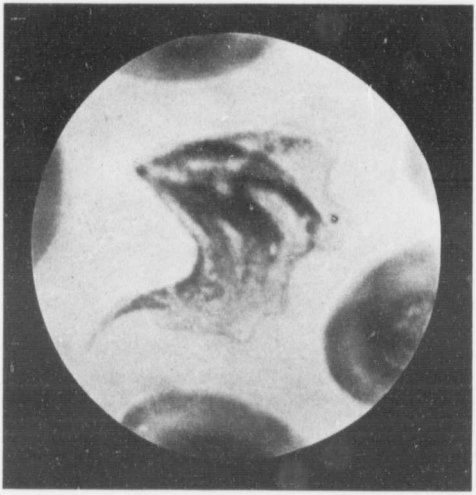
The Sleeping Sickness Commission of the Royal Society investigated the development and transmission of *T. gambiense* in *Glossina palpalis*. The procedure followed, in this investigation, was to place a cage of laboratory bred flies on an infected animal for some little time, then suddenly to transfer it to a healthy animal, and so backwards and forwards, for ten or fifteen minutes; thus imitating conditions in nature. The following conclusions were arrived at:—

1. The mechanical transmission of sleeping sickness, by means of *Glossina palpalis*, can take place, if the transference of the flies, from the infected to the healthy animal, is instantaneous—that is, by interrupted feeding.

2. This mechanical transmission does not take place, if an interval of time comes between the feedings.

3. Mechanical transmission plays a much smaller part (if any), in the spread of sleeping sickness, than has been supposed.

In this investigation, *T. gambiense* was never found in the proboscis, except immediately after an infective feed. In the fore, mid, and hind gut of the fly, the greatest development was seen. During the first few days, after an infective feed, the trypanosomes are merely degenerating forms, with karyorhexis and vacuolated cytoplasm. From the eighth to the forty-fourth day, a normal reproductive, or developing type is found. This form is longer and broader than the long broad form, and has a clear protoplasm, with normal nucleus and blepharoplast. The anterior extremity is elongated. Trypanosomes did not appear in the salivary glands, until



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Trypanosoma rotatorium.
Trypanosome infection of frog (Bufo regularis).

the twenty-fifth day, but after that time they were usually present. The Commission believes this invasion of the salivary glands to be of the greatest importance, in the development of *Trypanosoma gambiense*, in *Glossina palpalis*.

In the salivary glands alone, are the trypanosomes found to be of the ordinary blood type. What causes the reversion to the blood type, in the salivary glands of the fly, or how the trypanosomes find their way there, is undecided. It was found that, for twenty-eight days after an infective feed, the fly is non-infective, but after that it is usually capable of causing the disease by its bite. The renewal of infectivity, in the fly, is coincident with the invasion of the salivary glands by the trypanosomes.

The Commission concludes that—

1. In the course of the development of *Trypanosoma gambiense*, in *Glossina palpalis*, the proboscis does not become involved, as is the case with some other species.

2. A few days after an infective feed, the trypanosomes disappear out of the great majority of the flies, but, in a small percentage, this initial disappearance is followed by a renewal of development.

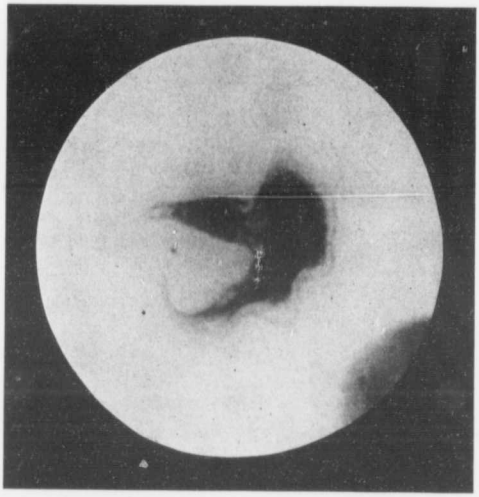
3. After a very short time, the flies which have been fed on an infected animal, become incapable of conveying the infection by their bites, and this non-infectivity lasts for some twenty-eight days, when a renewed infectivity takes place.

4. A fly, in which this renewed infectivity occurs, can remain infective for at least 96 days.

5. An invasion of the salivary glands occurs at the same time as this renewal of infectivity, and, without this invasion of the salivary glands, there can be no infectivity.

6. The type of trypanosome, found in the salivary glands, when the fly becomes infective, is similar to the short and stumpy form found in vertebrate blood, and it is believed that this reversion to the blood-type is a *sine qua non* in the infective process.

Until recently, it was believed that sleeping sickness was disseminated solely by *Glossina palpalis*, but the occurrence of a number of cases of the disease in the Nyasaland Protectorate, and North Eastern Rhodesia, from both of which *Glossina palpalis* is believed to be absent, caused grave suspicion to attach to *Glossina morsitans*, and *G. brevipalpis*.



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Trypanosoma costatum.
Trypanosome infection of frog (Bufo regularis).

Taute, working on the shore of Lake Tanganyika, has shown that *Glossina morsitans* may become permanently infected with the trypanosome of sleeping sickness. In the case of *Glossina morsitans*, the necessary period which must elapse before the essential propagative forms are developed, is apparently twenty-one days, being about the same as in *G. palpalis*. The investigation furnished positive results in sufficient number of cases, for Taute to conclude, that the transmission of *T. gambiense*, by *G. morsitans*, is not to be regarded as an exceptional occurrence.

In all probability, *Glossina morsitans* is the natural transmissive agent of *Trypanosoma rhodesiense*. At present it would appear that, not only tsetses, but all biting flies, must be considered as possible carriers.

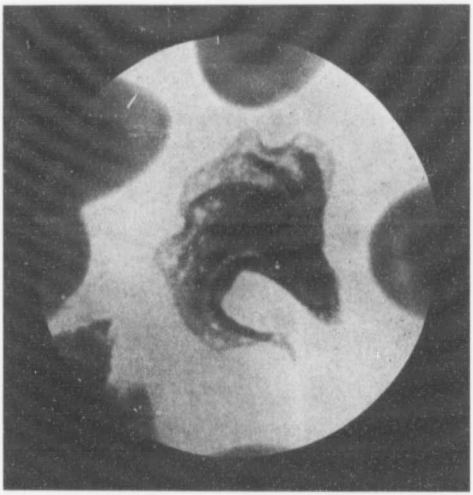
Infection per cutaneam.—From experiments on animals, Hindle concludes that *Trypanosoma gambiense* is able to penetrate a sound mucous membrane, and also an undamaged skin, and there is no reason to suspect that the parasite would not possess similar powers in man.

Infection per vaginam.—Koch drew attention to the probability of the disease being communicated by coitus. Of 26 women, in the German Segregation Camp, where there was a total of 425 cases, 7 had never been in sleeping sickness regions. It would seem that they had contracted the disease from their husbands, all of whom had died of sleeping sickness. When sleeping sickness was found outside the Glossina belt, women only were found to be infected, the children and men, who had not visited sleeping sickness districts, being unaffected.

Experiments, by Martin and Ringenbach, show that *Trypanosoma gambiense* can easily penetrate the vaginal mucous membrane. By carefully introducing infected blood into the vagina, Hindle infected six rats out of six.

Trypanosoma cruzi.

While organising measures against malaria, for a railway under construction in Brazil, Chagas heard of a biting insect known as Barbeiro. This hæmatophagous insect *(Conorhinus megistus)* seems to be distributed all over Brazil. It lives in human habitations, comes out at night, and attacks human beings chiefly on the face. During the day the bug remains hidden in cracks in the walls or



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Trypanosoma rotatorium.

ceiling. It is more than an inch long, the female somewhat larger than the male. These insects seek inhabited houses; they multiply abundantly in badly kept houses, constructed of beaten clay or wood, and therefore having numerous cracks and crevices, where they can shelter and lay their eggs. They are never found in abandoned houses.

In the intestinal tube of this insect, Chagas found a flagellate protozoon with the characters of Crithidia. He found the same parasite in the blood of a monkey, which had been bitten by the insect. At the same time, knowing of the existence of a disease with the same geographical distribution as "barbeiro," the symptoms of which were quite different from those of other known diseases, Chagas thought that the protozoon might be the cause. Some time after, the same protozoon was found by him in the blood of a sick child, thus confirming his hypothesis. Chagas created a new genus for these parasites *(Schizotrypanum)*, and named the new trypanosome *Schizotrypanum cruzi*.

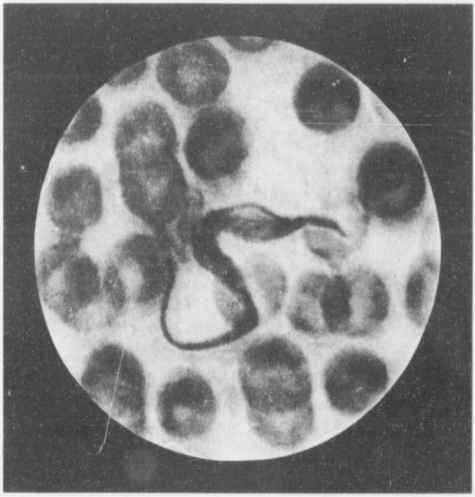
The investigation of *Schizotrypanum cruzi* by Carlos Chagas is a monument of scientific thoroughness. All subsequent work is only a repetition of previous observations.

Pathogenicity.—Rapid death of guinea pigs usually followed the bite of an infected "barbeiro," often with few or no parasites in the peripheral blood. In subinoculations, in the same species, life is prolonged; the animals may live two months and longer.

In some animals, a rapid disappearance of the parasites from the peripheral circulation was suggestive of a crisis in spirochætosis. The parasite is pathogenic, for rabbits, dogs, cats, and monkeys. In all animals, the parasites are constantly found in the peripheral blood. The monkey *(Callithrix)* had parasites in the blood, eight days after inoculation.

Virulence is weakened by repeated passage through animals of one species; when the virus is transmitted to another species, the virulence is regained. Guinea pigs, infected by inoculation of blood, may survive two months. Animals infected by the bite of "barbeiro" may die in five to ten days. In this form of infection, no parasites may be found in the peripheral blood.

The infection attacks the whole population; children probably all contract the disease in their first year, and either die, or pass over to the chronic stage.



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Trypanosoma peromysci. Watson.
Trypanosome infection of native prairie mouse.

Symptomatology.

The symptoms noted in this form of human trypanosomiasis are—extreme anæmia and delayed development, with infantilism, enlargement of all the peripheral glands, constant enlargement of the spleen, hypertrophy of the thyroid gland, and myxœdema of the subcutaneous cellular tissue.

Chagas reports acute and chronic forms of the disease.

In the acute form, which occurs almost exclusively in small children, there is continued fever with slight morning remissions.

In the chronic form, Chagas reports several varieties. The pseudo-myxœdematous is the most frequent, and occurs above the age of fifteen. These patients have hypertrophy of the thyroid gland, or at least stigmata of hyper-thyroidism, general hypertrophy of glands, cardiac disturbance, diarrhœa or constipation, and nervous symptoms.

The myxœdematous form is characterised especially by considerable swelling of the thyroid gland, and myxœdema of the subcutaneous cellular tissue.

In the nervous form are found motor disturbances, disturbances of speech, signs of infantilism, and idiocy.

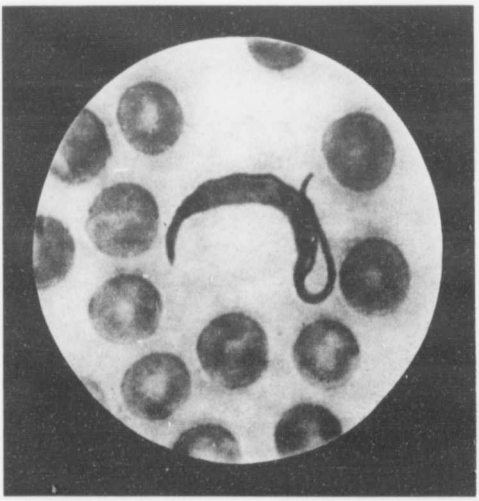
Diagnosis.

In a series of cases to which Chagas has referred, diagnosis of *Trypanosoma cruzi* was made microscopically 98 times, 12 times by direct observation of parasites in the blood of patients, 46 times by inoculation, into a guinea pig, of blood taken from children with a chronic infection, 39 times by inoculation, into a guinea pig, of the blood of adults chronically infected, and once by inoculation into a guinea pig of cerebro-spinal fluid.

In the acute stages, the parasites are very numerous, and found quite easily. The chronic form is diagnosed by injection of 10 c. c. of blood into a guinea pig.

Morphology.

In the blood of man, *Trypanosoma cruzi* is found in two forms. In one form, a large oval blepharoplast is situated near to the anterior extremity, with the long diameter transverse. It has a chromatin appendage. The nucleus is oval, or appears as a long chromatin



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Trypanosoma peromysci, Watson.
In blood of native prairie mouse
(Peromyscus maniculatus, P. nebracensis).

band, lying in the longitudinal direction. It contains a strongly coloured chromatin body. In the second form, the blepharoplast is more or less round, and smaller than in the first form. As a rule, the chromatin appendage is absent. The nucleus is round, and the chromatin less condensed. The body of the second form is broader than that of the other. The anterior extremity of the parasite is pointed. The flagellum has a free portion of variable length.

Development.

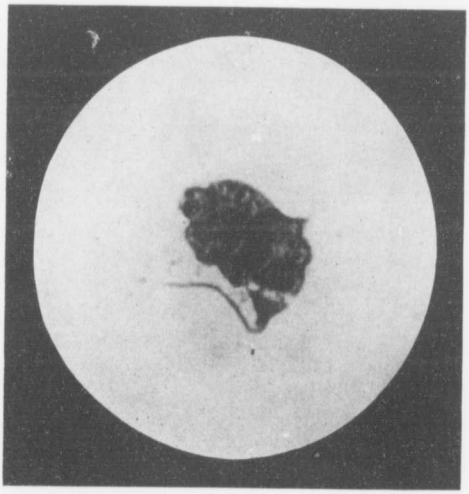
Both endoglobular and ectoglobular parasites are described. At the beginning of the infection, endoglobular forms are stated to be the more numerous, and are in some cases the only ones to be found in the peripheral blood. Later in infection, endoglobular forms are seldom seen. In some endoglobular forms, and those partly enclosed in corpuscles, the flagellum and undulating membrane are wanting.

Multiplication.

Longitudinal fission was never seen in the peripheral blood. Chagas has described the process of multiplication by schizogony, which takes place in the capillaries of the lungs. In this process, the flagellum and undulating membrane disappear, the nucleus comes forward, and blends with the blepharoplast; the anterior extremity approaches the posterior, and merges with it. The nuclear body then divides, forming eight club-shaped bodies. These young bodies escape from the enclosing membrane, and, after penetrating the red corpuscles, become flagellates.

Pathological histology.

Examination of the tissues has revealed the presence of parasites in patients, who did not show them in the circulation. Localisations of *Trypanosoma cruzi* are found in the tissues, by predilection, in the cardiac muscle, in the central nervous system, and in striated muscle. In the heart, the parasite multiplies actively in the muscle cell, forming an intracellular agglomeration of parasites; these intra-cystic parasites are rounded, have a nucleus and blepharoplast, but no flagellum or undulating membrane. Scattered foci of parasites are seen in the brain and spinal cord.



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Trypanosoma in blood of crow.

Development in Conorhinus.

Within the bug, *Trypanosoma cruzi* undergoes evolution in the Malpighian tubes. The parasites finally reach the salivary glands. Eight days are needed, after a feed, for the insects to become infective.

Chagas has also recorded another form of reproduction, which takes place in the hind-gut of the insect, and which ends in the production of organisms, which perpetuate the parasite in the bug, but are not pathogenic for man or animals.

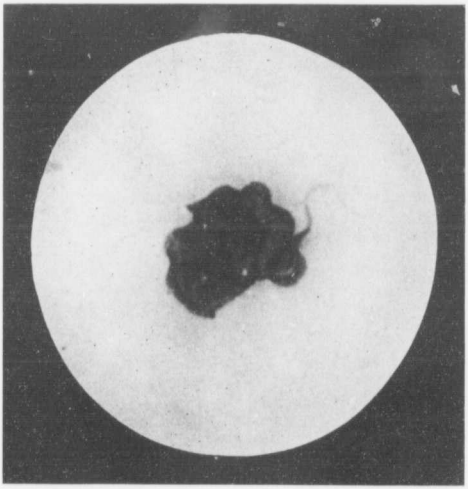
Trypanosoma brucei.
(Nagana.)

Nagana is a trypanosome infection of horses, cattle, and other animals, in Central Africa. Bruce discovered the parasite in 1894.

Morphology.—Trypanosoma brucei is markedly dimorphic, individuals vary from 13 μ to 35 μ in length. The two varieties are the long and slender, and the short and stumpy forms; others are intermediate. *Trypanosoma brucei* resembles *T. gambiense*, in having little or no translatory power, in the field of the microscope.

Plimmer and Bradford write, that the size and length of the body varies very much with the period of the disease at which the blood is examined, and with the kind of animal. The Nagana Commission of the Royal Society noted, that long forms may predominate in the blood on one day, and short forms on another.

Addari experimented with *T. brucei*, in guinea pigs, to determine the course of infection, when trypanosomes are injected into the subcutaneous tissue, and into the peritoneal and pleural cavities. The duration of infection was found to vary, according to the method of inoculation. The shortest period follows intrapleural inoculation, intraperitoneal and subcutaneous following in order. Trypanosomes appeared in the blood, after 11 days for subcutaneous, 7 days for peritoneal, and 6 days for pleural inoculations. The organs contained fewer parasites than the blood. Parasites were present in greatest number in the kidneys, the brain, the liver, and the lungs, in the order named. There were very few in the spleen and lymphatic glands. This fact, Addari thinks, strengthens the belief in the trypanolytic power of these organs, as held by Rodet and Vallet.



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Trypanosoma in blood of crow.

The symptoms of nagana are pyrexia, which is sometimes considerable, wasting, œdema, and anæmia.

The morbid lesions consist of enlargement of the lymph glands, and hypertrophy of the spleen.

The trypanosomes appear early in the blood, and their number increase, up to the death of the animal, and might number two to three millions per cubic millimeter.

Transmission.—It is generally considered that *Glossina morsitans* is the fly, which transmits the tsetse disease; *pallidipes* and *fusca* are also looked upon as probable carriers.

Trypanosoma pecaudi.

Like the trypanosomes previously described, *T. pecaudi* occurs in long slender forms, with a free flagellum, and short stout forms, with no free flagellum.

It affects particularly horses, mules, and donkeys, in Senegal, Bahr-El-Ghazal, and on the White Nile.

A disease, known as Baleri, the organism of which is *T. pecaudi*, is found in horses, donkeys, cattle, and dogs, in the valley of the Upper Niger; it is acute in horses and dogs, and chronic in cattle.

Trypanosoma pecaudi resembles *T. brucei*, morphologically, and in animal reactions.

The parasites are actively motile, and at times have a markedly granular cytoplasm.

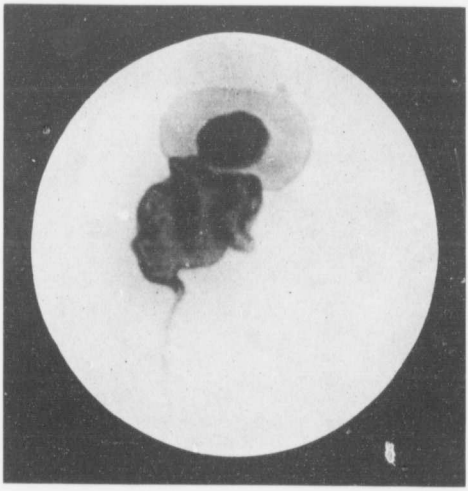
The average duration of the disease, in the smaller animals, is given by Fry (Khartoum) as follows,—dogs 23 days, monkeys 24 days, gerbils 15 days, and jerboas 7 days.

The chief transmitting agent is probably *Glossina morsitans*.

Bouet and Roubaud, investigating in Dahomey, found *Glossina longipalpis* naturally infected with *T. pecaudi*. *Glossina palpalis*, and *tachinoides*, in their observations, were never found infected with *Trypanosoma pecaudi*, in nature. They conclude that, in Dahomey, *Glossina longipalpis* constitutes the reservoir fly of *T. pecaudi*, to the exclusion of *palpalis* and *tachinoides*.

Trypanosoma evansi
(*Surra.*)

Trypanosoma evansi belongs to the group of pathogenic trypanosomata, which have always a free flagellum. It was identified by



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Trypanosoma in blood of crow.

Evans (1880) as the cause of Surra, a disease occurring in horses, cattle, sheep, and other animals, in India.

Like *Trypanosoma brucei*, it is pathogenic for nearly all species of animals. *T. evansi*, however, differs from *T. brucei*, and *pecaudi*, in being monomorphic.

Morphology.—In shape, *T. evansi* resembles very closely the intermediate forms of *T. brucei*.

In size, it varies from 18 μ to 34 μ, average about 24 μ.

A large proportion show no distinct granules; even when present, the granules in *evansi* are as a rule not so large, nor so numerous, nor so deeply stained, as in *T. pecaudi*.

Transmission of T. evansi.

It is the consensus of opinion, of practically all authorities on Surra, that the several species of biting flies, implicated in the transmission of the disease, act only as mechanical transmitters or accidental carriers.

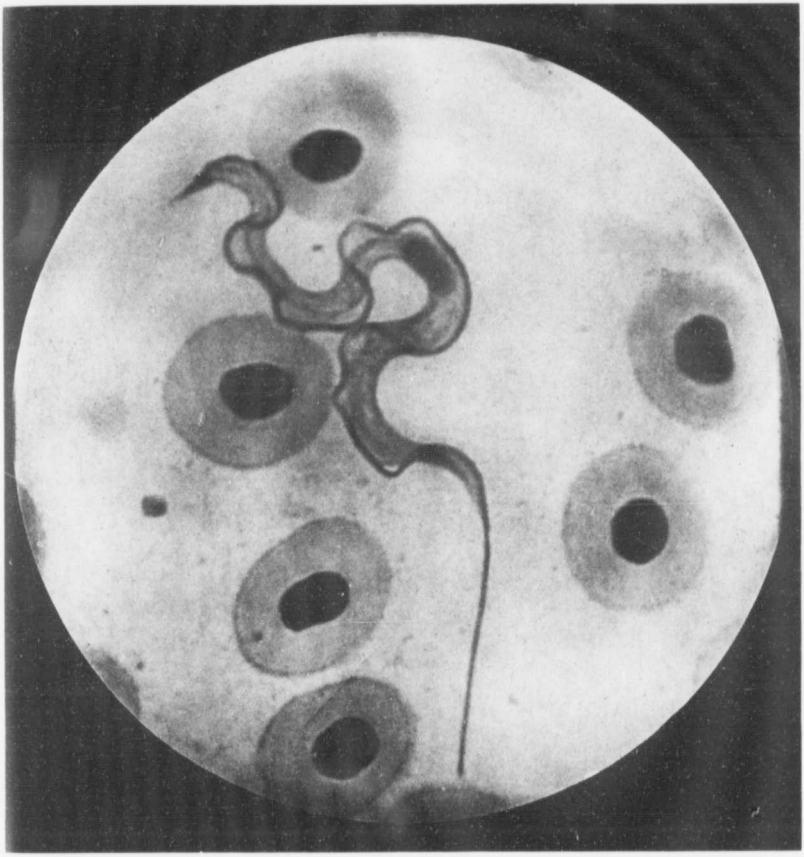
Direct mechanical transmission is defined as the transference to a clean animal, of the actual blood trypanosomes, taken from an infected animal

The chances, that the transmitting agent will convey the infection to a susceptible animal, by the direct or mechanical method, are greatest immediately after it has contaminated its proboscis, by feeding on an infected one. The invertebrate cleans its proboscis in a comparatively short time, when the danger of mechanical, or direct infection, ceases entirely

Leese states that Surra can spread, even in an arid region, provided a chronic case of the infection is imported there, and there are a few biting flies, although its spread in such places may be slight. In a real "Surra zone," the flies are so numerous, that one chronic case of Surra, imported, will often lead to the infection of all the other animals.

Leese made successful transmission experiments, with *Stomoxys*, *Tabanus*, and *Hæmatopota*. This observer noted that *Tabanus* has a habit of going quickly from one animal to another, and from experiments concludes, that *Tabanus* has more power to transmit surra, than *Stomoxys* has.

The Sergents (Algeria) investigated the method of transmission of the camel disease, known as El-Debab. They found that either species of *Tabanus* could convey the disease by the inter-



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Trypanosoma granulosum magna in blood of fresh-water eel.

rupted method of feeding, and that a single fly was enough. They publish a table, which shows that infection occurs only, when the feed on the healthy animal follows immediately that on the infected one.

Schat has attributed to the muscid *Lyperosia* a share in the spread of Surra in Java; Montgomery and Kinghorn believe that the trypanosomes of domestic stock, in Rhodesia, may be transmitted by this genus.

Experiments have failed to demonstrate any cyclical development of *T. evansi* in flies, flies being non-infective after 24 hours, by inoculation of either stomach, intestine, or salivary gland contents.

Trypanosoma lewisi.

This parasite belongs to a group of non-pathogenic trypanosomes, of small mammals.

The principal specific character of the group, of which *lewisi* is the type, is furnished by the fact, that they are not inoculable from one animal species to another.

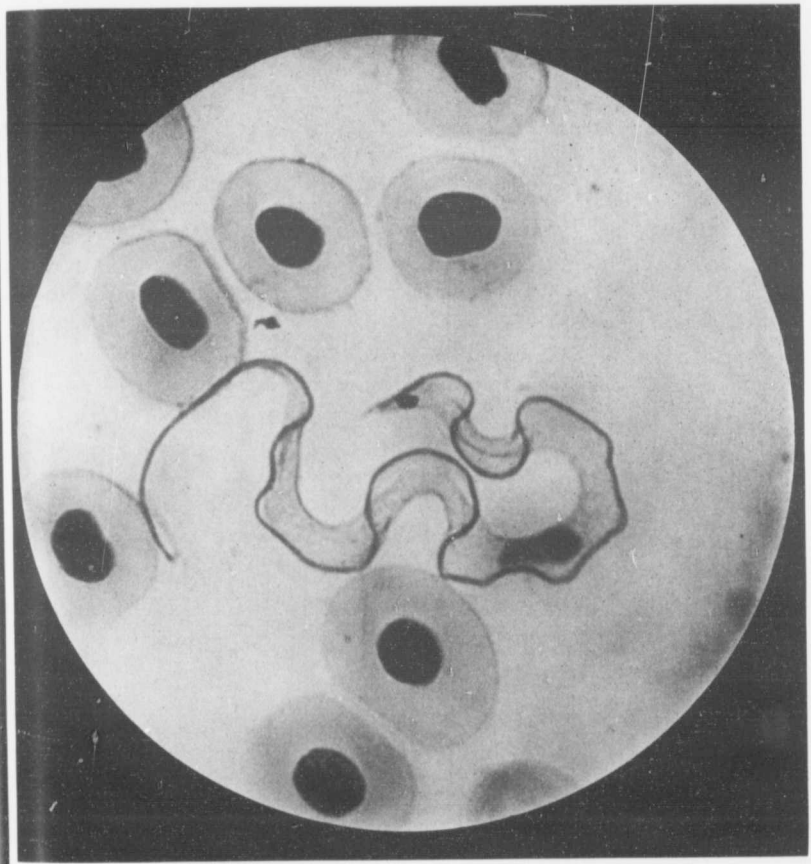
Trypanosomes abound in rats, both in Europe and the tropics, without causing any symptoms. When a rat is first infected with *T. lewisi*, the parasite multiplies in the blood very rapidly. After a certain length of time, the multiplication ceases entirely, and rather suddenly.

Transmission of T. lewisi.

The rat-flea (*Ceratophyllus fasciatus*), and the rat louse, (*Hæmatopinus spinulosus*) have been shown, experimentally, to be capable of transmitting *Trypanosoma lewisi*. It was demonstrated by Nuttal (1908), that this trypanosome is conveyed from rat to rat, by fleas. Nuttal transferred fleas from infected to healthy rats, and found that the latter generally became infected.

Manteufel, in Berlin, transmitted *T. lewisi*, by means of the rat louse, with ease. It is much easier to bring about transmission, with the rat-flea, which is looked upon as the natural transmitter of *T. lewisi*.

Direct transmission.—That some infections take place through the skin or mucous membrane, *i. e.*, by the rats eating the fleas, or by scratching the contents of the fleas into the skin, has been proved by the researches of Strickland, Francis, and Manteufel.



× 3000 diam.

Trypanosoma granulosum magna in blood of fresh-water eel.

Cyclical transmission.—This method of transmission, by the rat-flea, is by far the most common in nature. The rat-flea is a true host of the rat trypanosome, that is, one in which the parasite passes through a cycle of development, or series of changes, and generations, which ends in the production of forms, suitable for re-inoculation into the vertebrate host.

In studying the early phases of the developmental cycle, through which the rat trypanosome passes in the rat-flea, Minchin and Thomson found that the trypanosome penetrates into the cells of the epithelium, lining the stomach of the flea, and there goes through a process of multiplication. Only a small number of fleas, fed on infected rats, acquired a permanent infection.

Whether the trypanosomes succeed in establishing themselves in the flea, Minchin and Thomson think, depends on whether they succeed in penetrating the cells of the stomach, and going through the intracellular, multiplicative phase described. They also state that, in the majority of the fleas, the trypanosomes taken in, appear to be digested together with the blood, and to never succeed in establishing themselves in the flea, or in going through their developmental cycle; only in a relatively small number of cases, do they resist the digestive juices, and succeed in holding their own.

Further, Minchin and Thomson believe that the normal method of transmission, is that the ripe, infective form of the trypanosome, —the final form of the developmental cycle, which it passes through in the flea,—is regurgitated from the stomach of the flea, into the wound made by the proboscis of the flea, during the act of feeding.

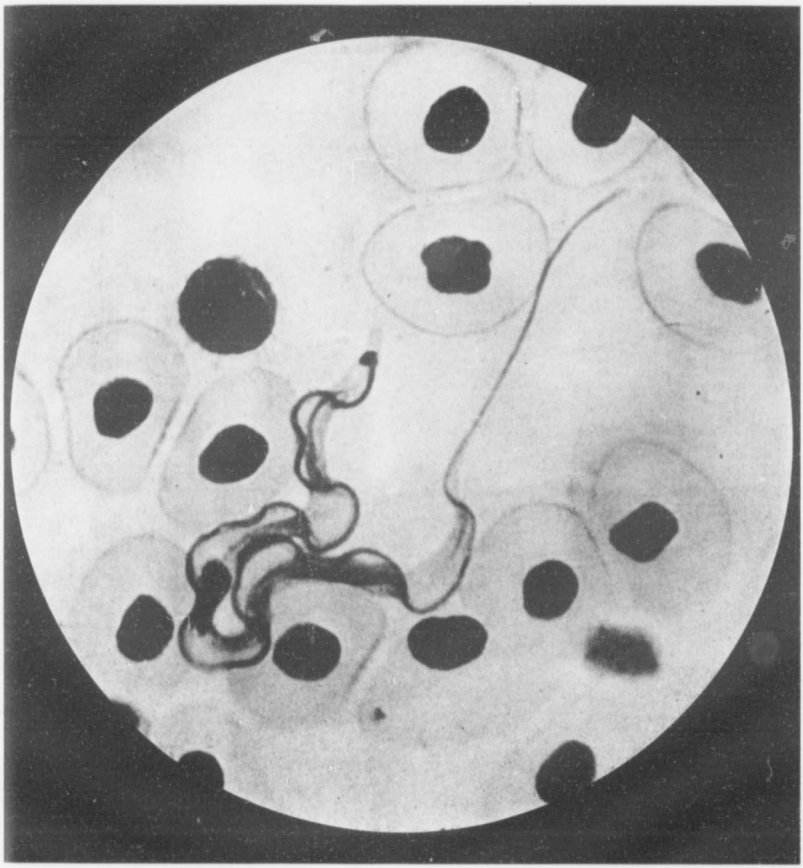
Trypanosoma equiperdum.

(*Dourine.*)

Trypanosoma equiperdum is the specific organism of dourine, or mal de coit. It is able to traverse healthy mucosa, and is transmitted from one animal to another by coitus.

Dourine has existed for centuries in Asia, whence it was introduced, during the early part of the nineteenth century, into Continental Europe, through the importation of breeding horses from the Orient.

Under natural conditions, dourine affects only the horse and ass. In the latter, the disease is in most cases confined to the local infection of the genital organs.



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Trypanosoma granulosum magna.

The specific causal agent of dourine was discovered by Rouget (1896); Doflein later gave to it the name *Trypanosoma equiperdum*.

Trypanosoma equiperdum has been found to vary greatly in virulence. Marek has pointed out, that the virus of dourine has much more virulence in the southern, than in the northern, countries. The disease appears to be more acute, and fatal, in Asia and Northern Africa, than in Europe, while, in America, the malady is even less acute and fatal, than in Europe.

After a period of incubation, varying from eight days to two months, local lesions appear on the genital organs; these consist of swelling and inflammation, accompanied by a muco-purulent discharge. Vesicles appear on the penis, vulva, and vagina, which rupture and leave ragged ulcers.

The constitutional disturbances may be delayed, for months or even a year, after the appearance of primary lesions. Urticarial eruptions, or plaques, break out in various parts of the body; they disappear in a few days, only to reappear elsewhere. The course of the disease is marked by weakness, anæmia, emaciation, and paralysis.

The duration of dourine varies from three months to three years.

Transmission of dourine.

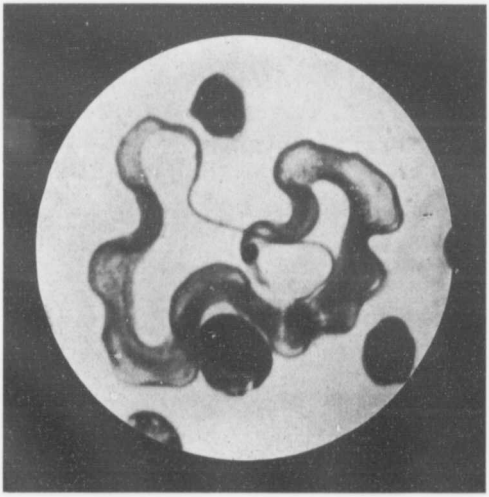
Infected animals are, as a rule, sterile. A stallion may transmit dourine, from an infected to a healthy mare, without contracting the disease. According to Roll, about 66 per cent. of mares exposed to infection become diseased.

Diagnosis.

Trypanosoma equiperdum is more numerous, and more virulent, in European dourine, than in the American disease; they are more difficult of detection in the European type than in the Asiatic and African.

Trypanosoma equiperdum is frequently absent from the peripheral blood, even in fairly well marked cases.

Trypanosomes are present in the serum, obtained by scarification of a recently formed plaque. In the absence of plaques, organisms are obtained from blood, or mucus from the infiltrated vaginal mucosa.



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Trypanosoma granulosum magna.

In the vaginal mucus, and the vaginal blood, the organisms were found by Watson (Lethbridge), in nearly the same proportion of preparations, namely, 40 and 38·8 per cent. respectively.

Trypanosoma nanum.

Trypanosoma nanum is a small trypanosome, pathogenic to cattle, which may recover from the infection.

Uniformity of morphology is considered, by Balfour, to be an outstanding characteristic of this species.

Trypanosoma nanum is not very active in fresh films, and is non-translatory.

The cytoplasm is homogeneous, and as a rule stains a clear pale blue.

The nucleus is oval, and situated about the centre of the body.

The blepharoplast is small and round; it is situated near or at the anterior extremity.

The undulatory membrane is inconspicuous.

There is no free flagellum, or, if present, it is very short.

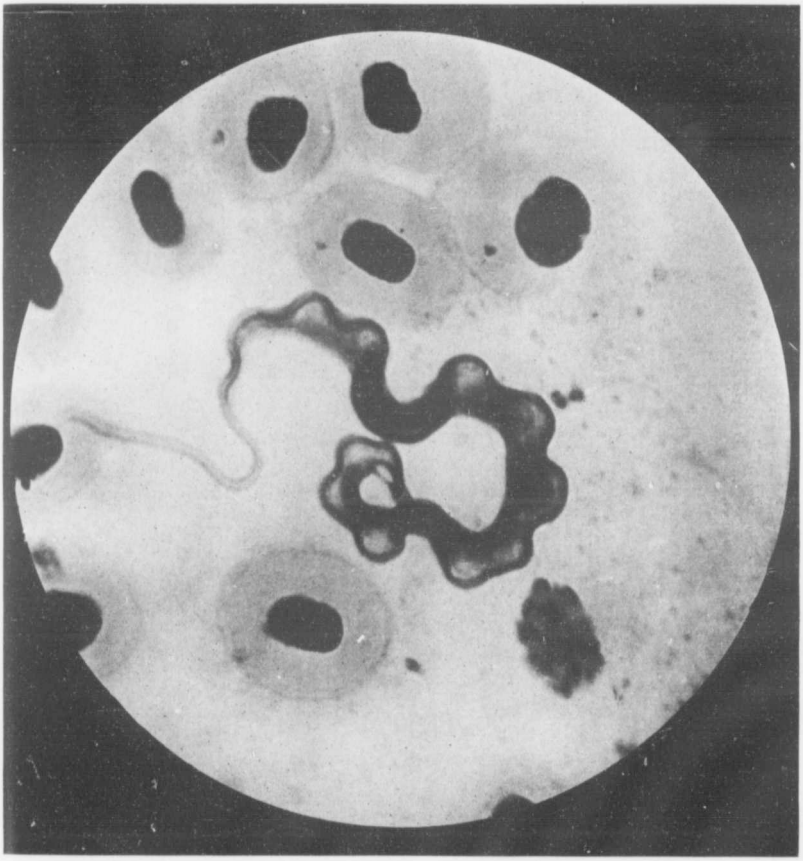
MICROFILARIA NOCTURNA.

The *microfilariæ* of man were discovered in Paris by Demarquay (1863) in the hydrocele fluid of a Havanese; they were next observed by Wucherer (Bahia) in the urine of tropical chyluria; Lewis of India (1872) discovered the embryos in the blood of man, and found they were always present in persons suffering with tropical chyluria, elephantiasis, and lymphatic enlargements.

Microfilaria nocturna is the original *Filaria sanguinis hominis* of Lewis.

Systematic search was made for the adult worm, and it was, at length, found by Bancroft of Brisbane (1876), who went a step further by suggesting that the mosquito was probably the intermediate host. Manson proved this to be correct, by direct observation (1877).

The females of certain species of mosquito, belonging to the genus *Culex*, which have fed on the blood of a filaria-infested individual, are transmitters of the infection.



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Trypanosoma granulosum magna.

The embryos do not grow to adult worms in the human body, but must leave it to develop further in an intermediate host, and then invade man anew.

The filarial larva is found in the head and proboscis of the mosquito, and is communicated by infected mosquitoes, in the act of feeding. According to Manson, filarial disease may be contracted by drinking of water polluted by mosquitoes, containing the larvæ of filariæ.

However introduced into the human body, the embryo finds its way into the lymphatics, where it attains sexual maturity. Fecundation is effected, and in due course new generations of embryos of *Filaria bancrofti* are poured into the lymph.

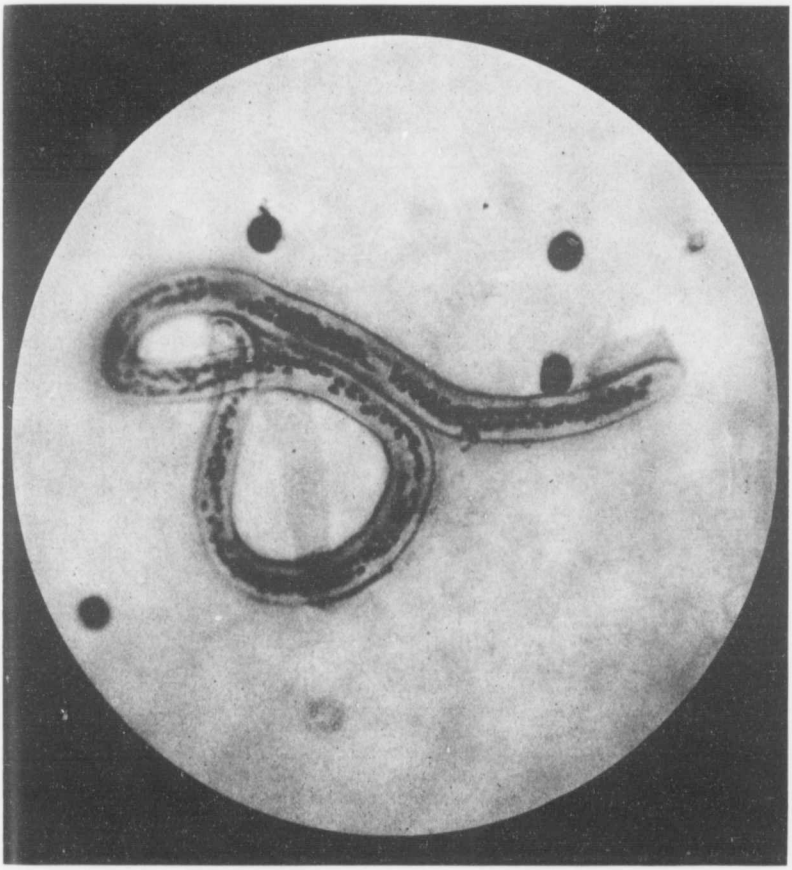
The lymphatic system is the normal habitat of *Filaria bancrofti*, particularly the larger lymphatic trunks, but they have also been found elsewhere, as in the heart and kidney.

The male and female worms are usually found in close contiguity.

Filaria bancrofti,—the adult worm,—discharges its embryos into the lymph stream, in which they are carried to the general circulation, where they exhibit the peculiar phenomenon known as filarial periodicity.

The nomenclature of filariæ is based on their characteristic periodicities. The distinctions between filariæ include different periodicities. Whilst *Microfilaria nocturna* appears in the blood at night, and disappears during the day,—*Microfilaria diurna* appears during the day and disappears during the night, and *Microfilaria perstans* observes no such periodicity.

The extraordinary fact of periodicity has received no explanation. The observation of nocturnal periodicity led to the suggestion, that the intermediate host was a night-flying insect, and that the night swarming of the nocturnal larvæ, in the peripheral circulation, is correlated with the life habits of its liberating agent. Other similar remarkable correlations in nature are mentioned by Sambon. Many flowers, which open early in the morning, are only visited by particular butterflies, which leave their nocturnal haunts at the same hour; other flowers do not open till sunset, and they are visited by hawk-moths, silk-moths, owlet-moths, etc., which commence their ramblings when dusk sets in. Then again, the development of the flower's fragrance is simultaneous with the time of flying of certain insects. Some flowers, which are visited by small nocturnal moths,



× 1180 diam.

Microfilaria nocturna.

exhale their fragrance in the evening; on the other hand, many flowers visited during the day are without fragrance at night.

What drives *Microfilaria nocturna* from the cutaneous circulation, or attracts it to the internal organs, during the day?

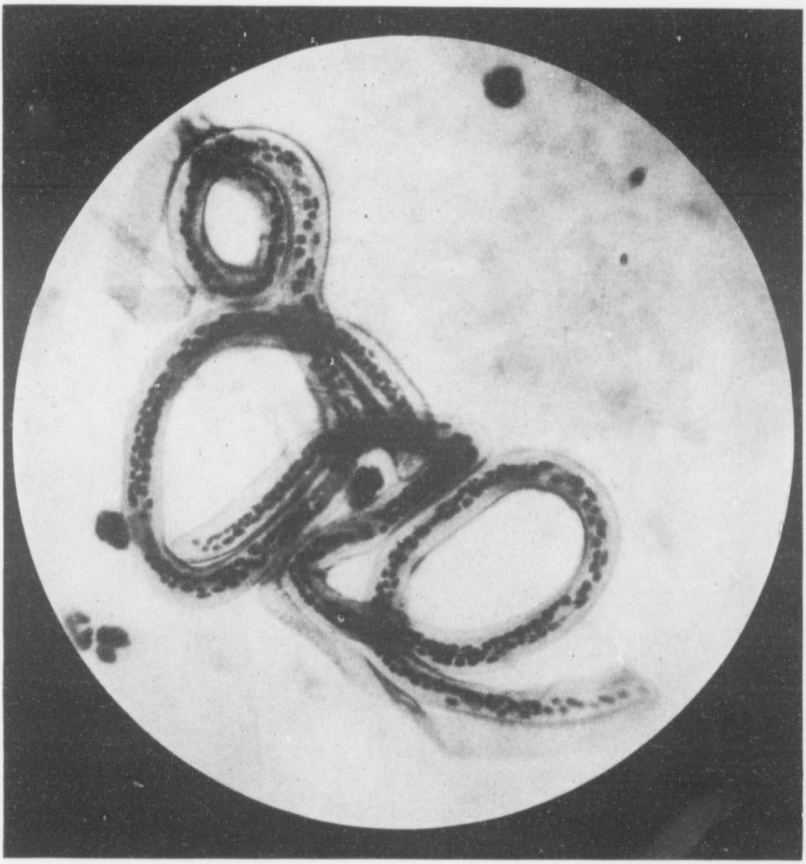
So far the phenomenon of filarial periodicity has received no satisfactory explanation. *Microfilaria nocturna*, during its temporary absence from the cutaneous circulation, is present in the larger blood-vessels, particularly in the arteries, the majority of embryos being lodged in the blood-vessels of the lungs.

The embryos of *Filaria bancrofti* begin to appear in the peripheral circulation about 5 or 6 in the evening, and are present in vast numbers by 9 p. m. Whyte (J. G.) states (1) that the hour at which the maximum number of microfilariæ appear in the blood is not, as has been frequently stated, always at midnight, but that, on the other hand, the number is often less at that hour than it is both earlier and later. (2) That the hour or hours at which the largest number of microfilariæ appear in the blood, though varying in different cases, will be found, *cæteris paribus*, fairly constant in repeated observations on the same case. (3) That filariasis is associated with eosinophilia, and that the degree of eosinophilia will often correspond with the number of microfilariæ in the circulating blood.

The appearance of *Microfilaria nocturna*, in the cutaneous circulation, concurs to a certain extent with the hours of sleeping, although their presence is not caused by sleep. Inversion of the hours of sleeping and waking suffices to bring about an inversion of the periodicity. It is stated that if sleep be taken at irregular intervals, by day and night, and this habit be kept up for several days, filarial periodicity becomes completely broken up, and is no longer maintained. Under such circumstances, filarial embryos are constantly present in the peripheral circulation.

The filaria of the South Sea Islands, which is identical with *Filaria nocturna*, exhibits no filarial periodicity. The periodicity of these filariæ has been altered, and modified, probably by the habits of their hosts.

Parturition in the parent worm is continuous, and exceedingly prolific. The number of microfilariæ varies extraordinarily. In some cases, they are so numerous in the blood, that, supposing that the proportionate number were equally distributed in the body, the total would amount to millions. Mackenzie computed their number in one case to be from thirty-six to forty millions.



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Microfilaria nocturna.

There can be little doubt that the number of embryos, found in the blood, is proportionate to the number of parental worms that are present in any particular case, and it is possible that, when the latter are few in number, the embryos may be so few in number as to escape observation. Manson's belief is, that before embryos can be found in the blood, by ordinary microscopic observation, large numbers of parent worms must be present in the lymphatics.

There are cases of filariasis, in which the embryos do not reach the blood at all. This is primarily the case, when the parent worms have caused complete obstruction of lymph. The disease to which the parasite gives rise,—lymphatic obstruction,—cuts its progeny off from the circulation.

Subjects of filariasis are generally infected by a number of specimens of *Filaria bancrofti*, and the number of microfilariæ found in the blood is some criterion of the number of adults in the subject of the infection.

If the microfilariæ are scarce, it is likely that there are few adult females, and if plentiful, it is probable that there are many adult females.

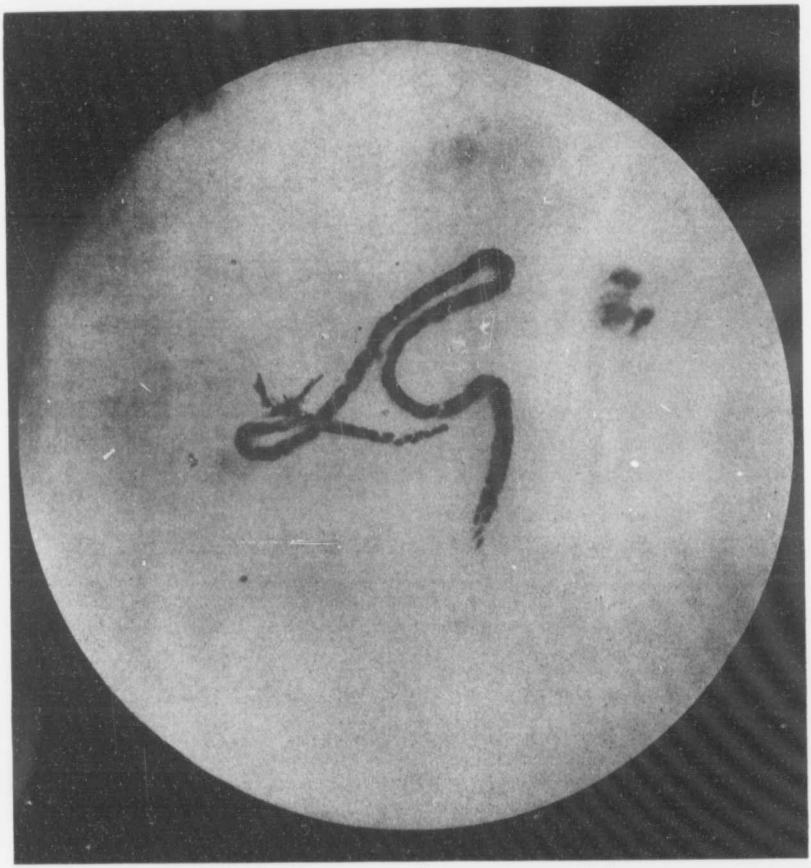
Cases of chyluria are often met with, in which the filariæ which had given rise to the disease, in the first place, had long since disappeared. The host is tolerant of these parasites, and, in the vast majority of instances, they give rise to no disease whatever.

Lymphatic obstruction, when present, is caused partly by the parasites themselves, partly by coagulated lymph, and in consequence of lymphangitis induced by the presence of the adult worms. The lesions they produce, and which are the proximate cause of filarial diseases, are permanent.

In elephantiasis of the legs and scrotum, the parent worms in most cases are situated in the lymphatic vessels, near the groin glands. Young (C. W.) reports a case of lymphatic obstruction, in which seventeen parent worms were found *post-mortem*.

In a subject of lymphangitis, Maitland (Madras) removed seven adult filariæ, which were coiled up in a mass in a lymphatic channel. Three of these were males, and the rest females. Although this colony of filariæ had managed to set up lymphangitis, yet the main circulation of lymph, throughout the limb, was in no way interfered with.

It is not known how long the embryo lives in the blood; Bancroft thinks that probably it may survive for several months. Sonsino has expressed the opinion that its life must be shorter,—a few days



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Microfilaria perstans.

only; otherwise in those subjects of filariasis, who do not suffer from loss of lymph, or blood, the number of microfilariæ would necessarily increase in a notable way every few days.

The opinion, generally entertained among helminthologists is, that the adult worm lives several years. Sonsino observed a filarious subject for twenty-three years. At the last examination, the condition was improved, but still with embryos in the blood, although perhaps in smaller numbers than formerly.

As elephantiasis and filaria have the same geographical distribution, it is probable that reinfection is continually going on. Where filariasis is prevalent, *Filaria nocturna* generally predominates.

Description of Mf. nocturna.

Microfilaria nocturna, when examined in fresh blood, is seen to be exceedingly active, but stationary. The embryo is enclosed in an exceedingly delicate sac, or sheath, in which it moves backwards and forwards. The sac, which is considerably longer than the worm dangling from either extremity, shows distinct structural markings. The structural marking appears as an exceedingly delicate striation. The sheath extends beyond the anterior extremity, and particularly beyond the posterior extremity, where it sometimes appears as a bag-like projection.

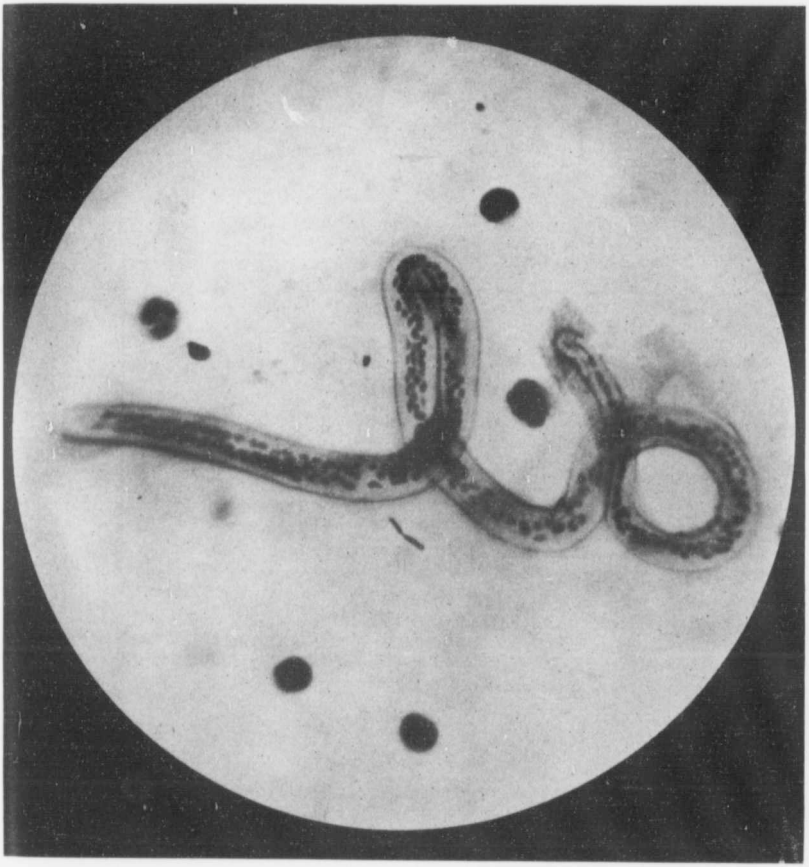
The movements of the embryo within the sheath are continuous and serpentine.

At a point, about one-fifth of the entire length of the organism backward from the cephalic extremity, a triangular shaped patch (Manson's V-spot) is found.

Another spot, similar to the preceding, though much smaller, is found a short distance from the caudal extremity. This is designated the "tail-spot." Slightly posterior to the V-spot, is seen a gap in the central column of nuclei, which is called the "break."

The most important differentiating structure is the so-called "internal body," which is only found in *Microfilaria nocturna*. This is an irregular aggregation of granular material, found about the posterior part of the middle third of the parasite. It is supposed to be a viscus of some sort, and it runs for some distance along the axis of the worm.

Staining shows that the parasite is principally composed of a



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Microfilaria nocturna.

closely packed column of cells, enclosed in a transversely striated musculo-cutaneous cylinder.

According to Manson, the V-spot is the rudiment of the future water vascular system, or of the generative organs, the tail-spot that of the anus, and posterior part of the alimentary canal. From about the tail-spot the caudal extremity tapers to a point.

In the living embryo, it is seen that the round cephalic end is constantly being covered, and uncovered, by a six-lipped prepuce, and further, from time to time, an extremely delicate filament or tongue is shot out from the cephalic end, and as suddenly retracted.

Microfilaria diurna.

The first historical reference to *Filaria loa* is contained in a book of travels on the Congo, in which Pigafetta (1598) describes the operative removal of the filaria from the conjunctiva.

The worm termed "loa" by the natives is particularly prevalent in the Congo, where it occurs not only in the natives, but also in Europeans.

The habitat of *Filaria loa* is the connective tissue, in which it moves about actively. When it approaches the skin, a certain amount of irritation, or a sensation of quivering, is felt, and the patient may be conscious of its movements. It has been observed to wander over the eye, beneath the conjunctiva, which was raised into a small ridge as it moved.

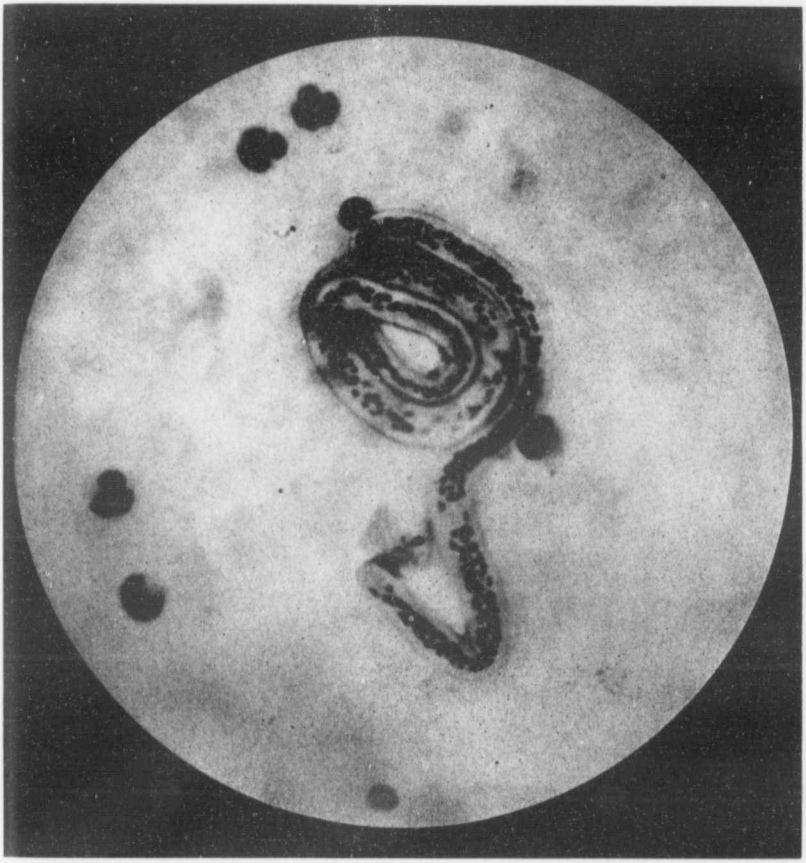
Filaria loa may appear under the skin of any part of the body, attracting attention only when it appears at a part where the skin is thin, or sensitive, or when it presents itself under the thin conjunctiva.

The wandering of the worm from one eye to the other, beneath the skin of the bridge of the nose, has been observed.

Leiper reports a case of scrotal infection with *Filaria loa*, in which twenty-one worms were obtained, *post-mortem*, from the scrotum, which was of normal appearance. There was enormous infection of the blood with embryos.

It is not clear why, in some cases, though adult worms are wandering about the subcutaneous tissues, no embryos are present in the blood.

Manson expressed the opinion that *Chrysops dimidiatus* (Van der Wulp), a species of fly that feeds by day, and which is common



× 1180 diam.

Microfilaria nocturna.

in Old Calabar, is the intermediate host; this was confirmed by Leiper's observation of the metamorphosis of *Microfilaria diurna* in the salivary gland of the fly.

Microfilaria diurna is the larval form of *Filaria loa*.

Microfilaria diurna observes a regular periodicity, but appears in the peripheral circulation, during the day, and disappears from the blood at night,—an arrangement exactly opposite to that which is found in *Mf. nocturna*.

The reversed periodicity of *Microfilaria diurna* has given rise to the supposition, that the intermediate host is a day-flying insect.

The embryos commence to appear in the cutaneous circulation, at about 9 or 10 a. m., they increase in numbers up to 1 or 2 p. m., then again decrease and disappear at 9 or 10 p. m.

In physical characteristics, *Mf. diurna* resembles *nocturna* in being sheathed, sharp-tailed, possessing a central column, a V-spot and tail-spot, and in having very similar oral and general movements.

In measurements, *Mf. diurna* is slightly shorter and narrower than nocturna.

Microfilaria diurna has a more delicate investing sheath, and the granular aggregation, seen about the middle of nocturna, is absent in *Mf. diurna*.

Microfilaria perstans.

Microfilaria perstans was discovered by Manson (1891) in the blood of a West African native. In 1897, the same worm was found in the blood of Carib Indians, of British Guiana.

In the following year, at the necropsy of two Demerara Indians, Daniels found the adult worm, both male and female, in the connective tissue at the base of the mesentery.

The habitat of the adult filariæ is the connective tissue, the mesentery, the pericardial fat, around the abdominal aorta, and around the pancreas.

Microfilaria perstans observes no periodicity, and is found in the blood by day as well as by night.

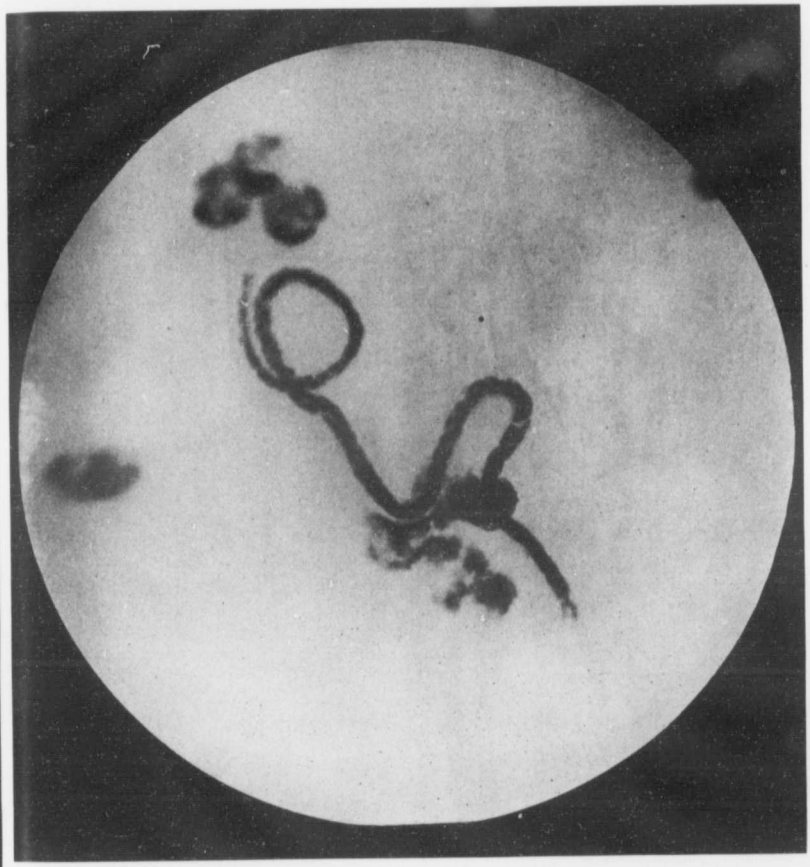
It is much smaller than *Mf. nocturna* and *diurna*.

It is devoid of sheath.

The caudal extremity is truncated.

Manson's V-spot is present.

The tail-spot may be marked or absent.



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Microfilaria perstans.

The movement of the worm is active and progredient.

There is no central granular aggregation.

The thickest part of the body is about one-third of the distance, behind the head; from this point, it gradually tapers off to the caudal extremity.

The cephalic extremity is provided with a retractile fang, which, like the tongue of a serpent, darts forward from time to time and is then withdrawn from sight.

Manson considers that the cephalic armature is a boring apparatus, which enables the worm to leave the blood-vessels, by its own efforts, and to have a somewhat different life history from the sheathed and non-locomotive microfilariæ. The intermediate host is unknown.

Microfilaria demarquayi.

Microfilaria demarquayi was discovered by Manson (1895), in blood films from natives of St. Vincent, West Indies.

Filaria demarquayi, the parent worm, is a parasite of jungly districts of certain West Indian Islands, St. Vincent, Dominica, Trinidad, St. Lucia, and Demerara. The sharp tailed embryos of the same parasite have been observed in blood preparations, in natives from New Guinea, and from the West Coast of Africa.

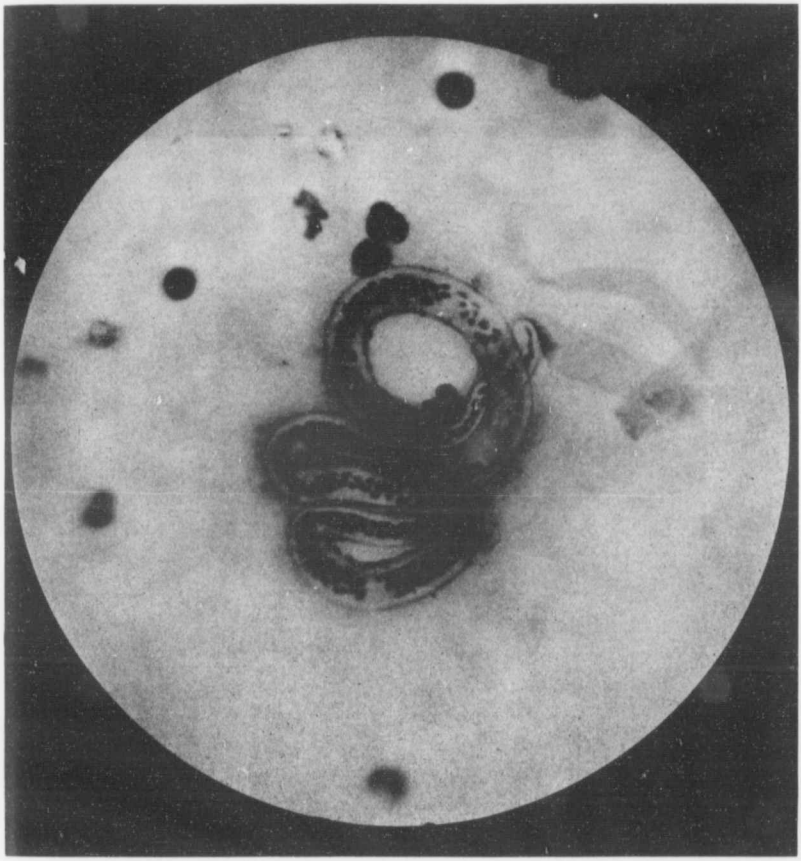
The adult female worm was found by Galgey in the body of a native of St. Lucia, in whose blood the embryos had been found during life. Five adult worms were present in the connective tissue of the mesentery.

As the habitat of the parent worm is in the loose connective tissue of the peritoneum, it cannot do much harm, as it does not implicate important structures.

The presence of the parental and larval forms of *Filaria demarquayi* seems to give rise to no pathological effects, or clinical symptoms, the diagnosis being made only by examination of the blood.

Microfilaria demarquayi has every resemblance to *Mf. perstans*, except in the conformation of the caudal extremity, which is sharp.

In stained specimens, the nuclei are found to extend to the top of the tail in *Mf. perstans*, whilst, in *Mf. demarquayi*, the finely pointed tail extends for some considerable distance beyond the last nucleus.



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Microfilaria nocturna.

Microfilaria demarquayi observes no periodicity, and is present in the peripheral blood, both by day and by night.

It is considerably smaller than *Mf. nocturna* and *diurna*.

It has no sheath.

A V-spot is present but is obscure.

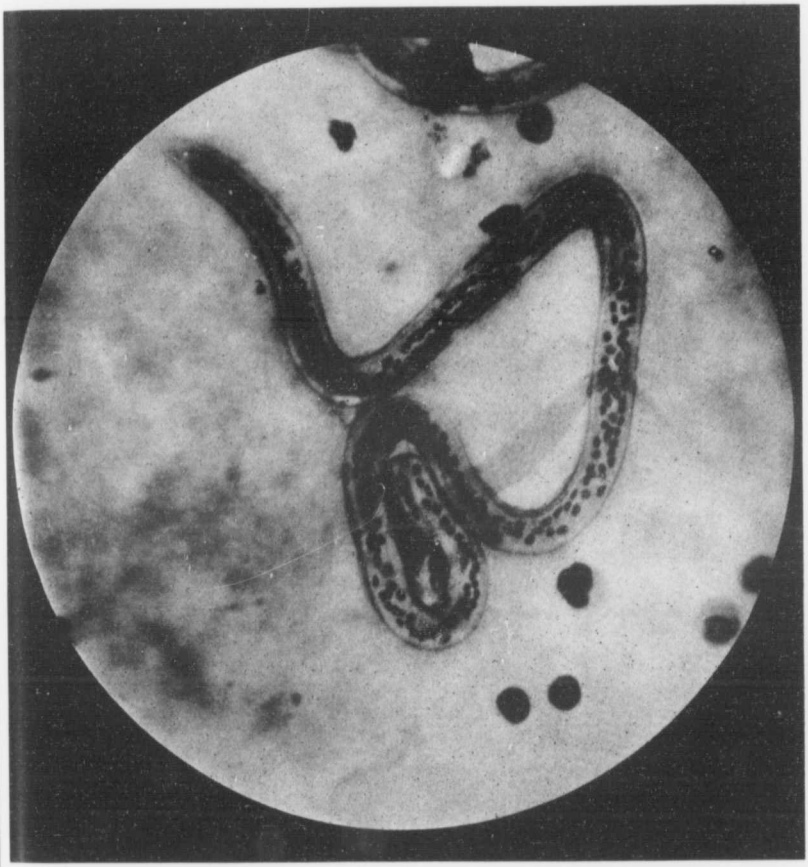
There is a faint indication of a tail-spot.

The movements are exceedingly active and progredient.

The cephalic armature consists of a poorly developed prepuce, not serrated, as is the case with *nocturna*, and more difficult to make out, and of a miniature spine, which is alternately pushed out and retracted.

The embryos have not been found in any of the natural excretions. Czarne found them, in one case, in the pus from an abscess in the arm.

The intermediate host is unknown.



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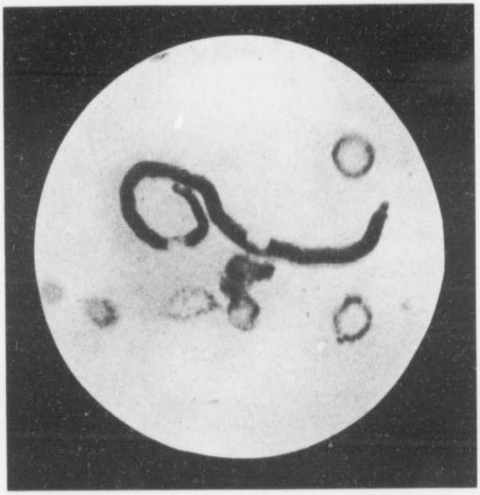
Microfilaria nocturna.



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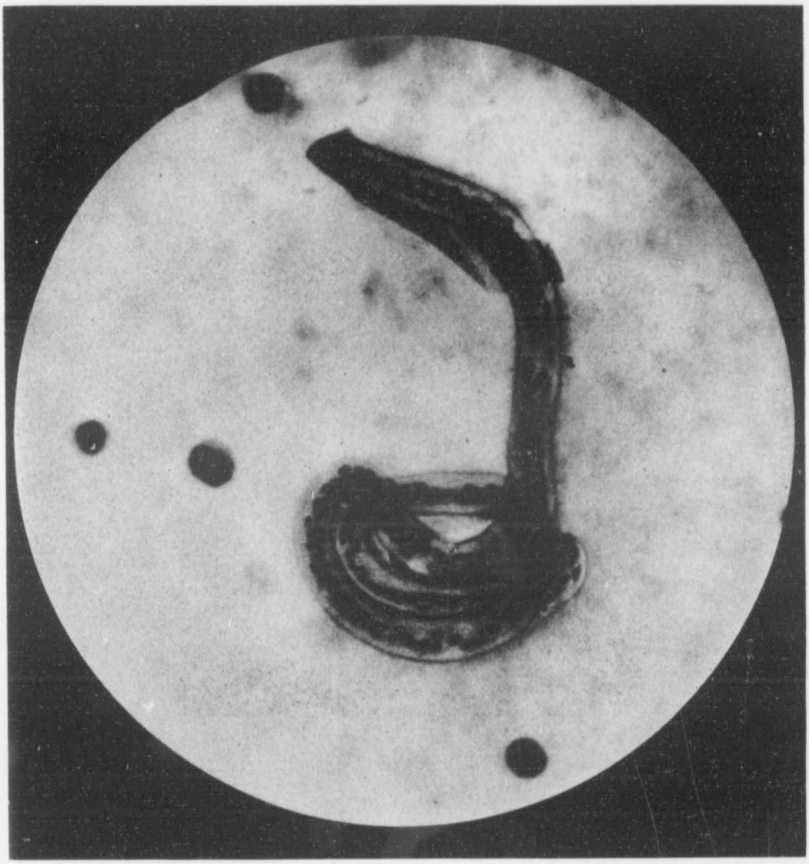
Microfilaria perstans.



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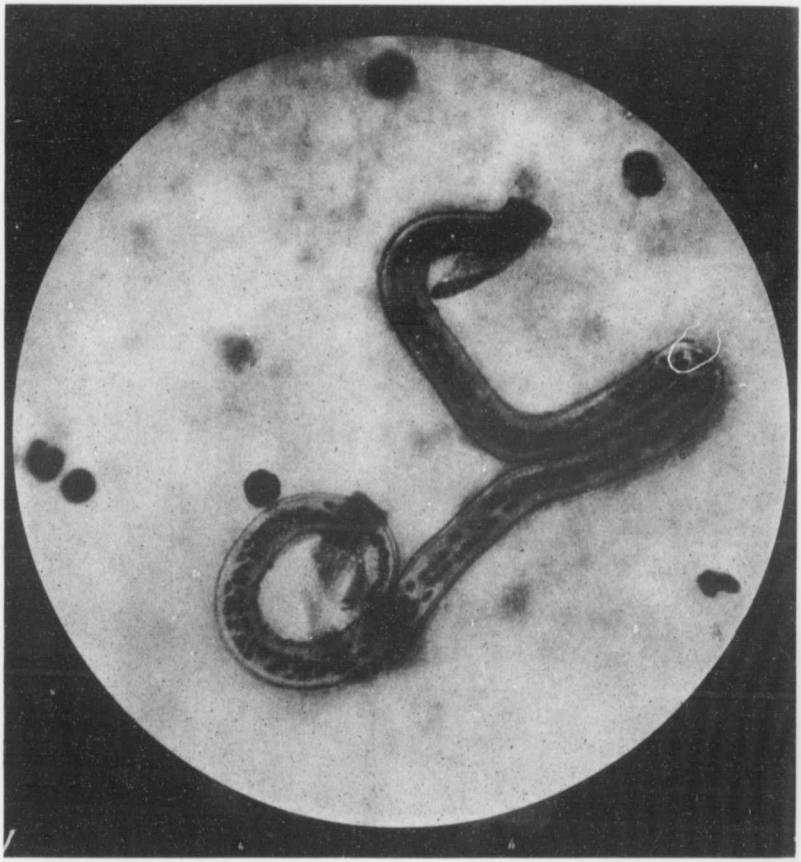
Microfilaria nocturna.



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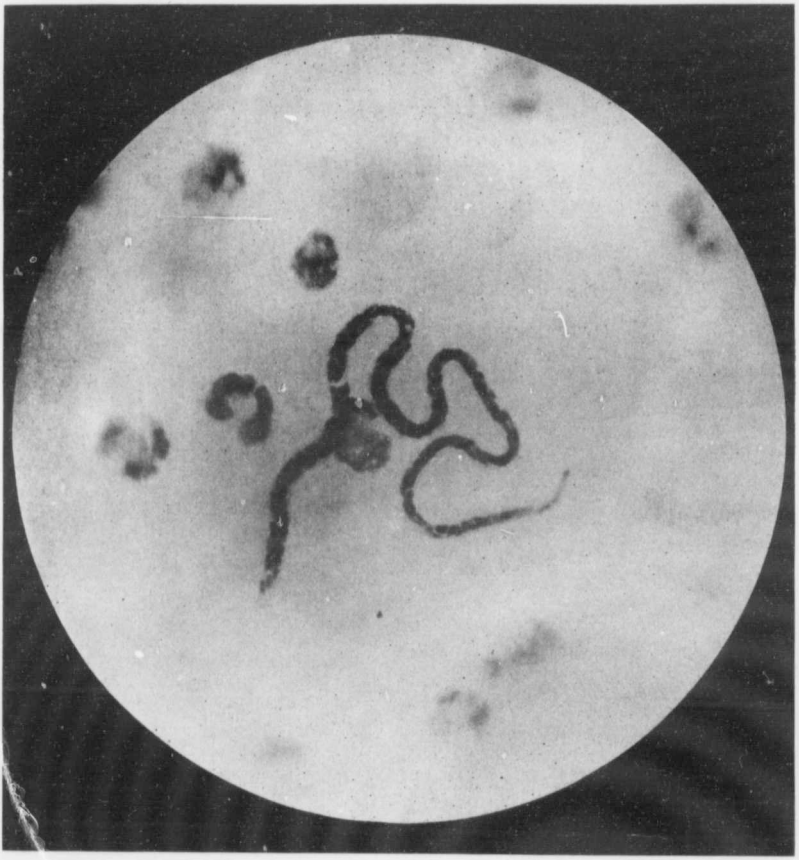
Microfilaria nocturna.



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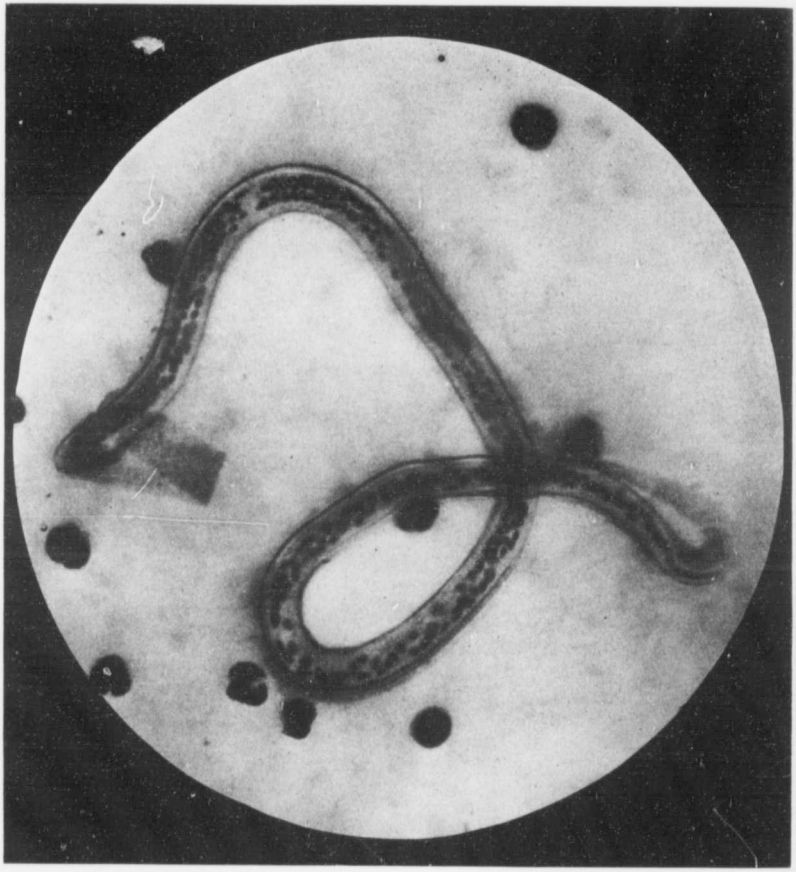
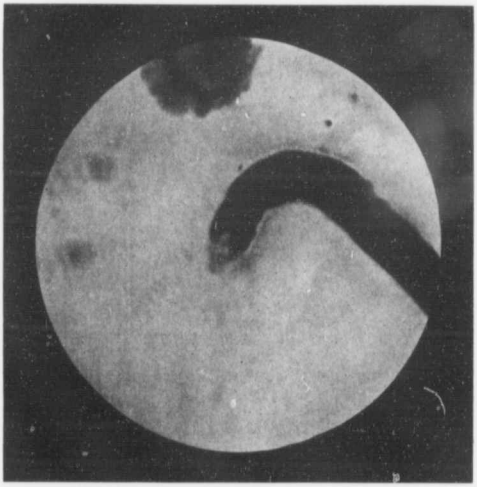
Microfilaria perstans.

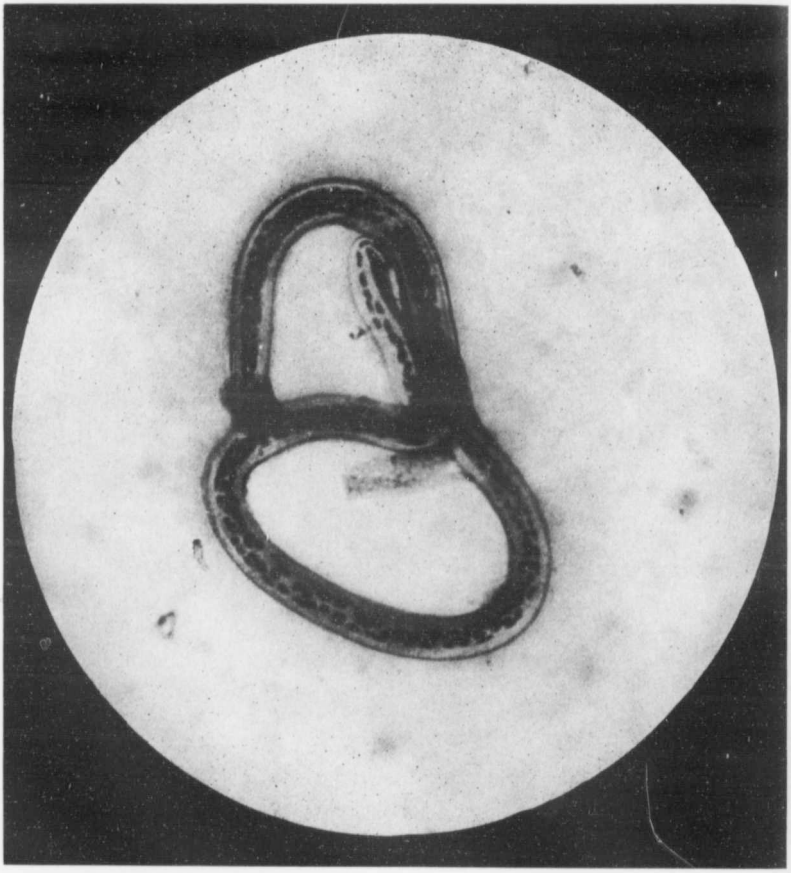


× 1180 diam.

Microfilaria nocturna.

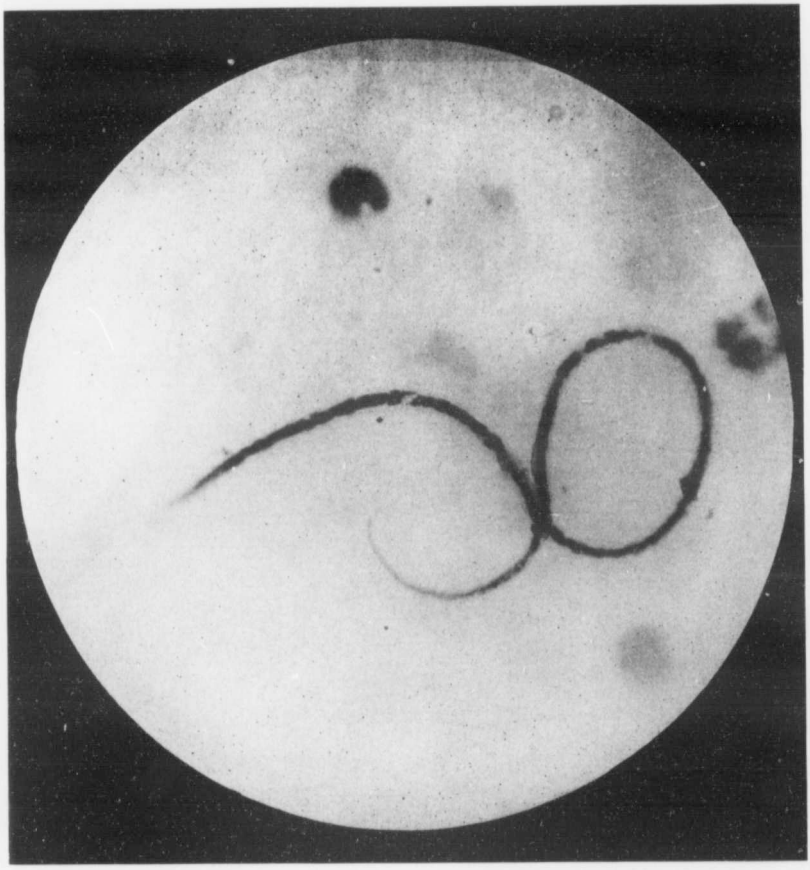


× 3000 diam.
Cephalic extremity of Microfilaria perstans.



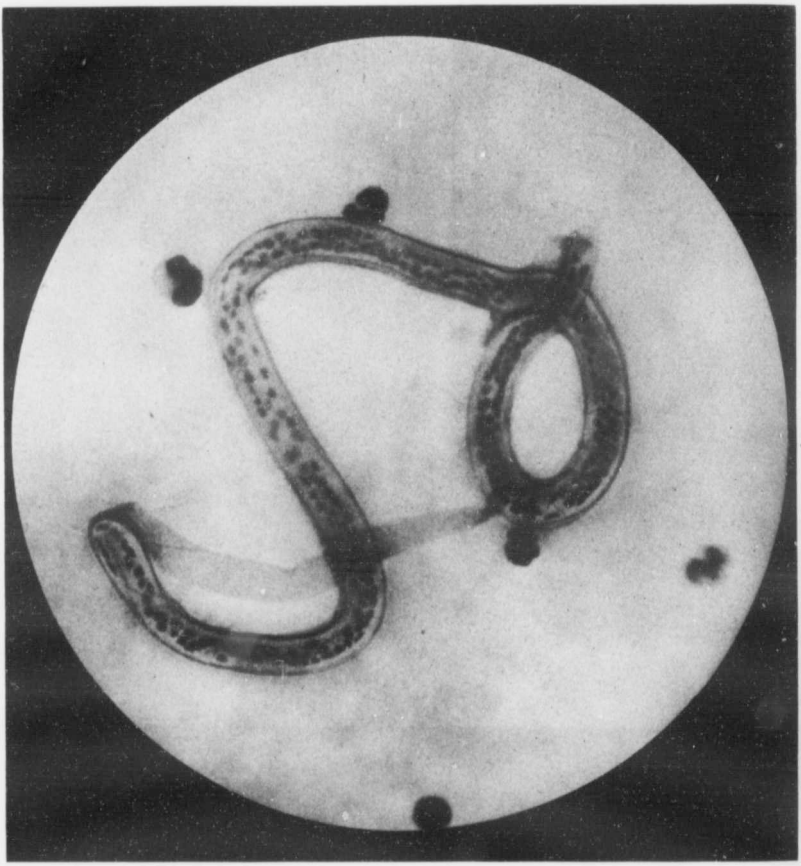
× 1180 diam.

Microfilaria nocturna.



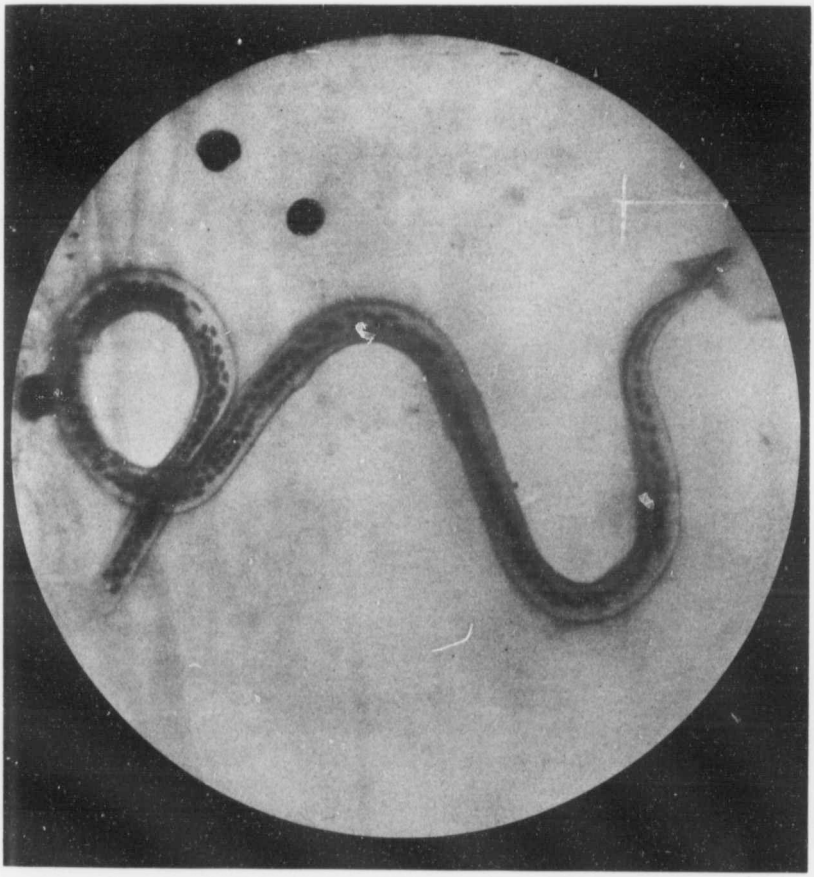
× 1180 diam.

Microfilaria demarquayi.



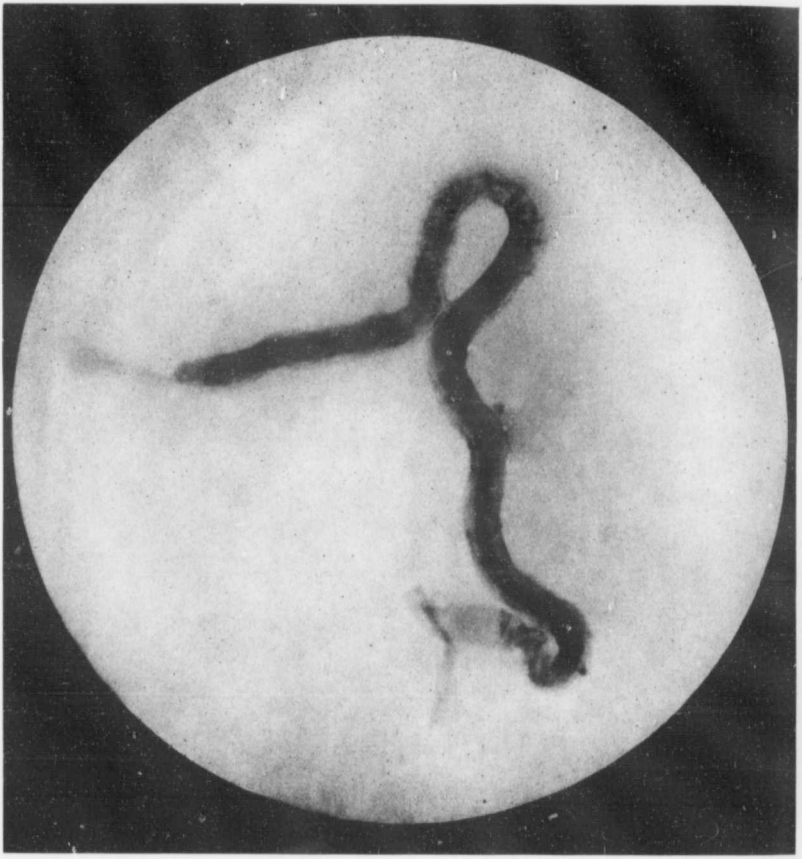
× 1180 diam.

Microfilaria nocturna.



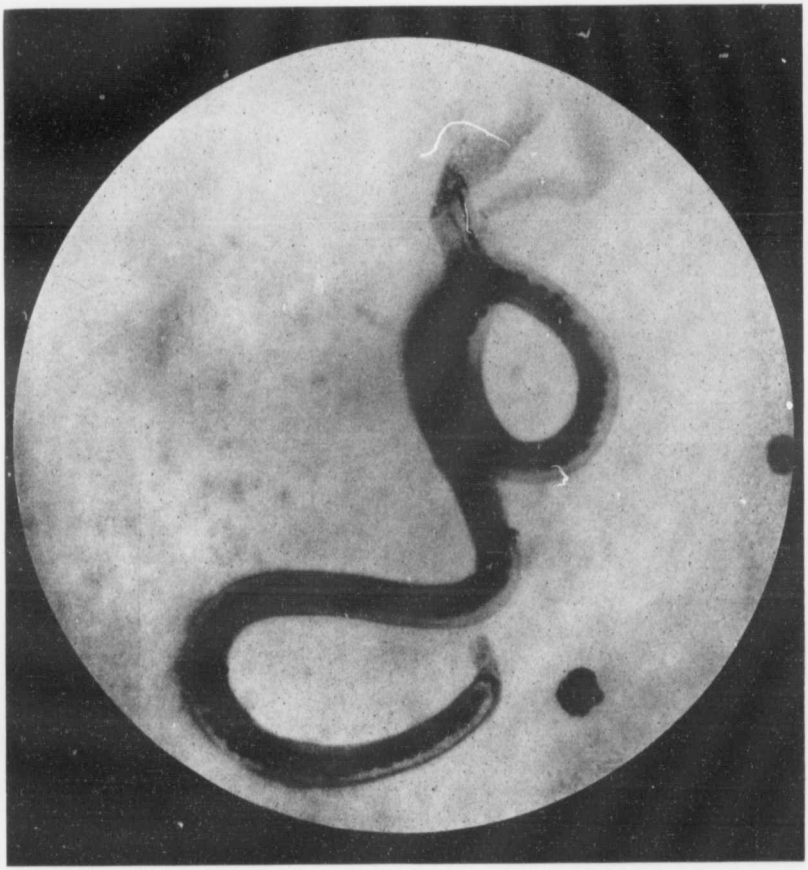
× 1180 diam.

Microfilaria nocturna.



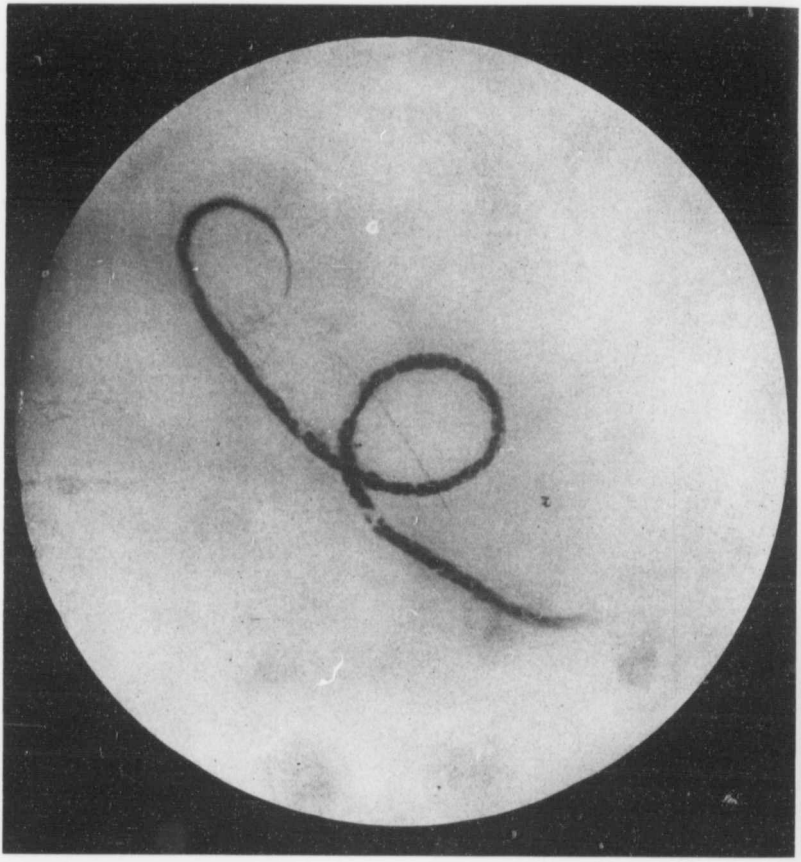
× 1180 diam.

Microfilaria diurna.



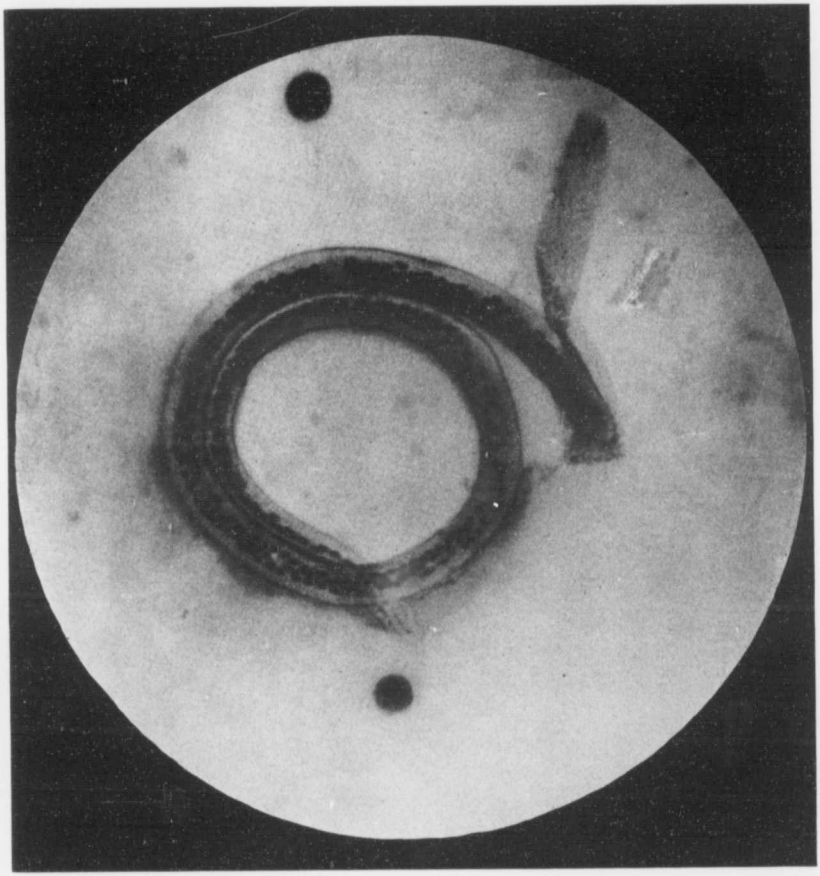
× 1180 diam.

Microfilaria nocturna.



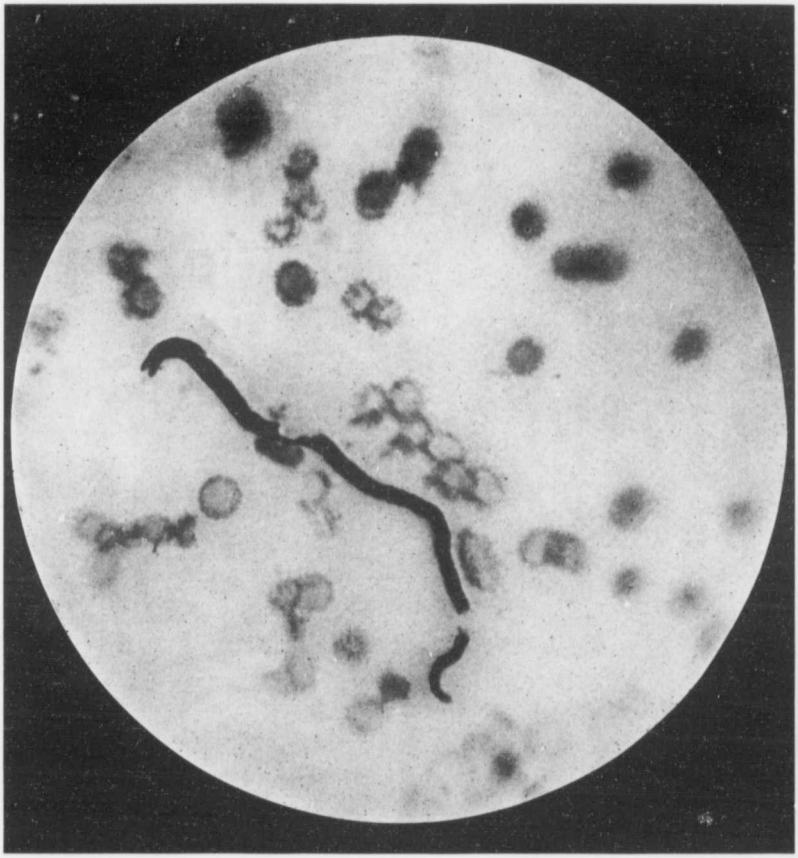
× 1180 diam.

Microfilaria demarquayi.



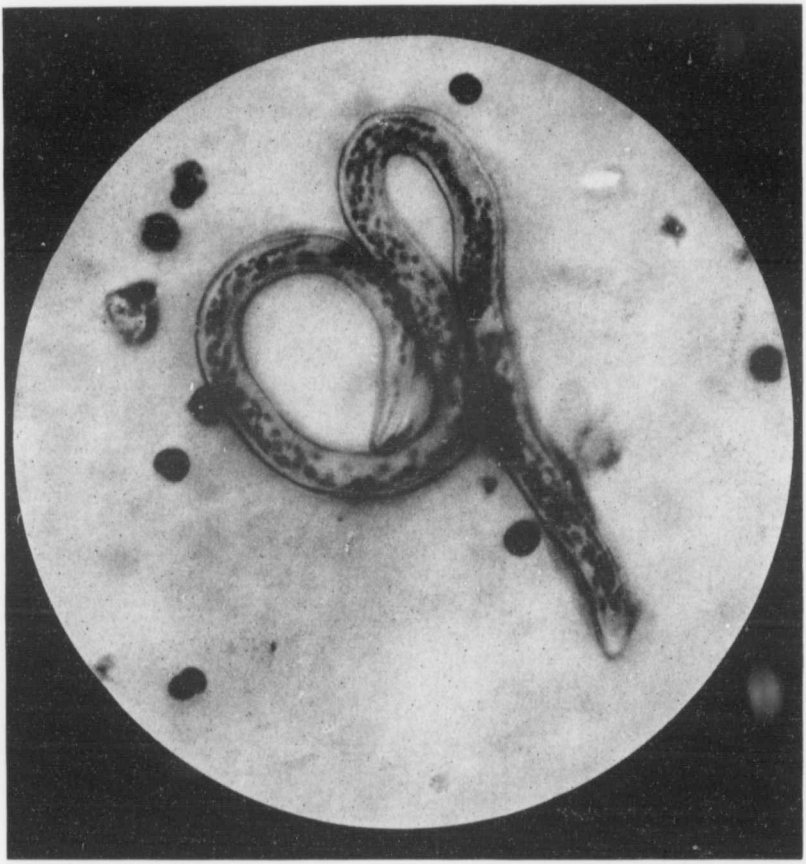
× 1180 diam.

Microfilaria nocturna.



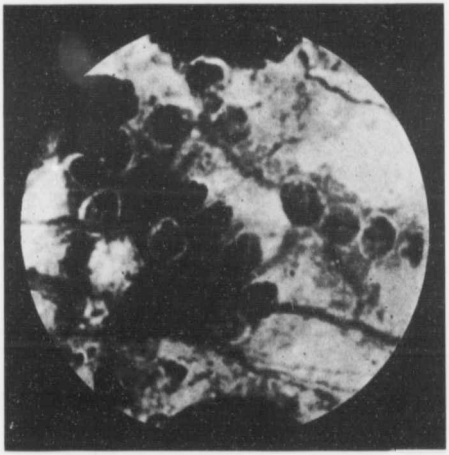
× 1180 diam.

Microfilaria perstans.



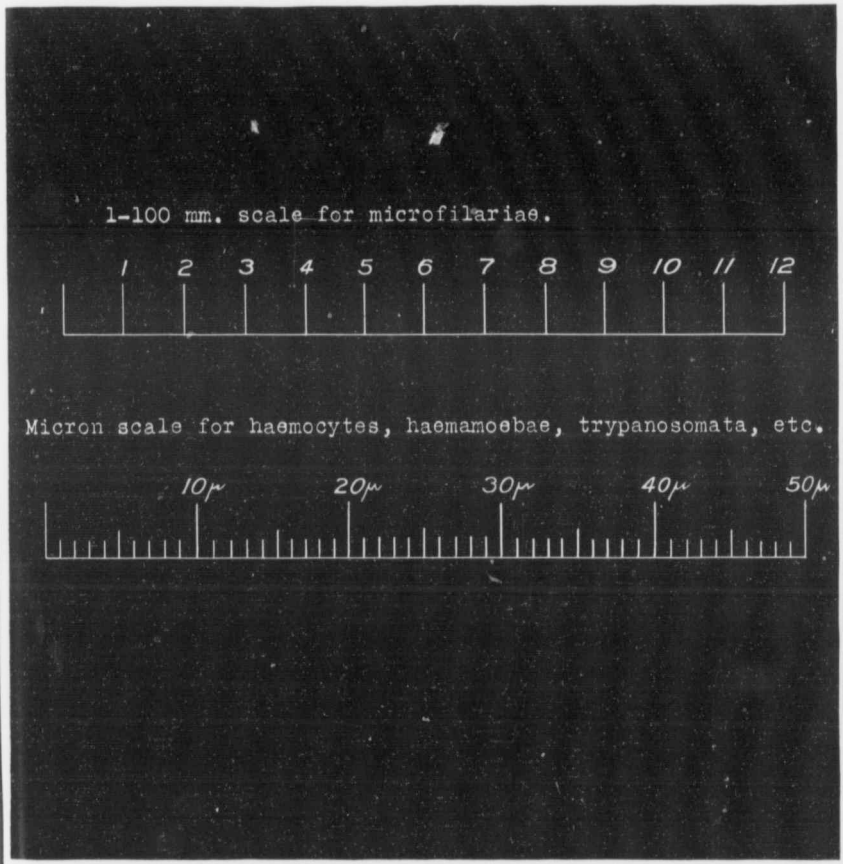
× 1180 diam.

Microfilaria nocturna.



× 3000 diam.

Saccharomyces farciminosus.
Parasite of epizootic lymphangitis of equines.


1-100 mm. scale for microfilariae.
1 2 3 4 5 6 7 8 9 10 11 12
Micron scale for haemocytes, haemamoebae, trypanosomata, etc.
10μ 20μ 30μ 40μ 50μ

INDEX TO MICROPHOTOGRAMS

GENERAL INDEX