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APPLIED PATHOLOGY IN DIAGNOSIS & TREATMENT

JULIUS M. BERNSTEIN

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APPLIED PATHOLOGY

BEING A GUIDE TO THE APPLICATION OF MODERN PATHOLOGICAL METHODS TO

DIAGNOSIS AND TREATMENT

BY

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ILLUSTRATED WITH FIVE COLOURED PLATES AND FORTY-SIX DRAWINGS

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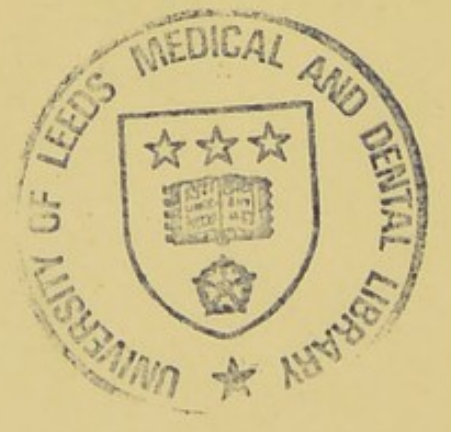

TO

RICHARD GRAINGER HEBB, M.A., M.D., F.R.C.P.

SENIOR PHYSICIAN AND PHYSICIAN-PATHOLOGIST

TO THE WESTMINSTER HOSPITAL

PREFACE

Some years ago the late Sir William Allchin suggested to me the utility of bringing the work of the newly-formed clinical laboratories before the practitioner in a comprehensible manner. At that time the general scheme was drawn up, but pressure of work prevented progress until, at the request of many students of the West London Postgraduate College I decided to publish my lectures on Clinical Pathology. Consequently these were taken down verbatim at the time of delivery, and their reproduction in lecture form must be the excuse for some of the imperfections in literary style.

No attempt has been made to produce a practical manual for the laboratory worker, for indeed there are already sufficient satisfactory works of this kind, and no technique is dealt with save that appertaining to the collection of specimens.

The book is, in fact, intended for the busy practitioner and senior student who wish to obtain a survey of the applications of clinical research, and contains the personal convictions of the writer—the result of many years' work in the wards and laboratories of the West London and Westminster Hospitals.

My thanks are due to many for assistance, but

especially to my brother, Dr. Alfred Bernstein, of Brompton Hospital, for considerable help with the sections dealing with Pulmonary Diseases and Tuberculin, and for the entire index; and to Dr. Eyre for permission to reproduce charts from his Erasmus Wilson lectures, and also for his encouraging criticism after reading the proofs; and to Dr. R. S. Frew for helpful criticism throughout. Dr. Charles Melland, of Manchester, has allowed me to select the beautiful coloured plates from his unrivalled collection of microphotographs of the blood, which have been prepared by him from his own cases, and Messrs. Pathé Frères have supplied me with cuttings from their cinematograph films of living micro-organisms seen by the dark-ground illumination.

J. M. B.

43 *Queen Anne-st., W.*

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CHAPTER I

INTRODUCTION

PATHOLOGY has long since ceased to be synonymous with Morbid Anatomy. Its ramifications have become so widespread and so complex that through them enthusiastic devotees have wandered into the realm of pure science, forgetful of the original motive, namely, the elucidation of disease. The work of the scientific devotees —useful though some of it may ultimately become —is for the moment of no import to the practising medical man, for not only is he unable to assimilate the rapidly outpouring material, but he cannot even understand the language in which it is put forth.

Chemical Pathology, Bacteriology, Immunity, and—notwithstanding an undeserved neglect—Morbid Anatomy, claim, each, their followers, who in youth are eager to throw themselves wholeheartedly into the pursuit; and if in riper years enthusiasm wanes, then, having ventured so far from the beaten track of empiricism, they must continue, *faute de mieux*.

To meet a demand for knowledge and assistance

there has arisen a new line of specialisation as represented by the so-called Clinical Pathologist, whose scope theoretically should be to act as intermediary between the scientific pathologist and the practising physician and surgeon: to cull from the scientific workers, who often fail to get recognition, what is of immediate practical utility to the practitioner, and to place it before him in a readily assimilable form.

But with the advent of the clinical pathologist there has arisen a new danger. In recent years these new laboratory aids to diagnosis have loomed so largely in the public eye as to gain an exaggerated importance, and just as there is an unfortunate tendency for medicine to be divorced from pathology, so there is a strong tendency for the clinical pathologist to ignore the medicine of experience and to see all disease diagnosed in the test-tube or through the microscope. There are those even amongst the leaders of fashion who avowedly consider that the medicine of the future will fall into the province of the so-called scientific worker, nay, even into the hands of that new product, the vaccinist—a man often young and lacking experience, trained for a few months at the fountain head, and treating disease about which, owing to his inexperience, he can know but little, with a few chosen bacteria with which he has familiarised himself. Such a man too frequently has no sound knowledge of the science of bacteriology, and he assumes the rôle of a therapeutist without incurring opposition. Indeed,

on the contrary, he receives praise and glory even from his elders, who, perhaps in their forgetfulness, or perhaps from an undue appreciation of this new treatment, regard him as a brother consultant.

Clinical pathology has indeed already produced new subdivisions, and we are already seeing evidence of the growth of consulting Wassermannites, men who will have every blood tested for syphilis; vaccinists who will have every disease and condition, from boils to abortion, treated with vaccines; and even spirochætologists,—just as recently we saw men trained in blood morphology pinning their faith in every case to a blood count. As aids to diagnosis these new products cannot do much harm, but the position is very different when they represent the sole lines of treatment.

At this stage the reader may be reminded that an infective process is often the result of infection on a system depressed by environment, insufficient nourishment, perhaps congenital weaknesses, and so on, and a line of treatment which is directed to one aspect alone cannot be, to say the least of it, logical. If this line of treatment be directed against the bacterium, regardless of the predisposing causes, it is evident that only the lesser evil is being attacked.

Now, clinical pathology should have its position clearly defined. It is a mongrel science and often a mongrel art. It is true that certain experiments, such as agglutination phenomena, the

Wassermann reaction, the demonstration of spirochæta, the tubercle bacillus, and the like, are to be depended on, and are often of themselves diagnostic. Laboratory methods result usually in the statement of facts, often based on broad principles, but often also on the same empiricism as clinical medicine. And if a comparison between these two be allowed it might be said that the facts of clinical pathology are to a great extent defined and that the methods can be learned in a short time, whereas clinical medicine is undeniably a matter of experience and commonsense, the former of which is an ever-increasing quantity. Clinical pathology, in fact, ignoring as it must the vital elements which cannot enter into laboratory technique, is compelled always to be only an adjunct to clinical medicine.

The clinical pathologist, so called, is himself a man of indefinite status, often having to devote his whole time to the technique of the laboratory. Much of this technique can and ought to be entrusted to the skilled laboratory assistant who is now rising up. We know that there are still amongst us those who disagree with this, and who would compel trained medical graduates to do the manual work themselves, to wear themselves out daily cutting sections of tissues and enumerating blood corpuscles, so that in time we feel they must degenerate into "hewers of paraffin and drawers of blood." But the technique is, after all, only skilled labour, and must be relegated to properly trained persons, whilst the trained observer must

be free to apply results to the problems of diagnosis.

In fact, we anticipate the time when the physician, who has been trending more and more towards a mere accentuation or duplication of the practitioner, will be replaced by the scientific physician or physician-pathologist. This scientific physician of the future will be versed in clinical data, have a sound knowledge of morbid anatomy, and be trained in all laboratory methods, so that he will be of assistance to the practitioner, to whom he will act as an addendum, telling of new methods of diagnosis, new aids to prognosis, and new suggestions for treatment. Such an one will be prepared to suggest and to carry out at the moment blood investigations to determine presence of pus or other cause of a pyrexia without any definite clinical signs; lumbar punctures to anticipate clinical manifestations of meningitis, so as to offer specific treatment before permanent damage results from the exudate; serum reactions to determine infections; bacteriological investigations of ulcers, diphtheritic exudates of the throat, etc., and, further, to act immediately on his findings. It is unnecessary to accentuate here the importance of early diagnosis in such conditions as diphtheria, cerebro-spinal fever, and, in the light of modern therapy, even syphilis, or the diagnosis of pyrexia without clinical evidence of the cause.

Thus, clinical medicine would be the province of

the experienced practitioner, who would have as a consulting authority the physician-pathologist. But there is no reason why medical men should not have a knowledge of laboratory technique, nor indeed that they should not be able to carry out many of the methods of investigation, such as an intelligent examination of the urine, morphological investigations of the blood, bacterioscopic investigations of diphtheria, the demonstration of spirochæta, etc., and even, if time could be found, cultural investigations which, in the case of diphtheria especially, would pave the way to diagnosis. The equipment for such work is simple, and could be obtained at no great expense, and the technique is not elaborate.

At the present day it is the fashion to send such investigations to one or other of the trade laboratories—places in which the interest in the work can be only of a commercial nature. How much more important would be the results obtained by a medical man examining material from his own patient, with a thorough knowledge of the facts to direct his investigations or to produce corroboration of his findings !

Such is the ideal of the new school of physician-pathologists. Meanwhile the transitional period is with us, with its trade laboratories pouring out reports at request—reports which often, to say the least, cannot be rightly understood, and which call for an interpreter to put these new findings into a language within the comprehension of all. This is the object aimed at in these pages, in

which attempt is also made to bridge the gap, which has unfortunately been allowed to get wider and wider, between pathology and clinical medicine. Although it is the custom to comment on the inseparability of these two divisions, practically they have been and are two branches, both in systematic and clinical medicines.

CHAPTER II

THE BLOOD

General description — Functions — Morphology — Serology — Chemical constituents — Salts in tissue respiration — Internal secretions — Toxins — Immune bodies — State of health dependent on blood — Deductions.

THE blood is a fluid medium permeating the tissues of the body.

A complete knowledge of the nature of this medium in health and disease would be the perfect index of the state of the whole body.

So limited, however, is our knowledge that we glean but comparatively little from an examination of the blood with our present methods, and even that little is but imperfectly understood.

Certain anatomical changes, certain chemical changes, and certain activities of bodies, many hypothetical, connected with Immunity we know as manifestations associated with certain diseased states. This is, however, only sufficient to teach us that, whilst we have some knowledge of the morphological variations which helps us considerably in diagnosis and prognosis, and a little of the serological changes which has opened up new paths of diagnosis and treatment, we are as yet

hardly on the threshold of the possibilities of hæmatology.

The blood, consisting of formed elements and plasma, is the great transporter of all nourishment to the tissues, the great remover of all end-products of tissue activity, the conveyer frequently of the cause and still more frequently of the results of disease, and the means by which the different parts of the economy are enabled to intercommunicate.

In different parts of the vascular system we believe that normally the constitution is different, though fairly constant within limits, and such gross differences as exist between arterial and venous blood, or in the portal system, or in the blood entering and leaving the kidney, are well recognised.

But, whilst emphasising the state of our ignorance on this subject, we feel that with the increase of knowledge, especially along lines of chemical research, the blood is destined to become the great indicator and source of diagnosis in the future.

Concerning some of the broad facts and interpretations we can now speak in general, and the details of those that are of practical importance will be dealt with in later chapters.

In the plasma are found products of digestion, namely soluble sugars, proteids and their precursors, fats and salts. For practical purposes disturbances of the metabolic processes are best determined by examination of the products excreted from the blood. Hence a discussion of these will be better deferred until the urine be dealt with.

But concerning the salts a little must be said

here. They give the characteristic alkaline reaction to the blood and take a great share in the respiratory function. It is in combination with the alkaline salts that carbon dioxide is carried from the tissues to the lungs. In cases of reduced alkalinity of the plasma and more especially in severe cases of diabetes, where acids accumulate in the blood stream, the salts are in great part held in combination with these acids, and so tissue exchange is interfered with, and carbon dioxide accumulates. This is the most feasible explanation of the "air hunger" that characterises diabetic coma.

The salts, as regards the chloride content, are also concerned in the formation of hydrochloric acid in the gastric juice, and it is on the salts also that the reaction of the urine depends.

In the plasma also are found katabolic products of tissue activity, which are carried to the kidneys, liver, skin and lungs to be excreted, sometimes undergoing a preparatory conversion in the liver, such as occurs with urea and uric acid. With these must be included the products of degeneration of the blood elements themselves. The hæmoglobin, which is the carrier of oxygen, is contained in the red corpuscles, on degeneration of which—either as a normal process or a diseased state—it is carried to the liver, where, losing its iron molecule, it becomes bile pigment, and as such is excreted. In some cases of excessive destruction of hæmoglobin, as in pernicious anæmia, there results an

enormous excess of iron in the liver, which can readily be demonstrated.

Normally also there exist in the blood the products of the glands producing internal secretions, such as the glycolytic ferment of the pancreas, the adrenal secretion which affects the blood pressure, and the lesser understood secretions of the thyroid and pituitary bodies, and perhaps also numerous secretions of analogous nature from other glands. Of these we know little, but there seems small doubt that many diseased states are due to variations in this process, and to changes, either in the nature of excess or deficiency, of these products in the blood stream. Such is the explanation of the condition of athyrea and myxœdema, with deficiency or absence of thyroid secretion, or the converse process of hyperthyrea with coma and death resulting from excess of secretion as seen in the terminal stage of some cases of goitre; also of some cases of true diabetes mellitus with destruction of the pancreas, or perhaps only of the cells which pour the glycolytic ferment into the blood; also of cases of Addison's disease associated with adrenal insufficiency; and by analogy also it is the explanation of the diseases characterised by change in the skeleton, *e. g.* acromegaly, which, indeed, is sometimes associated with characteristic lesions in the pituitary body.

We have already said that at the present time the urine is a great indicator of the state of the blood and this is especially so with regard to

abnormal products that may be present. Glycosuria will result from excess of sugar in the blood stream. Likewise foreign proteids such as egg albumin and albumoses will be rapidly excreted; also toxic substances such as result from intestinal putrefaction and other unknown poisons. Of these latter we have at present merely indications in certain diseased states such as the malaise and headaches, etc., associated with constipation. But it is certain that toxins enter the blood as a result of excessive muscular activity, or as a result of long-standing intestinal disturbances, in addition to more active toxins taken in chiefly with the food. It is highly probable that we must look to these continued insults to the system for the explanation of such chronic conditions as arteriosclerosis and chronic interstitial nephritis—perhaps, also of many conditions in advanced years that are not truly of physiological nature. Indeed we are inclined to regard many if not most of the so-called "senile changes" as really toxic in origin.

Many of the bacterial toxins of a more acute nature, as well as the bacteria themselves that thrive in the blood stream or are transported therein to form terminal foci, are well understood, and, it will be seen later, can be identified in the blood itself. Some of these, together with certain others of purely chemical nature, produce definite changes in the blood elements themselves, such as destruction of the red blood corpuscles as seen with quinine, potassium chlorate, etc.

But though many of these foreign elements cannot be directly recognised, an indication of the abnormal state of the plasma is to be found in a change in the formed elements. These depend on the plasma for their well-being, and so show changes indicating malnutrition, maloxidation, or even chronic intoxication, which constitute the manifestations of anæmia. In addition certain toxins have a direct hæmolytic action and cause excessive destruction of the red blood corpuscles with consequent increased production of bile with accompanying jaundice, and sometimes even hæmoglobin in the urine itself.

Of special importance are the abnormal changes in the hæmoglobin, such as the firm combination with carbon monoxide which interferes with oxidation, or the formation of sulph-hæmoglobin or of methæmoglobin resulting from chemical poisons or intestinal putrefaction. These are all readily identified either from the characteristic colour of the blood or by the aid of the spectroscope.

So far we have merely spoken of the chemical changes in the blood, but of great import are the true vital manifestations. The leucocytes are the elements that alone display the phenomena of life. They are the true cell elements of the blood and act as transport, carrying food material from the intestines and removing foreign particles to the lymph glands. Further they take a great part in the defensive processes of the body, destroying foreign elements, either in the blood stream or

at its terminals, and are predominant in the manifestations of acute inflammation. The activity of certain leucocytes under such conditions forms a feature of diagnostic value and at times the only feature.

Some leucocytes appear to be especially active during the period of growth, especially in the early years. In addition to the defensive property of the blood, due to its leucocytes, various protective bodies appear in the plasma as a result of infective processes. The seat of origin of these is unknown. It may be that they are formed by the cell elements of the blood or of the tissues or both. Though only few of these have been separated from the blood,—and many are manifested only by certain activities—it is possible to identify them; and indeed their recognition constitutes the most valuable aid to diagnosis of specific infections.

But notwithstanding this addition to our knowledge of the phenomena of immunity we are still ignorant of the processes at work in its production and especially with regard to the condition of natural immunity with its peculiar variations in different species. We know not why certain species are highly susceptible to an infection which will not affect other species; and in some cases, even, bacteria, highly virulent to one species, will flourish in the blood of another without producing disease.

From what has been said it will be evident that the state of well-being which constitutes health

must be dependent on the state of the blood. This in its turn is dependent on (1) the supply of normal products of digestion from the alimentary tract, oxygen from the lungs, and internal secretions from the various glands, and (2) the integrity of the excretory glands,—the liver, kidneys, skin and lungs,—to permit of removal of effete products.

Impairment of these functions must result in impairment of health. This is seen in starvation, maloxidation and the failure of certain internal secretions, in all of which there is a deficiency in the supply of normal products. And again, in such conditions as cholæmia or uræmia, where, owing to disease of the liver or kidneys, certain toxins fail to be excreted. Or yet again, as a result of the entry of abnormal products into the blood, such as putrefactive bodies or toxins, either chemical or bacterial, from the intestines, carbon monoxide from the lungs, bacteria or their toxins from the tissues.

We have said that the ideal should be to deduce from an examination of the blood knowledge of all these changes. At present even with our limited knowledge much can be done. Inflammation is denoted by the state of the leucocytes, malnutrition by changes in the red corpuscles and hæmoglobin. Bacteria can be cultivated from the blood stream and many infective processes diagnosed by the identification of specific protective bodies incited by their presence. Protozoal parasites, such as malarial plasmodia, trypanosomes, and Leishman-Donovan bodies, and other

parasites, can be readily identified in the stages when they appear in the blood stream.

Some intoxications of a coarse nature which produce combinations with hæmoglobin can be distinguished with the aid of the spectroscope, *e. g.* carbon monoxide, and sulphur, hæmoglobin. And even in other toxæmias, such as cholæmia and uræmia, where the toxic bodies are as yet unknown, the toxicity of the blood can be revealed by animal experiment.

The deductions of practical importance will be discussed in the following chapters. But there are other points to note in this connection.

An appreciation of the combination of hæmoglobin with gases, and the absorption of gases by the plasma, paves the way to a comprehension of the factors concerned in Caisson disease. The capacity of the blood to produce resistant bodies to infection forms the basis of serum treatment of disease, upon which an ever-growing structure has been founded; and the appreciation of phagocytosis and the general reactionary power of the blood to infection has more recently been made the first principles of bacteriotherapy.

As a vehicle for the exhibition of drugs the blood is of great value. Alkalies directly introduced into the circulation have for long been given to counteract the increased acidity that accompanies diabetic coma, with highly satisfactory, even if temporary, results.

But the most recent and hopeful work on chemotherapy makes use of the circulation for

transporting parasiticidal remedies throughout the system. From the success that has resulted from the use of salvarsan and other arsenical derivatives there is every reason to hope that many new drugs, resulting from the science of chemotherapy, will ultimately be administered by this means with curative effects.

Finally, the blood must be looked upon as analogous to other viscera, in that it is formed of cell elements, though more mobile, which cells can proliferate and produce conditions comparable with tumours. Such a condition is seen in leucocythæmia. But it must be remembered that the blood elements originate in certain blood-forming glands, and it is really the changes in these that are indicated by the manifestations in the blood. We shall see that though these manifestations are well defined and associated with certain constant symptoms we have much to learn about the processes underlying them. But, from the association of more recently discovered blood parasites, such as the Leishman-Donovan body, with certain conditions of splenomegaly, it is possible that some at least of the so-called blood diseases will be shown to be of protozoal origin.

CHAPTER III

BLOOD-HISTOLOGY

Normal blood-count—*Leucocytosis*,—digestive; posthæmorrhagic; inflammatory; pyogenic; in suppurations without pyrexia; in diagnosing between typhoid and appendicitis; in pneumonia—its prognostic value; in complications of typhoid fever; in pyæmia—*Lymphocytosis* in children; in typhoid; in malaria; in whooping-cough—*Eosinophilia* in parasitic infections—*Leucopenia* in typhoid; starvation; acute miliary tuberculosis.

In the early days of clinical laboratories the investigation of the blood formed by far the larger share of the work. Attention was then directed to morphology, and the consideration of blood cells became all-important. Metchnikoff had for years elaborated his fascinating theory of phagocytosis, and Ehrlich later on introduced new methods of staining, so as to differentiate the various leucocytes. But a host of imitators, finding no other outlet for their scientific enthusiasm, proceeded to elaborate what had already been discovered, and to make the subject more difficult by attaching new names to the blood elements and making new classifications. The consequence was that a subject which was previously straightforward, became unnecessarily complicated and overburdened with a nomenclature which obscured the practical outlook.

When, however, by the discovery of the bactericidal action of the blood serum apart from the leucocytes, new ground was broken and attention directed to this new and prolific field of research with its potentialities, blood morphology was allowed to rest, and it was recognised that for all practical purposes it had reached its limits. It is now possible, with the mass of statistics and the multitude of works on this subject which are available, to draw certain conclusions and to define the practical limitations of *blood counts*, and at the same time to simplify the nomenclature so that for the ordinary worker there may be no unnecessary difficulties.

A cubic millimetre of blood is described, from the morphological standpoint, as consisting of leucocytes, 5000–10,000; red corpuscles, 5,000,000; and platelets, which are not known at present to have practical importance.

The leucocytes are nucleated elements which can be subdivided into (1) *polymorphonuclear cells*, which are amœboid with an irregular nucleus, and protoplasm filled with granules. These, the usually accepted phagocytes of the blood, are further differentiated into the finely granular, constituting from 72 to 74 per cent. of the entire number of leucocytes, and the coarsely granular (eosinophiles), constituting from 1 to 3 per cent. (2) *Monomorphonuclear cells*, which have a round nucleus deeply staining, and which, according to the amount of protoplasm present, are further subdivided into small monomorpho-

nuclear cells (lymphocytes), which form 22 per cent. of the entire count, and large monomorphonuclears (hyaline cells), averaging about 1 per cent., and (3) *transitional cells*, in which the nucleus varies slightly in shape and which constitute 3 per cent. of the blood cells.

The red corpuscles are non-nucleated, elastic biconcave discs, which contain the hæmoglobin or colouring matter of the blood. The amount of hæmoglobin present in the normal blood is taken as the standard, namely, 100 per cent.

The blood plasma—or the fluid in which these formed elements subsist—has generally a definite relation in volume to the solid elements—a relationship which can be expressed as ratio of serum to corpuscles.

As variations in these elements form a characteristic feature, often of diagnostic value, in many diseased states, the individual elements may now be taken in series.

Leucocytosis

In a healthy adult the leucocytes are present in number varying from 5000[1] to 10,000, increasing during the digestion of a heavy meal. They may be either increased or diminished in number.

An increase that is transitory and symptomatic constitutes a *leucocytosis*. This has to be distinguished from a permanent increase which consti-

[1] Throughout, the figures refer to the content of a cubic millimetre of blood.

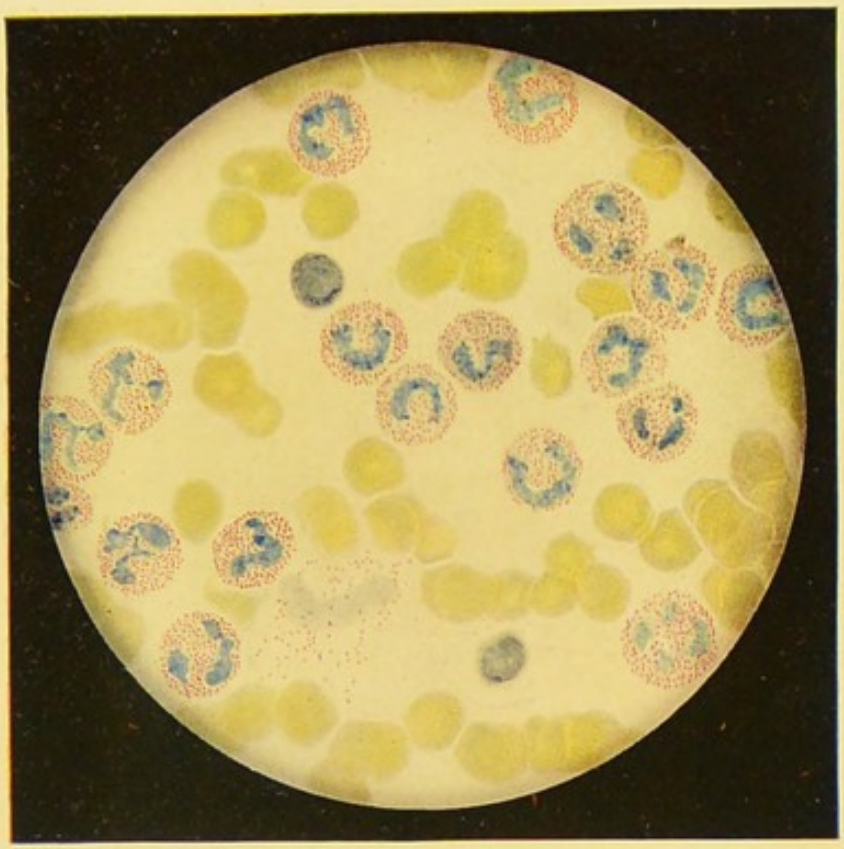


FIG. 1. LEUCOCYTOSIS (PYOGENIC).

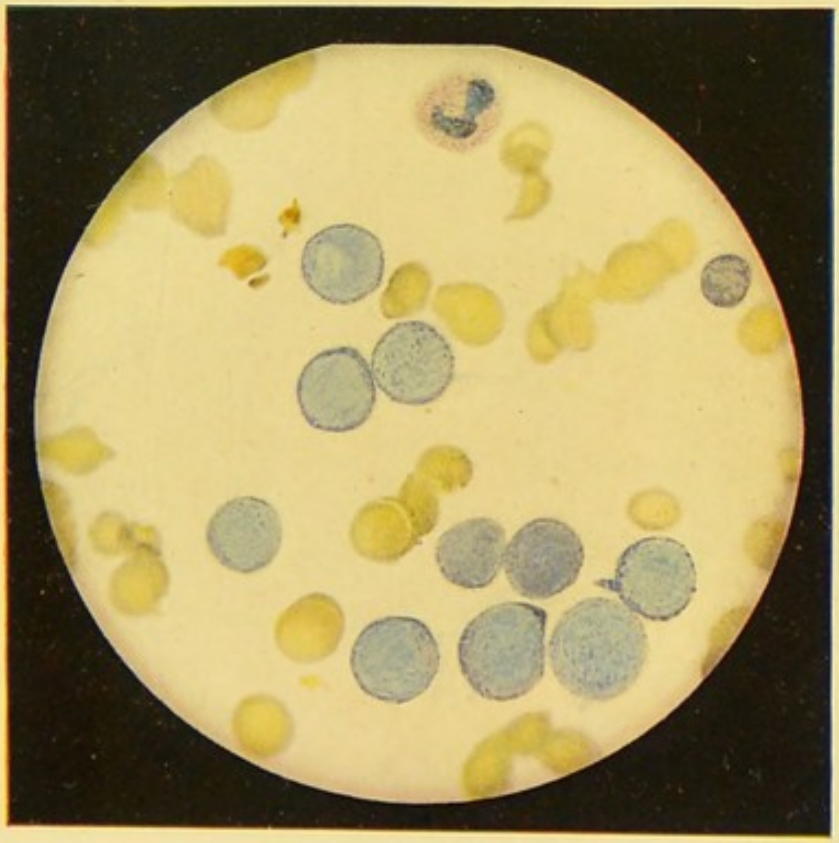


FIG. 2. LYMPHÆMIA (LARGE CELL TYPE).
(From a case of Acute Leukaemia. Many consider these cells to be myelocytes).

PLATE I. (BLOOD.)

(By Dr. Charles Melland.)

tutes a definite diseased state known as leukæmia or leucocythæmia.

For the appreciation of a leucocytosis some standard must be recognised as well as the variations from the normal. In some cases the leucocytes may have become so greatly diminished by disease such as typhoid, or by chronic conditions such as prolonged starvation, that a symptomatic increase is recognised as a leucocytosis only by comparison with the normal count for that state, and if taken by itself is by no means indicative of disturbance. In typhoid fever, for example, where a count below 5000 is the rule, the leucocytosis from some intercurrent inflammatory affection might be evidenced by a count of about 10,000, by no means abnormal in a healthy individual. Again, in the case of a starving man, where the leucocytes may be diminished to as small a number as 1000, inflammatory processes might produce a leucocytosis of 5000 or less. On the other hand, after severe hæmorrhages there results a leucocytosis which may reach from 18,000 to 20,000—the so-called *post-hæmorrhagic leucocytosis.*

The variations in the percentage of cells must also be noted. In children monomorphonuclear cells are increased relatively, so that they reach from 40 to 60 per cent. in infants, and gradually diminish with age.

The polymorphonuclear cells are the cells concerned in all inflammatory reactions. They are increased locally at the site of inflammation,

where they may accumulate in such numbers as to form pus, and universally in the blood serum. Their number, therefore, forms an index of the severity of the inflammation, though not exactly of the severity of the infective agent. They give, as a matter of fact, evidence of the reactionary power of the tissues. Should the resistance be so diminished that the infective agent, bacteria for example, meets with little response, there is little or no increase in the leucocytes. In that event, as is seen in some cases of pneumonia, death results from intoxication. If there is great power of resistance the leucocytes appear at the site of infection, and either overcome the infective agents, ending by a process of resolution, or accumulate to such an extent as to form pus. Generally speaking, then, all acute or pyogenic inflammations are accompanied by a leucocytosis, both absolute and relative—relative as regards the polymorphonuclear cells (Plate 1).

Inflammation is denoted by a count of from 15,000 to 20,000. Even at this figure the process may subside. In the stage of suppuration and abscess formation the count rises to 20,000 and upwards to 30,000 or even 40,000; at the same time the polymorphonuclear cells increase from 75 to 80 per cent. or more, and at times even above 90 per cent. It is impossible to give absolute figures, as each case must be taken on its merits. It is true that a count of 25,000, with an increase of polymorphonuclear cells above 80 per cent., is certainly diagnostic of abscess

formation, and at 20,000, with an increase of polymorphonuclear cells, most probably so. Nevertheless, one has seen a count of 20,000, with 80 per cent. of polymorphonuclear cells, in a case of simple fæcal obstruction from constipation, which subsided spontaneously, whereas a lesser count has revealed pus, *e. g.* 15,000 in cerebral abscess. The most valuable evidence, perhaps, is to be got by repeated counts at intervals of an hour or longer. An increasing leucocytosis is of extreme significance.

Leucocytosis is significant of pyogenic inflammation anywhere, whether it concern a serous membrane, as in meningitis, pleuritis, peritonitis and pericarditis, or a mucous membrane, as in enteritis and urethritis, or whether the pus be accumulating in liver, gall-bladder, ovary, kidney, brain, etc.

Blood examination, then, reveals the presence of pus, but its situation must be diagnosed by other means.

After evacuation of the pus or subsidence of the inflammation, even if an abscess remains encapsuled, the leucocyte count falls to normal.

The leucocytosis is of special value in two conditions. Firstly, in those cases of suppuration unaccompanied by pyrexia, such as seen in cerebral abscess and occasionally in appendicitis or other abdominal suppurations. One has seen a patient with very little discomfort and only slight pyrexia operated on because of a leucocytosis of 40,000, with the result that the abdomen was found to

contain considerable quantities of pus; and again, cases of cerebral abscess with subnormal temperature and marked leucocytosis. Secondly, in distinguishing the early stages of typhoid fever from appendicitis. In uncomplicated typhoid fever there is always a marked diminution of leucocytes

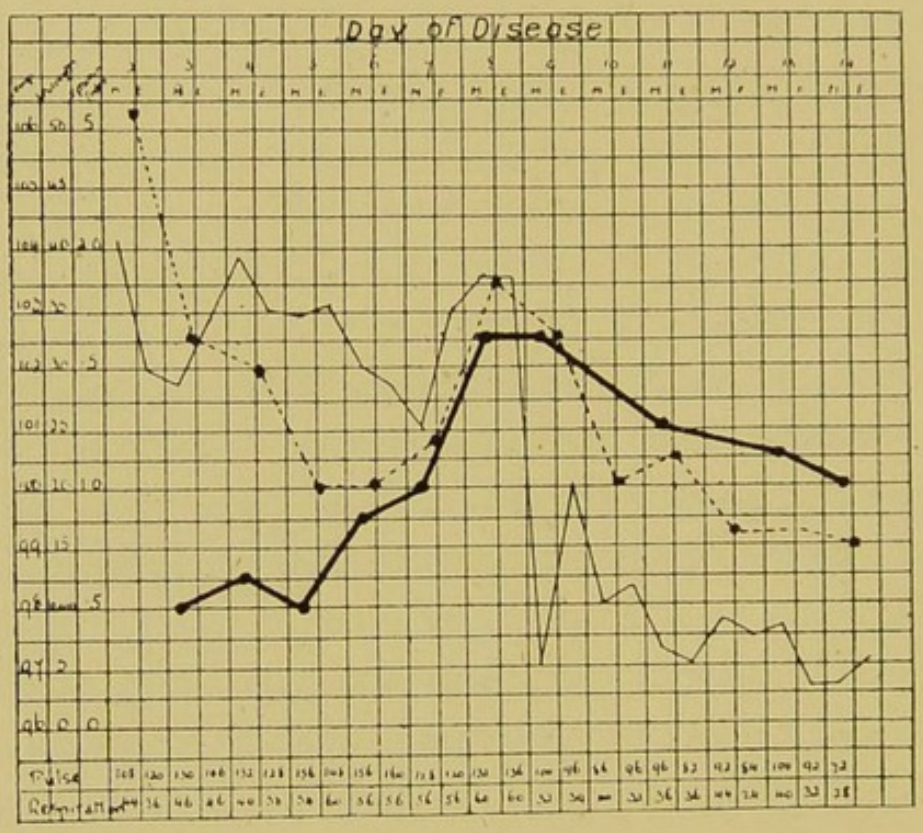


FIG. 1.—Case of pneumonia terminating by crisis. (*Eyre.*)
— = Temperature (1st column). ····· · = Leucocytes (2nd column, in thousands).

—a so-called leucopenia; the number falls below 5000, which contrasts strikingly with the leucocytosis obtained with appendicitis.

There is no difficulty in diagnosing abscesses in the neighbourhood of the appendix when the process is active and the leucocyte count reaches 20,000 or over, but there are many less definite cases which give a count under 20,000. Of these

it must be said that valuable evidence of the spread of the inflammatory process can be obtained by repeated counts at short intervals. An increasing leucocytosis is highly suggestive of pus accumulation.

Sometimes differential diagnosis can be made

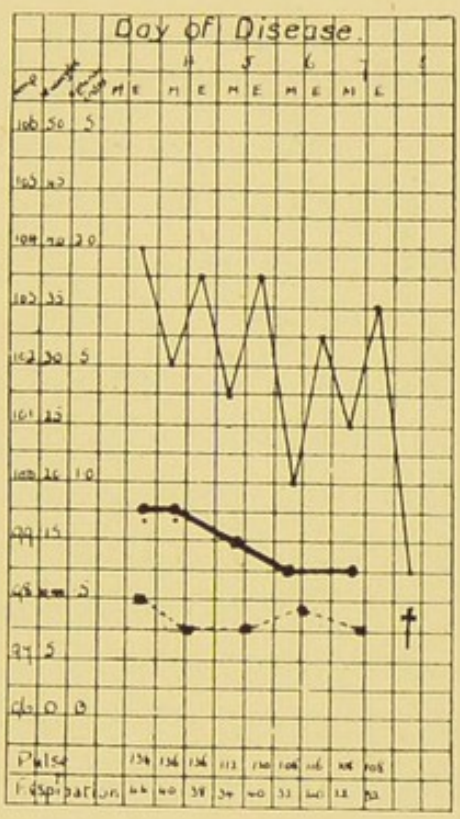


FIG. 2.—Fatal case of pneumococcic septicæmia. (*Eyre.*)
— = Temperature (1st column). ····· = Leucocytes (2nd column, in thousands).

between diphtheria and simple follicular tonsillitis. In the former there is no leucocytosis; in the latter, leucocytosis may vary from 10,000 to 30,000.

Leucocytosis, indicating as already stated the extent of the inflammation, is occasionally of prognostic value. In pneumonia the leucocytes show constant variations, though in this case the blood

count is seldom performed, as the clinical differences are more important, and the prognosis depends, not so much on the leucocytic response as on the virulence of the toxin and its action on the tissues. There is, nevertheless, a constant change in the leucocytes. In a case of lobar pneumonia, running a normal course, the leucocytes increase early, reaching from 20,000 to 30,000, and fall with the crisis, either just before or after. Leucocytosis is maintained in delayed resolution, and in empyema or abscess formation, where the count may be as much as 60,000. Leucocytosis is absent in the early stages of fatal cases with severe intoxication, and in mild cases with good resistance. The distinction between these is easily made. The leucocytosis becomes an important diagnostic feature in those pneumonias of the aged and the young where there are no localising symptoms, as, for example, in central pneumonias. In pneumonia, then, the leucocytosis can be taken as an indication of the severity of the reaction to infection (Figs. 1 and 2).

It has been pointed out that all pyrexias are not associated with changes in the leucocytes, but only those which are accompanied by pyogenic inflammation. In measles, malaria and tuberculosis, there is never a leucocytosis. In scarlet fever, the leucocytes may vary between 10,000 and 40,000, and the polymorphonuclears may average 90 per cent. In smallpox, leucocytosis appears only with suppuration and formation

of pustules, whilst previously there is steady diminution of polymorphonuclear cells.

Although in typhoid fever leucopenia is the rule, a leucocytosis is found with suppurative complications such as empyema and also when the typhoid bacillus acts as a pyogenic organism in parts of the body other than the intestine, as in periostitis, cholecystitis and pneumonia. But it must be noted that polymorphonuclear cells are always relatively fewer than in other pyogenic inflammations, though increased absolutely in contrast to the numbers found in uncomplicated typhoid infection. Similarly, leucocytosis in the course of typhoid accompanies such complications as peritonitis, empyema and pneumonia, though the absolute leucocyte count may not be very high as compared with the normal healthy count. In perforation the leucocyte count is of some assistance when there is any reason for doubt, but the remarks as to the absolute figures mentioned above must be borne in mind. A progressive increase in leucocytes, for which purpose the blood should be examined hourly, is significant. A count of 10,000 might represent a leucocytosis in typhoid. By this means it is sometimes possible to diagnose the local peritonitis that precedes the perforation, and thus by early operation give the patient a better chance of recovery. In fulminating perforations there is no leucocytic response, and the same applies to cases of fulminating appendicitis.

In septicæmia the leucocytic variation is in-

definite. In pyæmia with definite collections of pus there is a marked leucocytosis, with a relative increase in the polymorphonuclear cells.

Eosinophilia

The coarsely granular polymorphonuclear cells, or eosinophiles, which we do not consider to be markedly different from the true polymorphonuclear cells, are often increased in asthma of the true bronchial or idiopathic type, where they may reach 10 or 15 per cent., and so may be of assistance in distinguishing this type from the symptomatic asthmas. In some cases of skin disease also, such as pemphigus and urticaria, and in parasitic infections, such as trichinosis, echinococcus disease, and common intestinal worms, an increase of these cells is obtained, and occasionally a diagnosis of the condition can be made on this fact alone.

Lymphocytosis

Variations in the mononuclear leucocytes are often significant. An increase of the small lymphocytes—*i. e.* a *lymphocytosis*—is found in gastro-intestinal disturbances in children, in whom, it must be remembered, there is a relative lymphocytosis as compared with adults. It is constant in whooping-cough, even in the catarrhal stage, during which the presence of a leucocytosis of 40,000, coupled with a large increase in the lymphocytes, even from 40 to 50 per cent. in an adult, has led to an early diagnosis. This has proved to be especially valuable in the cases of nurses who have

been isolated before the characteristic cough appeared. An increase in the monomorphonuclear cells is found in chronic malaria, and in patients coming from malarial districts this increase can be found even in the quiescent intervals.

Leucopenia

A decrease of leucocytes, or leucopenia, is found in typhoid fever, where the number is frequently below 5000. It occurs also in acute miliary tuberculosis, influenza and malaria. In chronic intoxications and in starvation, the decrease has been noted, and in the last-named the leucocytes have been found to fall below 1000.

In these conditions it is important to recognise that a low count is usual, for when a secondary infection results in inflammation the diagnostic leucocytosis is only recognised as such by comparison with the leucopenic state. (See also p. 26.)

CHAPTER IV

LEUKÆMIA

Definition—Types—Chronic leukæmia; *Lymphæmia*; *Myelæmia* — Pseudo-leukæmia — Acute leukæmia — Importance of blood examination in diagnosing enlargements of spleen and lymph glands—Splenic anæmia—Anæmia in children—Etiology—Prognosis.

The leukæmias form a group of diseases with definite clinical manifestations accompanied by a marked increase in the number of leucocytes in the blood. This increase is usually absolute, and pertains to all the leucocytes, but it is occasionally relative, referring only to some special element amongst them. The name attached to the disease is determined by the kind of cell which is increased in the blood stream. It is true that various clinical manifestations, such as glandular enlargement or splenomegaly, will permit of a name being given to the condition, but other diseases can be associated with these same clinical manifestations, particularly with the splenomegaly, without any distinctive blood change. Hence it was only with the advent of morphological investigation of the blood that these diseases could be classified. But it is

necessary to remember that here, as in all other diseases, although we may give a name to a disease, or rather to a series of symptoms and signs, exactly the same marked variations from type are obtained as in diseases elsewhere in the body.

Lymphæmia

Leukæmias are usually divided into chronic, which are the more common, and acute, which are rare. Chronic leukæmias are further subdivided into two main groups. The one group, which is the rarer, is associated with a condition of gradual enlargement of all the glands of the body—both the external and the internal glands—in the cervical region, the axilla, the thorax, the abdomen, and the groin. The enlargement is discrete, but it is in no way different clinically from the enlargement found in Hodgkin's disease, which is called pseudoleucocythæmia. The blood change is characteristic. On examining a fresh film of the blood it is seen at once that the normal picture of a field containing red corpuscles and occasional leucocytes—in the proportion of 500 to 1—is completely changed, owing to the appearance of an enormous number of white corpuscles. The number of leucocytes represents a great increase over the normal 5000, and there may occasionally be found as many as 600,000 leucocytes. This, with the associated

anæmia, which is secondary, sometimes makes the white corpuscles approximate in number to the red.

A differential count reveals even a more marked variation. In the normal blood the polymorphonuclears are present to the extent of 75 per cent., but in this type of disease they may be reduced to as little as 3 per cent., while the lymphocytes may be raised to 95 per cent. The blood picture in a lymphatic leucocythæmia (lymphæmia), is one in which there is an absolute proliferation and preponderance of lymphocytes, and an almost total disappearance of polymorphonuclear cells.

The lymphæmic type is further subdivided into two varieties according to the type of cell which preponderates. If this be the small type of cell—the small monomorphonuclear leucocyte —we have a variety of lymphæmia which is the most fatal (Plates 1 and 2).

Case.—M. æt. 53 (enlargement of spleen, liver and glands everywhere).

Leucocytes	600,000
Polymorphonuclear cells	1 %
Monomorphonuclear cells—	
Small (lymphocytes)	87 %
Large	12 %
Red corpuscles	2,550,000
Hæmoglobin	40 %

Small type of lymphæmia. Death occurred shortly after this blood count was made.

Case.—Female, æt. 40.

	Feb. 8	Mar. 3	Aug. 7
Leucocytes	59,400	148,000	66,000
Red corpuscles	2,000,000	2,040,000	1,600,000
Hæmoglobin	40 %	40 %	30 %
Monomorphonuclear cells—			
Small	86 %	98 %	98 %
Large	8 %		
Polymorphonuclear cells	6 %	2 %	2 %

Small type of lymphæmia treated with liquor arsenicalis.

Myelæmia

The second type of chronic leukæmia is clinically marked by the presence of an enlarged spleen, which may extend down as low as, and often into, the pelvis. This type is associated with changes in the spleen and in the bone marrow. The blood picture again reveals an enormous increase in leucocytes, which may reach several hundred thousands. The differential count is somewhat complicated. There is a preponderance of a number of cells which do not occur in normal blood. Most striking is that known as the *myelocyte*, a large monomorphonuclear cell, normally present in the bone marrow, resembling the hyaline cell of the blood, but with a granular cytoplasm. These may proliferate to 24 per cent., or 40 per cent., or even more. The constant feature is the myelocythæmia, which is taken to denote the increased activity of the bone marrow with the entry into the blood stream of these cells. The condition is known as spleno-medullary

leukæmia, or as myelæmia in accordance with later views, the changes being supposed to occur primarily and mainly in the bone marrow. (Pl. 2.)

Case.—M., æt. 46 (Splenomegaly).

	July 19	Aug. 13	Sept. 20
Leucocytes	150,000	166,000	34,200
Myelocytes	28 %	26 %	22 %
Polymorphonuclear cells.	46 %	44 %	49 %
Monomorphonuclear cells	18 %	16 %	12 %
Other cells	8 %	14 %	17 %
Red corpuscles	3,400,000	3,800,000	3,500,000
Hæmoglobin	40 %	70 %	65 %

Case of myelæmia treated with arsenic with much improvement.

Case.—F., æt. 39 (Splenomegaly).

Leucocytes	485,000
Polymorphonuclear cells	43 %
Myelocytes	41 %
Monomorphonuclear cells	7 %
Eosinophiles, etc.	9 %
Red corpuscles	3,550,000
Hæmoglobin	70 %

Myelæmia, treated with arsenic, and leucocytes fell to 200,000, with apparent improvement.

Although two distinct types of chronic blood disease have been mentioned here, a large number of cases will be met with which do not fall into any one of these categories, either clinically or pathologically. There is thus a group of mixed leukæmias, and cases will often be encountered in which the spleen is enlarged and the glands also to a varying degree, the blood picture showing a combination of both types. But for working

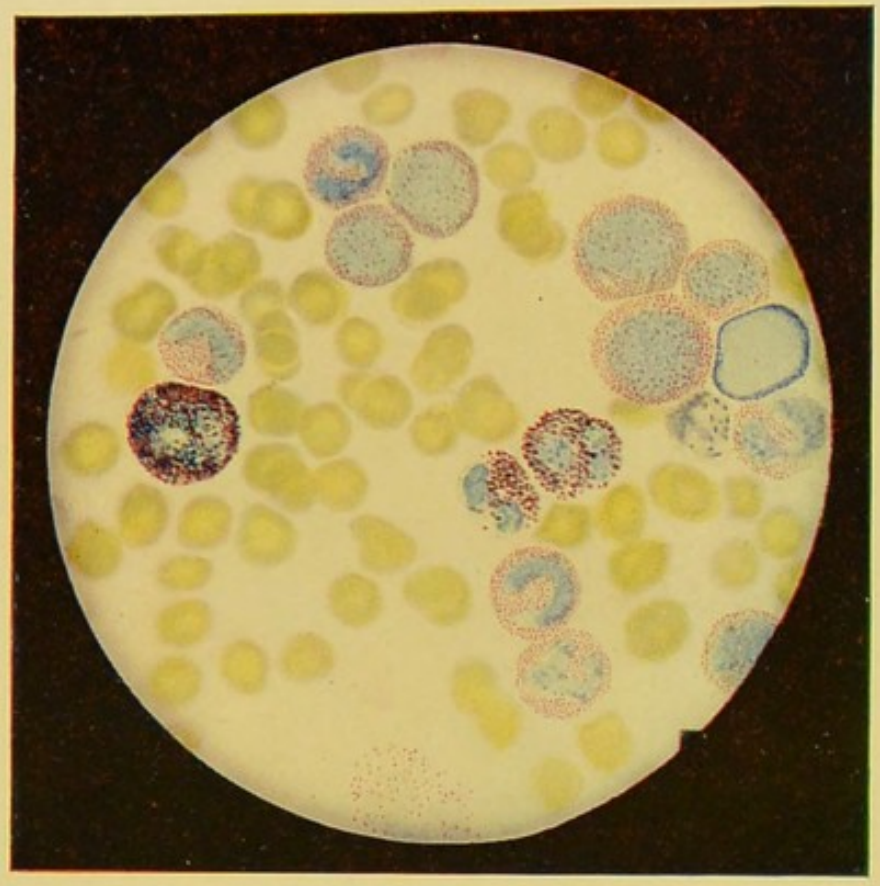


FIG. 1. MYELÆMIA.
(Myelocytes above, polymorphonuclear cells below, eosinophiles in centre.)

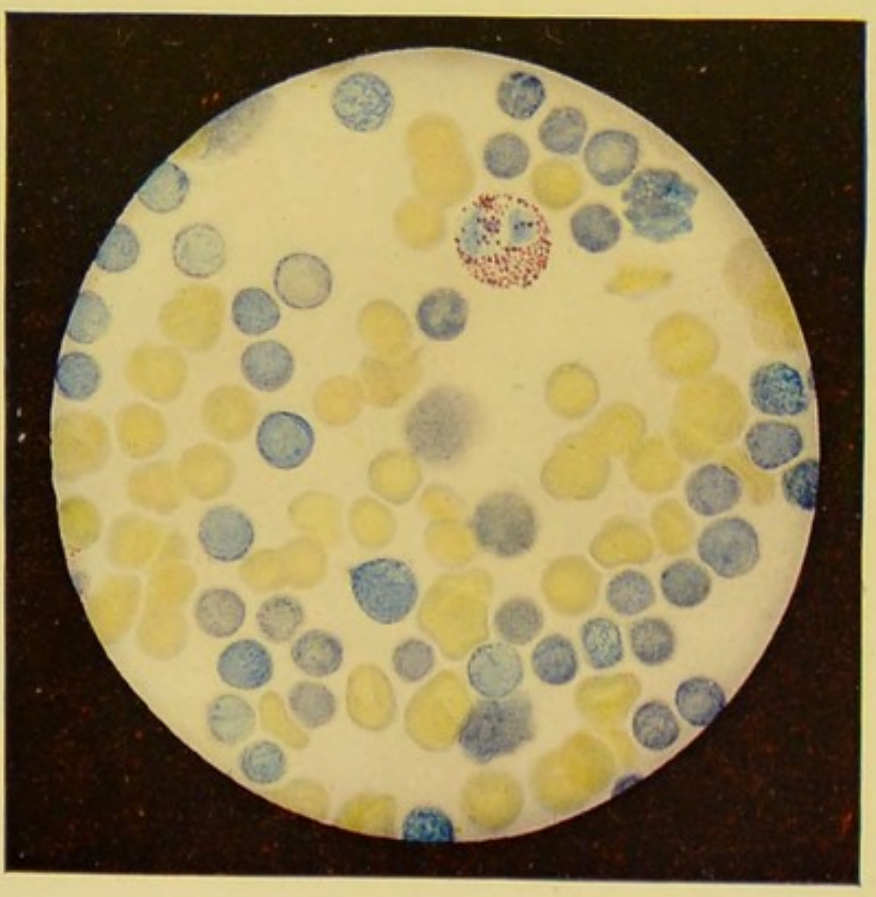


FIG. 2. LYMPHÆMIA (SMALL CELL TYPE).

PLATE 2. (BLOOD.)

(By Dr. Charles Melland.)

purposes the one above given is perhaps the best practical classification. Bearing on this fact also is the interesting observation that the splenomedullary leukæmia, or true myelæmia, has occasionally been noted to change in the later stages into the lymphatic type, so that a varying series of pictures between these two apparently extreme types is obtained. In addition, all these diseases produce marked secondary anæmia, which is evidenced by diminution both in the red cells and in the hæmoglobin—the chlorotic type of anæmia.

Acute Leukæmia

It is necessary also to recognise an acute variety of leukæmia. Acute leukæmias run a course of a few days or a few weeks, and are often so rapid that there is no time for enlargement of the spleen or the glands. They are of the lymphatic type. Clinically, they simulate scurvy, inasmuch as they are marked by spongy gums and by hæmorrhages. When the blood is examined it is found that there may or may not be an absolute increase in leucocytes, but that there is a marked relative increase in lymphocytes. This, together with the clinical symptoms, allows us to diagnose these cases, which are invariably fatal, and also to distinguish them from the scorbutic cases which simulate them. Acute leukæmias are rare, but they all can be diagnosed by the routine investigation of the blood. (Pl. 1.)

Case.—Child, æt. 5; few weeks' illness, gingivitis, hæmorrhages, death.

Leucocytes	30,000
Monomorphonuclear cells—	
Small (lymphocytes)	14 %
Large	85 %
Polymorphonuclear cells	1 %
Red corpuscles	1,800,000
Hæmoglobin	32 %

It will be seen how important is the blood investigation in diagnosing between the leukæmias and the conditions which simulate them. These are, in the one case, enlargements of the glands due to Hodgkin's disease, or to syphilis or lymphosarcoma (which only in the early stages would simulate lymphæmia), etc.; and in the other case, splenomegalies, such as found in kala azar, and in chronic infections, *e. g.* malaria or chronic heart disease, perhaps also the large spleens in children due to rickets or syphilis, etc.: none of these, however, exhibits at any time the huge size of the spleen in myelogenous leukæmia.

Splenic Anæmia

In addition to these diseases, which are characterised by a more or less constant train of symptoms and signs, there are other blood diseases without such striking appearances. For instance, there occurs a condition of enlarged spleen in which there is a paucity of all the blood elements—a so-called *splenic anæmia*. The spleen is large, though never below the umbilicus, and the red cor-

puscles, the hæmoglobin and the leucocytes are all diminished. These factors constitute a picture, somewhat constant, to which is ascribed the term splenic leukæmia. Occasionally there is vomiting of blood, too, and occasionally other hæmorrhages. Under the impression that the cause of splenic leukæmia lies in the spleen, splenectomy has been carried out with some success in certain cases.

Anæmias in Children

In children, again, peculiar variations are met with. There may be a simple anæmia, or a diminution of all the elements, with a marked enlargement of the spleen, and hæmorrhages in various parts; and although the leucocytes are diminished absolutely, a slight increase may be obtained in the lymphocytes. Differential counts give different details in various cases, but there is very little to be made out of this children's disease other than what we know already of the adult condition of splenic anæmia. To yet another variety the special name of *anæmia pseudo-leukæmia infantum* has been given. In this there is a relative increase of myelocytes as well as the changes characteristic of a severe anæmia, and the spleen is enormously enlarged. We have already pointed out that a lymphocytosis in the growing period of life, and especially in children, has not the same significance as in adults.

Etiology

The etiology of the various leukæmias is unknown. It is necessary, however, to devote some consideration to this point, for to have a disease, which it is possible to describe only by a mere reiteration of symptoms and signs such as this, does not give any hope of scientific treatment, and allows only of a prognosis being made by experience of past cases. All that can be done in such circumstances is to keep these cases under observation, and to count the blood month after month and, in some, year after year until death occurs.

For many years a parasite has been sought for, and occasionally bodies have been described in the cells as causal agents, but no corroboration of this has been forthcoming.

In more recent times certain conditions of enlargement of the spleen, particularly kala azar, have become noteworthy, because some have been shown to be associated with a protozoan parasite. The parasite found in the spleen in cases of kala azar is the Leishman-Donovan body, which has been cultivated in special media. By analogy one would hope that all these other conditions of enlargement of the spleen would prove to be the result of a parasitic infection. But as yet, no organism has been discovered; the various bodies that have been described are most probably products of cell degeneration.

The most feasible view as to the etiology is that

they are analogous to the conditions which obtain in cancer. Cancer is characterised by an abnormal proliferation of the existing cells of tissue. In the normal physiological process of tissue proliferation the various elemental constituents proliferate in a definite and harmonious manner which maintains the normal anatomical relationship of tissues. Occasionally, however, one type of cell will proliferate without regard to cells of other types, and there results an overgrowth of this cell which is out of harmony with the normal growth around it. This constitutes a tumour, and when the cell-overgrowth invades the neighbouring tissues the characteristic appearance of cancer is produced. In these blood diseases there occurs an abnormal proliferation of certain blood elements either in the blood or in the bone marrow, and these preponderate over the other cells. Here, therefore, there is seen a condition analogous to that which obtains in sarcoma, and the theory that these diseases are cancers of the blood appears to hold good. Moreover, as the disease when once initiated invariably goes on to a fatal result, we have a malignant feature which supports this view.

Nevertheless, it is necessary to keep in mind that there may be a group of infective diseases in which splenomegaly is a marked feature, so that although some of the conditions described in this chapter may be regarded as cancerous in nature it may still prove possible to find parasites which are producing conditions resembling these.

As to prognosis, it has only to be said that the

disease invariably ends fatally, the lymphatic type more quickly than the myelæmic. Some cases last several years. In the course of the disease marked variations may be obtained with treatment. One drug that seems to produce improvement is arsenic. X-ray treatment has resulted in a diminution in the size of the spleen and an improvement in the blood count, but all forms of treatment are only palliative and not permanent. Finally, in the course of the myelæmic type, cases have been noted to change into the lymphatic.

Chloroma

There is one very rare disease which must be mentioned in connection with these blood disorders. It is that peculiar condition known as chloroma, characterised by the presence of green tumours on bones, generally on the skull. It is impossible at present to say where the green pigment comes from, but it is accompanied by a characteristic feature in the blood in the shape of an increase of lymphocytes.

Case.—F., æt. 4. With olive-green tumours on and within the skull.

	Nov. 9.	Nov. 30.	Dec. 7.
Red corpuscles . .	4,100,000	1,690,000	1,612,000
Hæmoglobin . . .	60 %	30 %	35 %
Leucocytes . . .	40,000	37,400	27,100
Polymorphonuclears	15 %	7 %	21 %
Monomorphonuclears	85 %	93 %	71 %
	(Large = 65 %	=66%)	Myelocytes = 8 %

CHAPTER V

ANÆMIA

Definition — *Chlorotic type;* hæmoglobinæmia — *Pernicious type;* hæmolysis—in hæmorrhages—in septicæmia, plumbism, etc.—Morphological changes in red corpuscles—Cachexia simulating pernicious anæmia—Syphilis—*Polycythæmia*—*Pallor*—Coagulation of blood—Examination of live blood films.

THE term "anæmia" is here used to denote a numerical reduction in the red cells and in the amount of hæmoglobin. We content ourselves, perforce, with estimating these two factors, but it must be remembered that an important factor in anæmias is the change found in the blood plasma, which nourishes the formed elements of the blood. The red blood corpuscles, which average five millions per cubic millimetre, are normally of uniform size and shape, presenting a symmetrical picture of biconcave discs containing hæmoglobin. The relative quantity of hæmoglobin found in normal blood is taken as a standard, namely, 100 per cent., and the relation of hæmoglobin to the red blood corpuscles gives what is known as the colour index; this in normal blood is reckoned as one. This colour index forms a most important diagnostic feature.

Chlorotic type

There are two main types of anæmia. In the first the hæmoglobin is diminished to a greater extent than the corpuscles, so that the colour index falls below one. (For example, red corpuscles 4,000,000; hæmoglobin 40 per cent. = colour index 0·6.) This constitutes what is known as *hæmoglobinæmia*, and is a constant feature in simple and secondary anæmias, being most marked in chlorosis.

Case.—F., æt. 44. Chlorosis. Rapid improvement under Iron and Laxatives.

	Dec. 6	Dec. 21	Jan. 8
Red corpuscles . .	2,770,000	3,710,000	4,400,000
Hæmoglobin . . .	40 %	60 %	75 %
Colour index . . .	0·7	0·8	0·85

Pernicious type

In the second type the corpuscles and hæmoglobin are again diminished, but the hæmoglobin to a lesser extent than the corpuscles, so that the colour index is greater than one. (For example, red corpuscles 1,500,000; hæmoglobin 35 per cent. = colour index 1·16.) This is seen in the pernicious condition and in other severe idiopathic anæmias. It is probable that the excess of hæmoglobin over corpuscles arises from the destruction of the corpuscles and the setting free of the hæmoglobin into the blood serum, which indeed is frequently highly pigmented. Further evidence in support of this theory of the destruction of the red blood corpuscles is found in the

associated hæmatogenous jaundice, and the accumulation of iron in the viscera. It is on the theory that this hæmolysis is of a toxic nature, the toxin being of intestinal origin, that the most satisfactory line of treatment is based. In this type the corpuscles may be reduced to as few as 500,000.

Case.—F., Pernicious Anæmia, improving under Arsenic and Intestinal antiseptics.

	Sep. 19.	Sep. 29.	Oct. 9.	Nov. 1.	Nov. 22.	Dec. 2.	Mar. 1.
Red corpuscles	1,035,000	1,000,000	1,285,000	1,900,000	2,400,000	2,700,000	3,000,000
Hæmoglobin	30%	36%	40%	55%	75%	80%	80%
Colour Index	1·5	1·7	1·5	1·4	1·5	1·5	1·1

After severe hæmorrhages the blood volume is rapidly regained by dilution from the lymph, but the number of red cells is replaced more slowly, and the hæmoglobin still later. In *chronic repeated hæmorrhages*, such as in epistaxis, piles and internal lesions, the anæmia is very marked, and the count may fall as low as 1,000,000, simulating the more severe anæmias and even cancerous cachexia. With removal of the source of hæmorrhage, repair goes on very slowly, the red cells rising gradually to normal in the course of weeks, and the colour index increasing. Marked anæmia of the chlorotic type is seen in intoxications, such as the infective diseases, and perhaps most markedly of all in septicæmia, in plumbism, in chronic starvation, and sometimes in syphilis. In acute rheumatism the anæmia is of rapid onset and marked character, so that the corpuscles may fall to 2,000,000, or even to 1,000,000.

In *septicæmia* there is often great destruction of

red corpuscles, with severe anæmia, and the appearance in the blood of many nucleated red corpuscles.

Morphological Changes in Corpuscles

In addition to the alteration in number of the blood elements, the shape and size of the red corpuscles show variations. In diseased states there appear corpuscles which are distorted (poikilocytes), or small (microcytes), or large (megalocytes). In more severe conditions nucleated red cells (normoblasts) are found, as well as nucleated varieties of the forms just mentioned, called respectively, poikiloblasts, microblasts and megaloblasts, and occasionally still larger cells known as gigantoblasts. These cells appear in all anæmias in varying proportion according to the severity. None of them can be called typical of any one condition, although the megaloblasts and the gigantoblasts and the extreme variations in size and shape in untreated and severe pernicious anæmia are such that sometimes it is possible to diagnose this condition from the blood picture alone (Plate 3). Corroboration has always to be sought, however, in the high colour index. Further change is found in some red corpuscles in that they take the stain badly and appear dark in colour and contain many granules. This is regarded as a result of degeneration, and is found in the more severe types of anæmia.

The blood examination is of special value in distinguishing between pernicious anæmia and

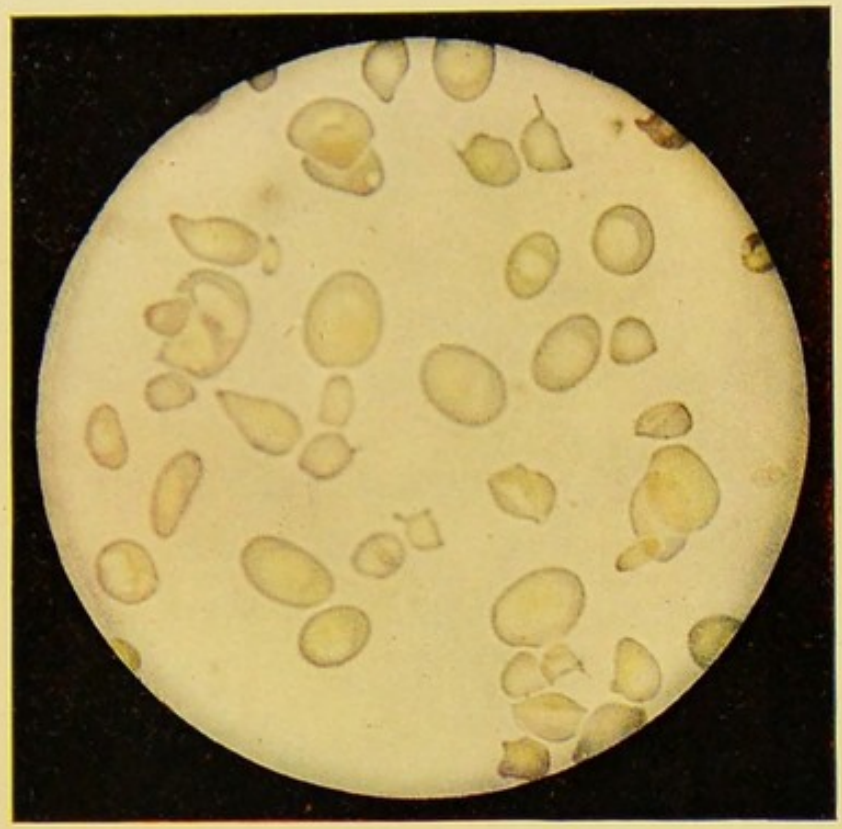


FIG. 1. PERNICIOUS ANÆMIA.

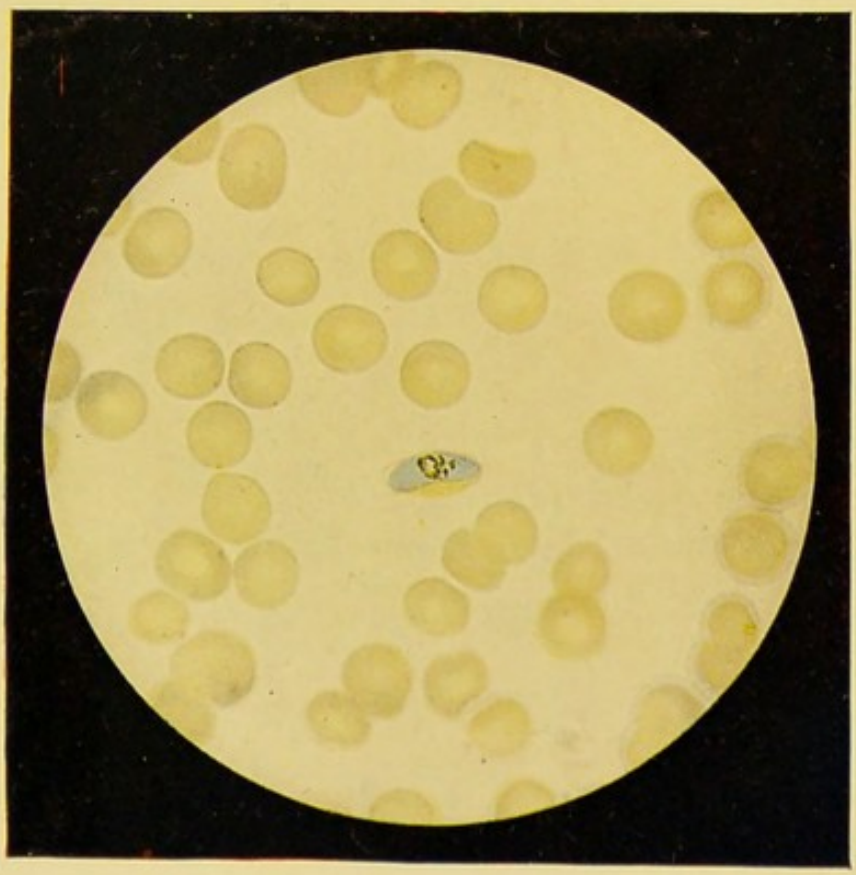


FIG. 2. MALARIA (CRESCENT PARASITE)

PLATE 3. (BLOOD.)

(By Dr. Charles Melland.

those conditions of cachexia which simulate it, though to the trained eye the tint of the patient who has pernicious anæmia is of itself characteristic enough to prevent error. Cancer of the stomach is, perhaps, most frequently mistaken for an anæmic condition, but the red blood corpuscles here seldom fall as low as in pernicious anæmia, where a count of 600,000 is not infrequent. Furthermore, there are by no means the marked variations in the red cells, and the colour index is always below one.

In *syphilis* the anæmia of the chlorotic type is so marked in the early stages, where sometimes the hæmoglobin falls to 30 per cent. or less, that it is often used as a diagnostic feature in early chancres. In some tertiary cases the change in the corpuscles is so very evident and the anæmia so great that a diagnosis has to be made from pernicious anæmia.

Polycythæmia

In contrast to a condition of paucity of the blood elements is the condition in which these are found in excess. To this is applied the term *polycythæmia.* Here the red corpuscles are increased from 6,000,000 even to 10,000,000, and the hæmoglobin to 120 per cent. or more. A mild example of this increase is found in plethoric individuals, but the true type is to be met with in chronic cardiac conditions, especially congenital lesions with cyanosis, and in one condition, known as *polycythæmia rubra,* in which there is cyanosis

with enlarged spleen. Its significance is at present unknown.

Case.—M., æt. 54. Cyanosis, splenomegaly. Symptoms noted for 6 years only.

	Nov. 26.	Jan. 17.	Mar. 1.
Red corpuscles . .	11,610,000	7,430,000	9,380,000
Hæmoglobin . . .	130 %	100 %	112 %
Leucocytes . . .	34,800	13,400	13,800

The diminished count on Jan. 17 followed a venesection, and was maintained for many weeks.

Pallor

A note of warning must here be struck: many cases are classed as anæmias on account of a marked pallor. Such pallor is found especially among girls of adipose tendency, and is often mistaken for the more characteristic tint of chlorosis. But the blood count in these cases often shows a slight increase of red cells (6,000,000), and the normal amount or a slight increase of hæmoglobin. Whereas chlorosis with its true hæmoglobinæmia is a comparatively rare condition, these pallid, constipated females are met with frequently. The condition is probably one of blood concentration, and is always associated with constipation.

The relation of serum to corpuscles gives a little information as to the concentration of the blood. After severe vomiting, as in intestinal obstruction, this is noted, and allowances should be made in interpreting a blood count, though in well-marked cases of leucocytosis it can make but little difference. It has been pointed out that the fluid elements are rapidly restored.

Coagulation of the Blood

Only a rough estimate of this can be obtained, and it is merely of comparative value. Two methods are in common use for determining the coagulation time : Wright's method, which tests

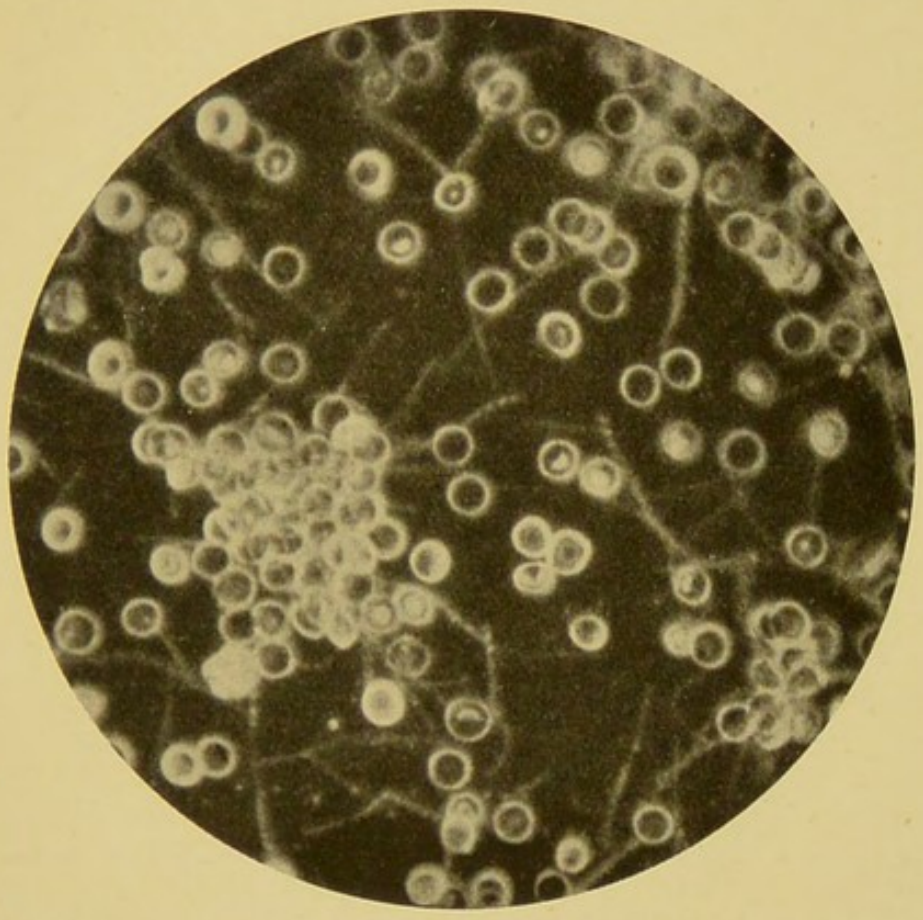


Fig. 3.—Spirochæta obermeieri of relapsing fever in blood. From a photograph by Pathé Frères, dark ground illumination.

the coagulation of blood drawn into a series of capillary tubes, and Mercier's method, which determines coagulation by the appearance of fibrin threads in a drop of blood on a glass slide. The latter, which is extremely simple, not requiring any elaborate apparatus, is nevertheless very reliable. In the present state of our ignorance

as to the factors concerned, little information is at hand. In hæmorrhagic diathesis the coagulation is delayed—in purpura, from ten to twenty minutes. In some cases of hæmophilia the coagulation time has been found to be forty or fifty minutes, whereas in others it has been four or five minutes, *i. e.* about normal.

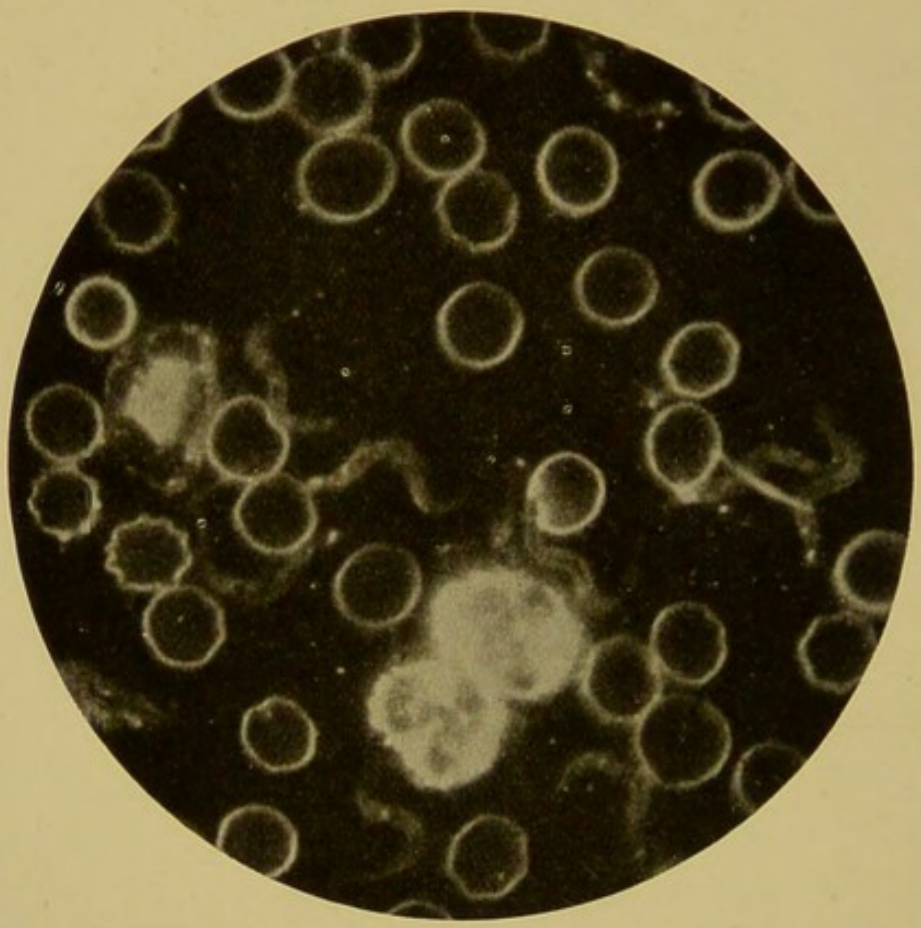


Fig. 4.—Trypanosomes in blood (from a photograph by Pathé Frères, dark ground illumination).

In pneumonia the coagulability is increased, and hence large coagula are found in the heart and great vessels of the fatal cases. This is in marked contrast to other types of septicæmia, in which the coagulability is impeded so that the blood remains fluid long after death.

Examination of Live Blood

A few words may be said with regard to the examination of fresh blood films. Too much stress cannot be laid upon the importance of such as a means of diagnosis. The stained film

FIG. 5.—Filaria loa in blood seen by dark-ground illumination. From film by Pathé Frères.

shows all the elements to which allusion has been made, and presents a beautiful picture, but the live blood film reveals other things in addition. The excessive leucocytosis can be seen, though it is not always possible to distinguish between the different leucocytes. The red cells can be discovered in their natural form; and their elasticity, and the variations in shape and size noted to the

best advantage, so that it is possible to identify cases of severe anæmia. Parasites also can be seen. The malaria parasite can be picked out very readily in the live film by virtue of the extreme motility of the pigment. Trypanosomes can be seen lashing about vigorously. Filaria swarm in the blood at appropriate times of the day. With a dark-ground illumination it is possible to detect the spirillum of relapsing fever. In addition, though this is not a diagnostic feature, the whole process of phagocytosis can be followed out, the amœboid activity of the leucocytes can be seen, and the leucocytes watched as they approach any foreign body, engulf it, and digest it.

A word must be said about the use of dark-ground illumination in examining live blood films. Trypanosomes, filaria, spirochæta, etc., can all be seen to the best advantage by this method (see Figs. 3–5; 7).

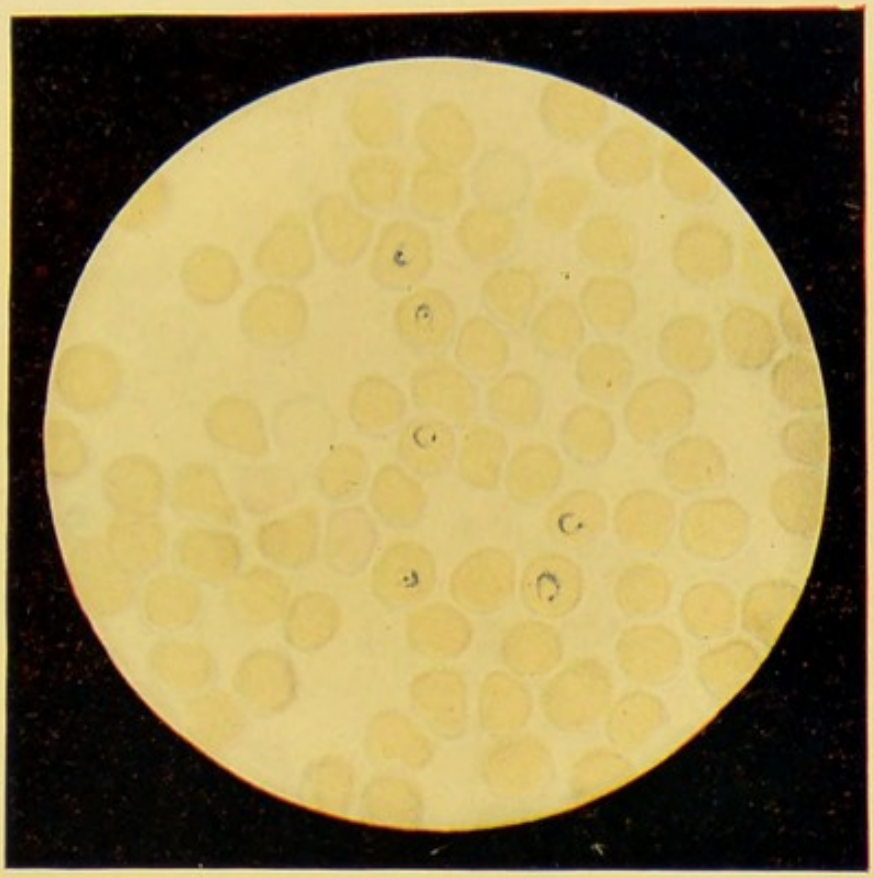


FIG. 1. MALARIA (BENIGN TERTIAN-RING PARASITE).

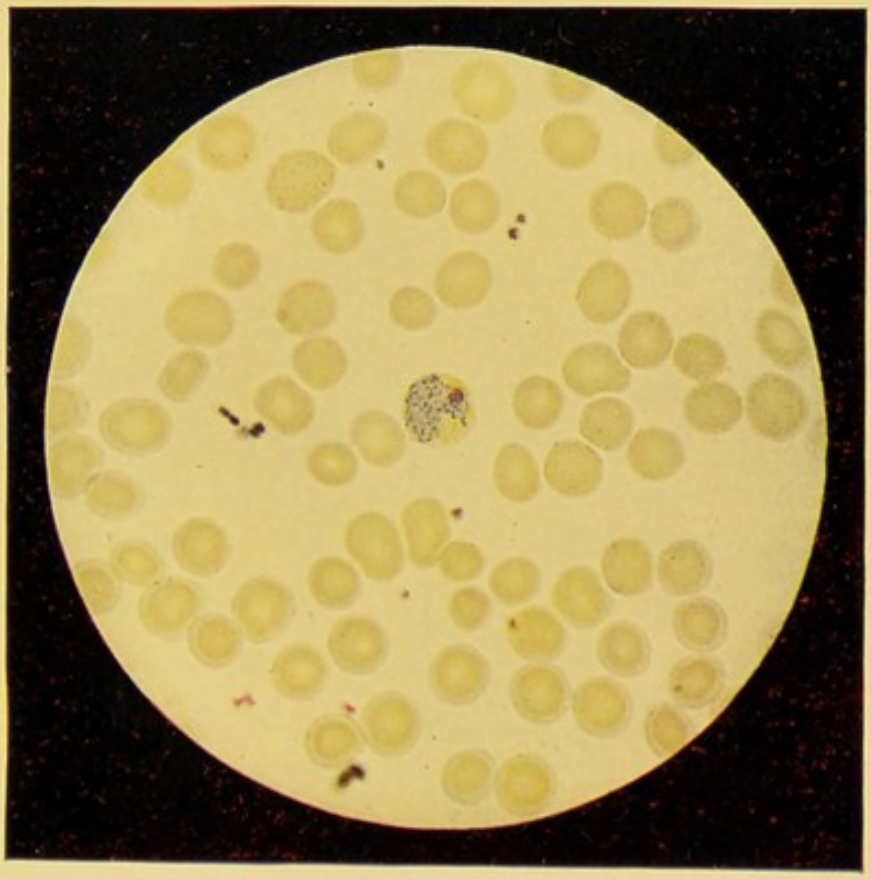


FIG. 2. MALARIA (BENIGN TERTIAN-RING PARASITE IN LATER STAGE).

PLATE 4. (BLOOD.)

(By Dr. Charles Melland.)

CHAPTER VI

BACTERIOLOGY OF THE BLOOD

Exaltation of saprophytes—Hæmatogenous infections—Direct method useless—*Cultural methods*—technique—*Infective endocarditis*—Acute and chronic infections—Streptococcus—Typhoid and paratyphoid bacilli—Influenza—Pneumococcus—Gonococcus, etc.—Terminal infections.

It is probable that under ordinary physiological conditions bacteria are always obtaining entry into the blood stream, whence, if they are not destroyed, they are eliminated. If they should reach any tissue of diminished vitality, even the lowly virulent organisms ordinarily saprophytic in the intestine or the tonsils may set up a focus of disease. This is probably the explanation of what are called hæmatogenous infections, such as bacilluria, coli pyelonephritis, chronic infective endocarditis, gonorrhœal arthritis, and many other chronic conditions. Some more virulent organisms also may be eliminated from the blood stream and so account for the repeated outbreaks of purulent foci in pyæmia: in other cases where definite pathogenic organisms obtain an entry into the blood, they proliferate there and set up a condition of septicæmia, either chronic or acute.

The existence of bacteria in the blood stream can be determined either by finding the bacteria

themselves or by identifying in the serum the antibodies produced by the host in response to infection. This chapter is concerned with the former.

The direct examination of blood films is not a practical means of finding bacteria. They are seldom, if ever, present in such quantities as to be seen direct, so that the usual method is to take larger quantities of blood (five cubic centimetres), and cultivate in suitable media to obtain growths of the organisms. It is useless to attempt to isolate organisms from a few drops of blood

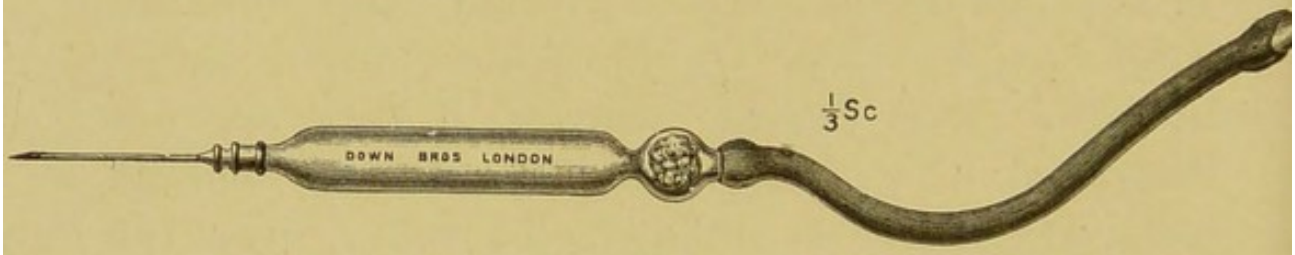


FIG. 6.—Needle and glass tube for collecting blood for bacteriological investigation, suggested by Dr. Hebb. The bulbous end is plugged with cotton wool and the whole sterilised by dry heat in a large sterilised tube, in which it is kept until required for use.

collected from the ear or finger in a capillary tube; such are almost invariably contaminated with a white staphylococcus derived from the skin.

Technique

It is necessary to sterilise the skin over the antecubital fossa with acetone, followed by tincture of iodine; then by means of a tourniquet on the upper arm cause the veins to stand out prominently, and plunge directly into a vein a sterilised needle attached either to an ordinary record syringe or to the specially designed glass bulb shown in

Fig. 6. The direction of the needle makes little difference, for the blood flows rapidly into the syringe if the vein has been entered. Some 5 to 10 c.c. are collected and amounts varying from a few drops to several cubic centimetres are inseminated in successive tubes of media and incubated. Sterilised sodium citrate is often used to prevent coagulation, but this merely adds another risk of contamination, and does not appear to improve the results. It is useful, however, if no culture media be at hand for immediate insemination. By this means it is easy to obtain positive results in the acute infections, but in the chronic septicæmias it is often necessary to make repeated examinations. It has been suggested that the bactericidal properties of the blood serum will inhibit the growth of bacteria when removed from the body, and, to counteract this occurrence, large volumes of media should be inseminated with small quantities of blood. This is not definitely established, but certainly more constant results have been obtained by this method, especially in typhoid fever. Special media also have to be used for different organisms, such as ox-bile and peptone to favour the growth of the bacillus typhosus; or glucose broth to favour the growth of the so-called rheumatococcus. The gonococcus will find its suitable medium in the blood of the patient. Care must be taken to eliminate contaminations by bacteria from the skin, but with a cautious technique this is not very difficult.

Proofs of the pathogenicity of an organism

obtained in pure culture by this means are forthcoming on investigating the cultural characteristics; in some cases also by obtaining positive agglutination results with the patient's own serum, and sometimes by animal experiment. Cultures in all cases should be allowed to grow for several days, though occasionally in acute septicæmia a prolific growth of streptococcus appears within twenty-four hours, and may even render the broth turbid. In several cases of virulent septicæmia the hæmolytic action of the streptococci has resulted in a rapid solution of the corpuscles with consequent laking of the culture tubes. This is not, however, of frequent occurrence and usually the corpuscles sink to the bottom or are bound up in the coagulum. In two cases of chronic infective endocarditis the organism was obtained only after incubating for five days.

Blood cultures are of special diagnostic value in cases of prolonged pyrexia of unknown origin, and more particularly in those cases where the absence of actual collections of pus has been demonstrated by the leucocyte count.

Infective Endocarditis

In *infective endocarditis* much work has been done, particularly in those borderland cases where it is impossible to say whether the condition is one of simple endocarditis or an "infective" variety. Though it would seem that the distinction between these is merely an arbitrary one, as all varieties are associated with micro-

organisms, and the designation simple or infective has a clinical derivation depending on the course and termination of the disease. Here blood cultures, if not at first, at least after repeated trials, will reveal the cause. Therefore in all cases of cardiac disease with valvular mischief and slight pyrexia, which is persistent, the blood should be examined bacteriologically. In those cases of mural endocarditis, fortunately rare, where, although the valves are not affected, the walls of the auricles are covered with vegetations, the chronic pyrexia should lead to an examination of the blood. In the acute cases organisms such as the *influenza bacillus*, the *pneumococcus*, and occasionally the *gonococcus*, are readily isolated. In the chronic cases, which may last for months, accompanied by occasional emboli containing organisms of little or no virulence, a *streptococcus* has been most frequently isolated. This is an organism of low virulence which often produces no suppuration around the emboli in the kidney, spleen, brain, etc., until the later stages, when the resistance of the tissues is almost eliminated. It probably owes its origin to the streptococci of the mouth or the intestines (*S. fæcalis*).

The *typhoid bacillus* can often be isolated, in suitable media,—and perhaps more readily by using large bulk,—in the early stages of infection, and before the agglutinin reaction can be obtained from the serum.

The *paratyphoid infections*, with their milder symptoms, more frequently reveal in the blood the

paratyphoid bacilli, which can readily be obtained, and the variety determined.

In *pneumonia*, especially in the more severe types, the septicæmic nature of the infection can be determined by the ready finding of the pneumococcus in the blood stream. In *rheumatic fever* the rheumatococcus has been described, but we have only found an organism corresponding to this in the blood from cases of chronic infective endocarditis.

Other organisms that can be found are anthrax bacilli in splenic fever, glanders bacilli (though only in the terminal stages) and the bacillus aërogenes capsulatus.

It must be pointed out that in the later stages of fatal diseases the resistance may be so diminished that bacteria can obtain entry and proliferate in the blood stream, producing the so-called terminal infections. The finding of the B. coli or of the streptococcus, therefore, is of little value in these circumstances.

Besides being of diagnostic value, the discovery and isolation of bacteria from the blood stream have an important bearing on treatment. At present bacteriotherapy has not proved of much assistance in blood infections. Nevertheless, its harmlessness makes it essential that it should be tried. Furthermore, in the very chronic diseases, where time permits, it may be possible to produce in experimental animals antitoxic sera which can be used to combat the infection.

CHAPTER VII

SEROLOGY

Bactericidal property of serum—*Antibodies* in general—Opsonins—Cytolysins, hæmolysins, gastrolysins in gastric ulcer—Bacteriolysins—Mode of action of antibodies varies —*Complement*—Its use in diagnosis—Agglutinins in typhoid and paratyphoid fever—in food poisoning, Malta fever, etc.; group reactions; persistence of agglutinins in blood—*Typhoid carriers*—*Precipitins* in diagnosis of blood stains, meats, etc.

We have said that the morphology of the blood for all practical purposes is now a subject whose limits are defined. But in dealing with the fluid constituents of the blood we find there are no such limitations, and at the present time our knowledge takes us only to the threshold of the subject. From the mass of facts, often disconnected, that have resulted from the scientific workers searching into the problem of immunity, a few points have crept into practical medicine and assisted towards the elucidation of infective diseases.

Ever since the bactericidal property of the blood serum was recognised, attention has been directed to the serum in various infective processes as well as in health.

At the present day, though we do not comprehend the processes concerned in immunity we recognise that the resistance to infection with

toxins, bacteria, proteins, etc., is due to, or at least is associated with, the presence of different bodies which are present and can be identified in, though not isolated from, the blood serum. These are known collectively as *antibodies*. Of these the best known are the *antitoxins*, which are formed in response to infection with different toxins, bacterial or vegetable or chemical in origin. These will be more fully dealt with later.

But just as antitoxins have been shown to be formed against toxins, so a host of antibodies have been shown to exist as a result of infection with many different organic substances, and an appreciation of their existence and activities is of assistance in the diagnosis and treatment of disease. Though some are as yet merely of interest to the scientific worker and have not come into the realm of practical medicine, such as the cytolysins, others are of extreme importance and have formed the foundation of new therapeutic measures, such as serum therapy and bacteriotherapy, and of new diagnostic measures, such as the agglutination phenomenon and the complement fixation method of diagnosis.

The better known antibodies are the antitoxins, bacteriolysins, antiferments, cytolysins, agglutinins, precipitins and opsonins.

In the first place it is necessary to point out that all normal serums contain antibodies to a greater or lesser extent, sometimes so little as to be ignored ; at other times sufficient to cause hesitation in diagnosis.

All, however, can be manufactured: that is to say, they can be produced artificially by inoculating animals with specific toxins or protein materials. The antibody that is produced against any of these materials is, with slight reservations, specific to the body, called the "antigen," which is inoculated. Antitoxins, for example, can be produced by inoculating an animal with some toxin, either bacterial or chemical. Diphtheria or tetanus toxin can be inoculated into an animal until a high degree of immunity is acquired, and a specific antitoxin can be found in the animal serum. For a discussion of the antitoxins see Chap. XI.

Again, by inoculating animals with cell materials a large series of *cytolysins* can be produced. The red-blood corpuscles of one animal inoculated into another of a different species lead to the production of an antibody which is capable of dissolving the red-blood corpuscles in question. This substance is known as *hæmolysin*, and is specific to the corpuscles which are used. The serum of a rabbit inoculated with sheep's corpuscles acquires the property of dissolving sheep's corpuscles in dilutions up to 10,000, or even 100,000.

Furthermore, by taking the emulsified gastric mucosa of one animal and inoculating it into an animal of a different species, the serum of this latter animal can be made to form an antibody known as *gastrolysin*, which is solvent to the stomach of the animal used as antigen. Perhaps it is in connection with gastrolysins that the most fascinating

work has been done during the last few years. Bolton has found that after inoculating guinea-pigs with the emulsified mucosa of a cat's stomach, a serum can be obtained from the guinea-pig which, on inoculation into any cat, produces a solution of the gastric mucosa leading to gastric ulceration. This experimental production of gastric ulcer reveals a new line of research which has been opened up by these cell-solvents. There are, similarly, *nephrolysins*, *hepatolysins*, etc., which can be produced by inoculating kidney, liver, etc., into animals of a different species.

To the cytolysins we have, perhaps, to look for the causation of such mysterious diseases as acute yellow atrophy, which is characterised by a rapid destruction of liver tissue (autolysis); and also, perhaps, for the clue to treatment of those exaggerations of cell proliferation which characterise cancer. On these lines, indeed, much tentative work has been done by investigators who have experimented with cancer cells with a view to producing a serum which will have the property of dissolving cancer cells.

When certain bacteria are inoculated into the blood stream, bodies are produced which are solvent to bacteria—the so-called *bacteriolysins*. The serum of patients, or of experimental animals, convalescent from cholera is able to dissolve cholera bacilli when brought into contact with them.

Again, it is possible to produce, by means of the inoculation of some bacteria, certain bodies

which have the property of causing a clumping and a cessation of motility on the part of the specific bacteria when mixed with them. These bodies are known as *agglutinins*, and occur in the blood of patients infected with the bacteria of typhoid or cholera or other diseases. In Fig. 8 the marked agglutinative property of a serum of a fowl affected with spirochætes is well seen.

Also, there has to be considered an important group of *precipitins*. These are antibodies, formed in response to the inoculation of proteid or albuminous materials, and they cause a precipitation of these albuminous bodies in any fluid in which they may be present.

Finally, there is a group of antibodies which is of more recent date than all the others, but which has become more prominent than they, namely, *the opsonins*. These are antibodies which have the power of facilitating the destruction of bacteria by the phagocytes in the blood stream. It is not possible to say whether the opsonins are single bodies or combinations of other bodies, nor can they be separated from the blood, but they can be proved to be present by their activity. It is found that opsonins are formed in the blood stream as a result of—or rather in response to—infection with certain bacteria. They will be dealt with in Chap. VIII.

These antibodies may be divided into two groups so far as their mode of action is concerned. Antitoxins work directly on the toxin, which can be counteracted in the test-tube ; thus a lethal dose

of a toxin, *e. g.* tetano-toxin, can be mixed with a definite amount of antitoxin and then inoculated into an animal without any ill effects being produced. Agglutinins agglutinate bacteria in the test-tube; precipitins precipitate their corresponding albuminous materials directly. Hæmolysin,

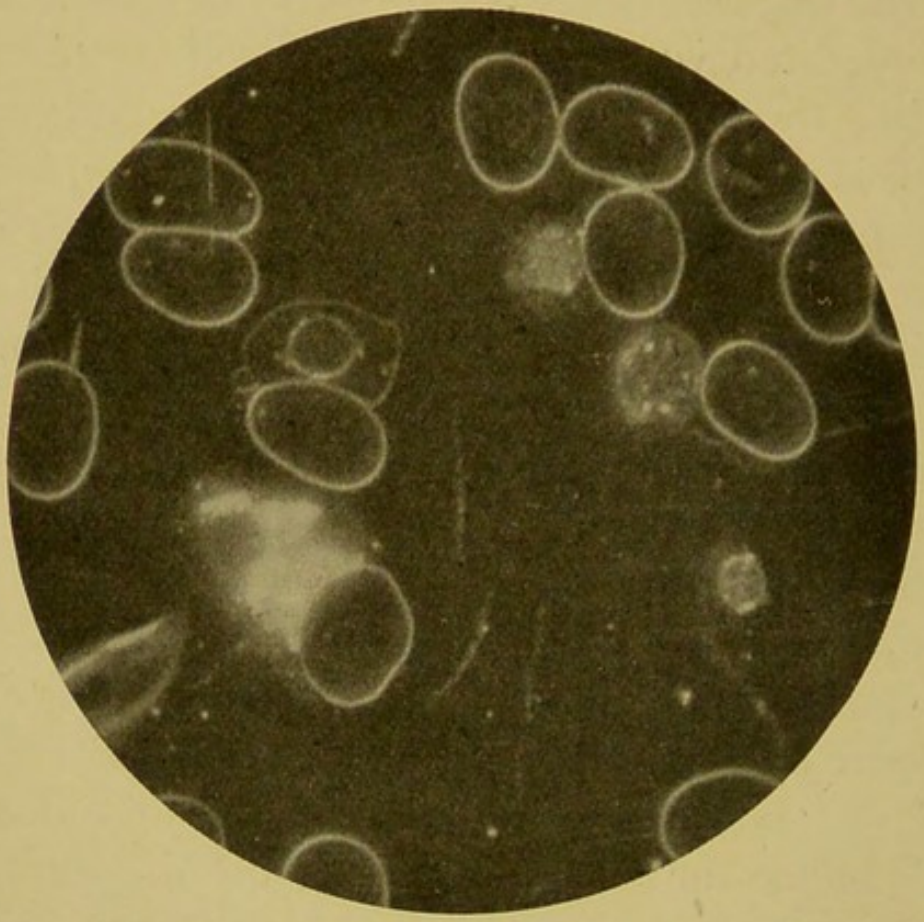


Fig. 7.—Spirochæta gallinarum (in blood of fowl). Dark-ground illumination. From film by Pathé Frères.

however, will not hæmolyse blood corpuscles outside the human body unaided. Injected into the circulation of the specific animal, hæmolysin will produce a solution of blood corpuscles, and consequent hæmoglobinuria. Cytolysins likewise will not produce solution of cells unaided *in vitro*.

The whole of this second group of antibodies necessitates the presence of some vital principle,

which has never been separated and the nature of which has never been determined, but whose existence is sufficiently shown by its activities. It is known as *complement*. This is a body present in the serum of all animals to a greater or a lesser extent, and it is not specific.

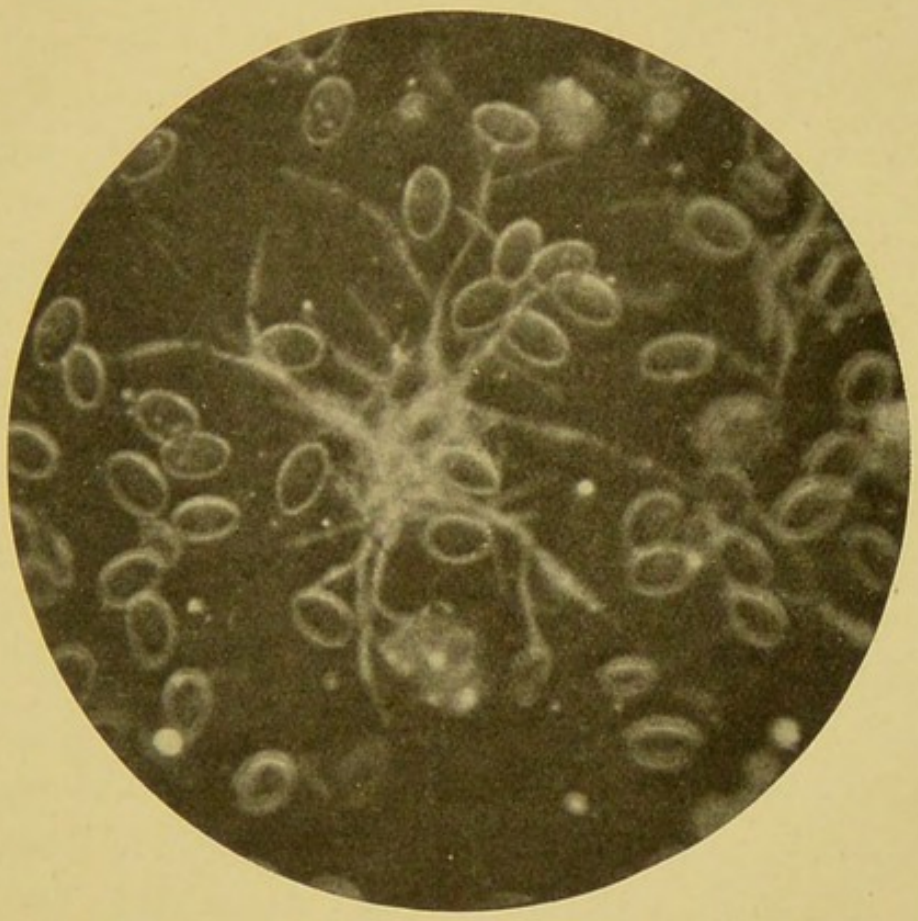


FIG. 8.—Agglutination of spirochæta gallinarum in blood of fowl as a result of mixing with drop of blood of a fowl convalescent from the same infection. Dark-ground illumination. From photo by Pathé Frères.

Cytolysin, plus complement, plus specific cell, results in cytolysis.

Hæmolysin, plus corpuscles, plus complement, results in hæmolysis.

Hence, for these antibodies to work, three factors are necessary, namely, the antibody itself (for

example, the hæmolysin), the specific antigen (*e. g.* the corpuscle) and the complement. The importance of this is very great, and will be appreciated when it is stated that the whole of the work on the modern diagnosis of syphilis and of some other diseases is based upon this recognition of complement: this is known as *diagnosis by complement fixation.* It will be evident that if hæmolysin and corpuscles be present a test can be made for the presence or otherwise of complement. If complement be present hæmolysis is obtained; if absent, there is no hæmolysis at all, and the red corpuscles sink to the bottom of the tube (see Plate 5).

Further, the discovery of hæmolysin has revealed a method of actually seeing with the naked eye what is occurring. If red-blood corpuscles be mixed with colourless serum and colourless complement, a good index will be obtained as to what is happening: the corpuscles either sink to the bottom if not hæmolysed, leaving a clear fluid above, or else they go into solution, and a red-stained fluid is the result. With bacteriolysin no such change can be observed, but the introduction of hæmolysin has enabled vast strides to be made in the question of immunity, because we deduce by analogy that what happens with hæmolysin happens in the case of some other antibodies. With regard to gastrolysin, etc., the work is as yet hardly beyond the laboratory stage.

The foregoing is necessarily a disconnected account of definite bodies which have been identified by the workers in the field of immunity.

But there are a few further developments which are of special interest to those who care to carry their minds beyond the mere practical work of the moment. It has been stated that antibodies can be formed in response to inoculation with certain materials. But it is also true that by inoculating antibodies into animals it is possible to form an antibody to the antibody—an anti-antibody. For example, leech extract, which prevents blood coagulating, inoculated into a rabbit, leads to the production of an antibody in the serum: this placed on a leech-bite wound, will cause the blood to coagulate by counteracting the anticoagulative body.

It is an interesting fact with regard to the hæmolysins that the serum from breast-fed children is more hæmolytic to rabbit corpuscles than serum from bottle-fed children. The natural hæmolysin of the mother passes into the child through the milk. One can make the hypothesis that the antibodies of the mother which are most prominent will pass from the mother to the child, and hence the breast-fed child is more immune to infection than the bottle-fed child.

It appears then that innumerable antibodies are formed in response to infection with different bacteria, proteins, etc., and further that each of these is specific.

Hence the subject of immunity is rendered even more difficult, and perhaps even chaotic. It is possible, however, that ultimately all the experimental facts, which at present seem disconnected,

will be brought into line and explained by some broad general principles, so that the problem will be considerably simplified.

Some of this large group of antibodies which can be formed by inoculation with so many different kinds of organic material can be dried and obtained in the form of powders. In this form the agglutinins are sold commercially. Hæmolysins can also be obtained in the form of dried stains on blotting paper, and as dried powders.

It is now necessary to discuss the practical bearing of some of the more important of these antibodies.

Agglutinins

These are antibodies that produce agglutination or clumping of bacteria. They are formed in response to certain bacterial infections, and their demonstration offers a very valuable means of diagnosis in some infective processes. Typhoid fever is invariably diagnosed by means of the agglutinin reaction. When a case is suspected, the laboratory culture of the bacillus typhosus is taken, and mixed with different dilutions of the blood serum of the patient. If the patient be suffering from typhoid infection the agglutination reaction, with certain reservations, is obtained. In the early stages of typhoid fever, however, this is not so: it takes several days, frequently a week, for sufficient agglutinins to be formed to produce the specific reacting and in children often longer. For practical purposes it is necessary to dilute the patient's serum ten times, twenty times, and

even as much as one hundred times, for normal sera contain often a little agglutinin: this, however, works only in more concentrated solution. The usual report gives the activity of the patient's serum in dilutions of 1 in 20 and of 1 in 100. If it agglutinate rapidly in dilutions of 1 in 20 and slowly in 1 in 100, it can be said that the patient is infected with the typhoid bacillus. Further, it is necessary to remember that bacteria, numerous though they are, can be grouped into certain classes containing closely allied species, and the typhoid group of organisms includes a large number of closely allied varieties, from the usually harmless bacillus coli up to the virulent bacillus typhosus. Between these two extremes such organisms are obtained as the paracolon bacillus, and the paratyphoid bacillus, while closely related are the dysentery

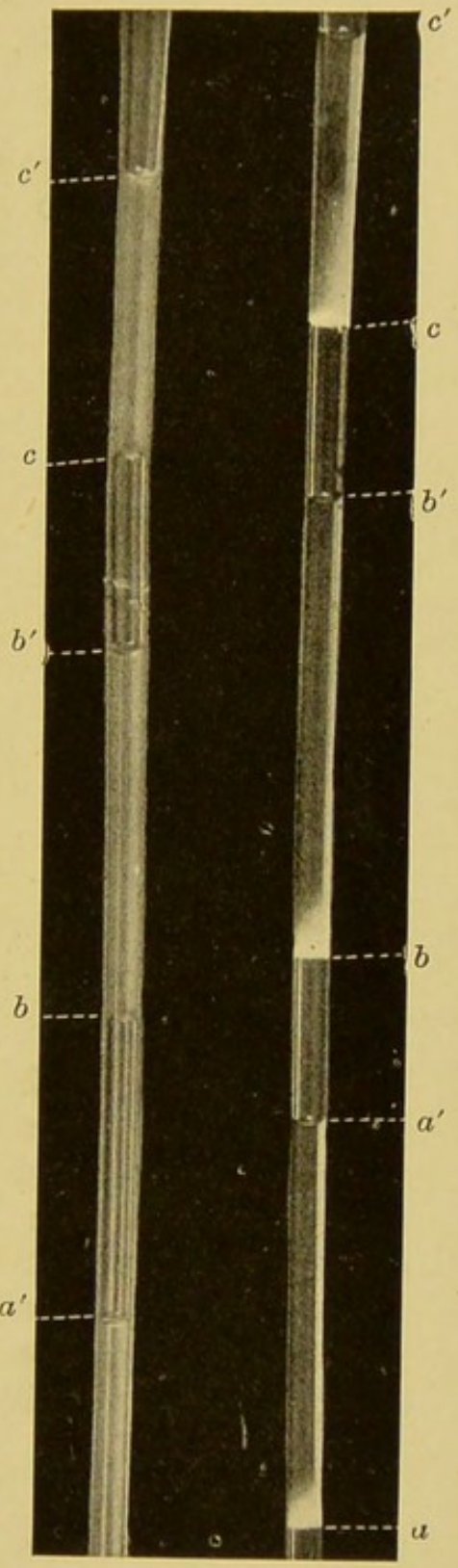


FIG. 9.—Macroscopic agglutination reaction. In each tube are three columns of serum mixed with emulsion of typhoid bacilli—the respective dilutions are $aa' = \times 20$; $bb' = \times 50$; $cc' = \times 200$. The left is the control with normal serum: the columns are uniformly turbid. The right is with serum of a typhoid patient and shows sedimentation of bacilli, more marked in the lesser dilutions (from a photograph by F. R. Chopping).

group of organisms and the bacillus of Gaertner. Closely allied organisms will be agglutinated by a serum of an infected case, but with much lower dilutions than the specific organism itself. This

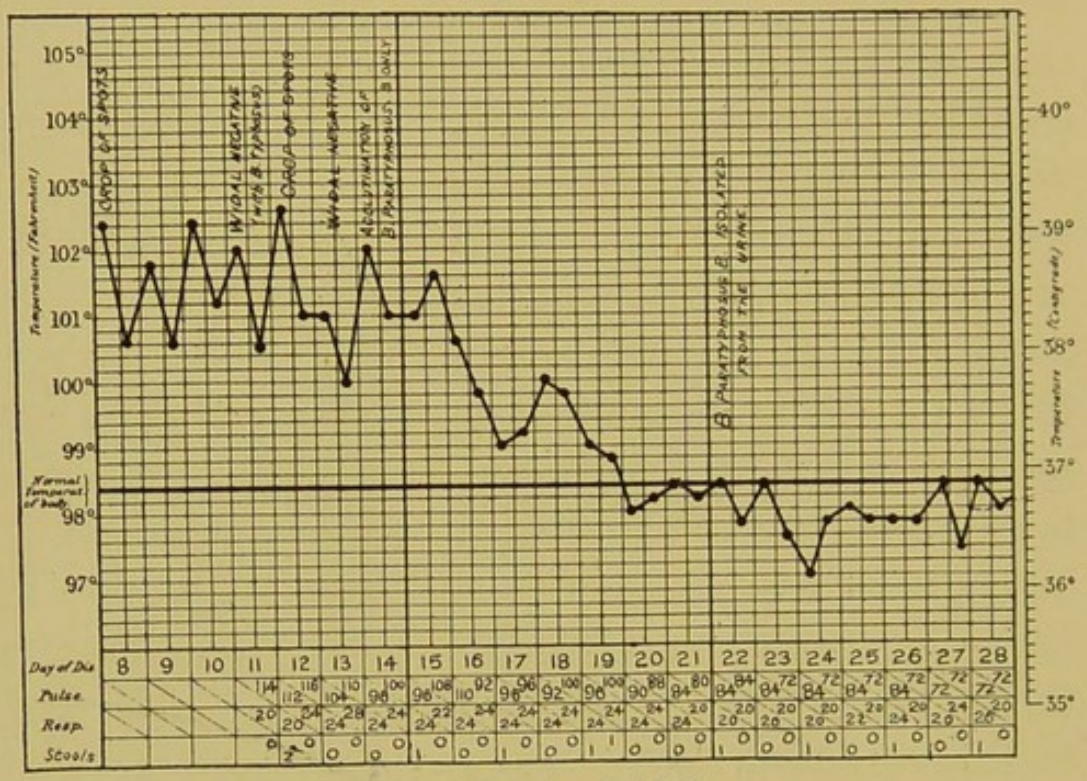


FIG. 10.—Paratyphoid Fever.

Case of female, aet. 20 (see chart), malaise for week preceding admission, typical roseolar eruption on 6th day of disease and again on 8th and 12th day. Constipation throughout. Agglutination reaction: negative to *B. typhosus* and *B. paratyphosus* α, but positive to *B. paratyphosus* β in dilutions of × 800. The same bacillus was isolated from urine, and gave the same agglutination reactions with patient's serum. Recovery complete; bacilli disappeared from urine.

constitutes what is called a group reaction. A paratyphoid serum, for example, may give the agglutinative reaction with B. typhosus in dilutions of 1 in 20 or occasionally 1 in 50. But in the higher dilutions specific reactions alone are obtained, so that a serum of a paratyphoid case in dilutions of

100 or 200 will only agglutinate the variety of B. paratyphosus concerned (Fig. 10). For practical purposes a dilution of 1 in 100 is sufficient.

The reaction is of great value in paratyphoid infections. These used to be grouped with the mild cases of typhoid fever. As in some cases there may be no diarrhœa, or even no spots, and little more than a low pyrexia lasting for some weeks, the only means of diagnosis depends on the finding of paratyphoid bacilli in the blood or the demonstration of the specific agglutinins. In these conditions sufficient agglutinins are formed after the first few days to give a typical Widal reaction, the typhoid bacilli being agglutinated with dilutions of serum of 1 in 50, but not beyond. If the paratyphoid strain A or B be taken and tested against the patient's serum, agglutination may be obtained in 1 in 50, 1 in 100, or perhaps 1 in 200 with the strain of bacillus that is producing the infection. In paratyphoid fever this is of even greater value than in typhoid fever, because paratyphoid fever is so much less definite in its clinical appearances.

Food Poisoning

The agglutination reaction is of value again in the investigation of epidemics of *food poisoning*. An organism has, perhaps, been isolated from the blood or the excreta or the remnants of, for example, tinned food. If this organism be agglutinated by the serum of the patient or other infected person, then this is highly suggestive of its etiological connection with the disease in question

Or if no organism has been so isolated, serum from infected cases can be tested against various laboratory strains of bacteria, and an agglutination of one of these will suggest the causal agent.

The bacteria usually concerned in food poisoning are Gaertner's bacillus and a variety of the paratyphoid bacillus. There are two varieties of this latter, and one is indistinguishable from Gaertner's bacillus.

Agglutinins are used as a diagnostic aid in other infections, including Malta fever and, frequently, cholera, and also in glanders, which, although usually associated with horses, is, as pointed out in Chap. XXVII, not unknown and not even infrequent in man. On the Continent the diagnosis of glanders by this method is a routine procedure.

A word of warning has to be uttered. These agglutinins—which are present not only in the blood serum but in the bile, the milk, and the pericardial fluid, and are occasionally transmitted to the fœtus—persist in the blood serum for a variable period after convalescence. Although it is usual for them to disappear in the course of a few weeks, or months, after the disease, occasionally they remain in the blood for years. *Typhoid carriers* are persons, apparently healthy, who have the bacillus typhosus hidden away internally, perhaps in the gall bladder, and in whom the bacillus can periodically become active and be discharged in the fæces. Such cases are a constant source of infection to their neighbours, and it is to them that the persistence of

endemic cases, with occasional epidemic outbreaks, can often be traced. It has occasionally been found on investigating endemic recurrences of typhoid fever in large institutions that certain of the inmates have given a positive agglutination reaction. Occasionally, also, the bacilli have been isolated from their excreta.

Finally, a certain proportion of typhoid fever cases—about five per cent.—do not give the agglutination reaction. The significance of this is not yet known.

In children the onset of the agglutination reaction is delayed often until the second or third week.

Precipitins

The precipitins are of importance, not so much to the ordinary medical practitioner as to the medical jurist. They are specific substances, which can be produced in response to the inoculation with any albuminous body, but the more important ones are those formed against the albuminous bodies in the blood. For example, a rabbit inoculated with the blood serum of a man several weeks in succession will form in its serum a precipitin which will be active against the albumins of human blood. This serum, when mixed with human blood serum or a solution of a blood-stain, will cause a precipitation in the test-tube: only human blood will be precipitated by that human-rabbit precipitin (Fig. 11). Similarly, if a rabbit be inoculated with the blood serum of a cat or dog or any animal, the rabbit will form

in its blood the specific precipitin for the animal concerned. It has been shown as a result of experimenting with a large series of animals that these precipitins are specific, but with the reservation that there is a slight group reaction in animals closely related.

The importance of this will be understood when it is said that it has solved the difficult medico-legal question as to whether a stain is due to human blood or not, for until the precipitin reaction was introduced it was impossible to assert positively that a bloodstain was anything more than the stain of mammal blood. But with the advent of this scientific test it can be stated definitely that a bloodstain is that of man or some domestic animal. It is true that animals closely allied to man—in ordinary circumstances this may be ignored—will give the same reactions, but in lesser dilutions; the practical conclusions centre round the degree of dilution. But the only animal which could be found by Nuttall to give anything like a group reaction with human blood was one of the highest types of ape. This group reaction, however, disappears in higher dilutions, so that ultimately only the specific reaction obtains. So delicate is the test that experimentally there

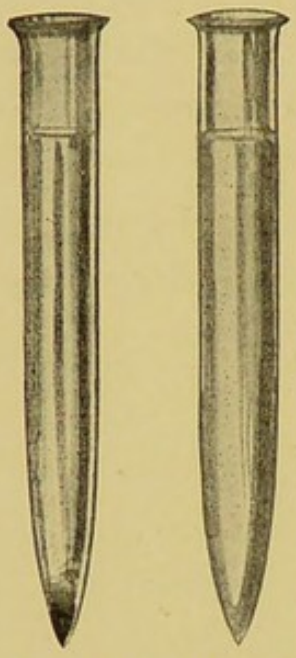


FIG. 11.—Precipitin reaction seen as a result of adding human-rabbit serum to a blood stain diluted × 200. Control tube contains normal saline and diluted stain.

has been produced a blood serum which after diluting one million times still gave a definite specific reaction against the blood-stain to be tested. It is necessary to have in the medico-legal laboratory a series of these sera which can be preserved for some time on ice—sera which have been made to contain precipitins against the various domestic animals of the part of the world in which the laboratory is placed. These may be labelled sheep-rabbit, cat-rabbit, man-rabbit, etc.

Precipitins have also been prepared from the various animal proteids and attempts made to use them to diagnose the constitution of sausages, etc., and also to differentiate between the various types of albumin found in pathological urine, but many difficulties beset the path of workers in these fields.

CHAPTER VIII

BACTERIOTHERAPY

Introduction—Relation of bacteria to disease—Bacteria benevolent or malevolent—Resistance of organisms to infection—*Opsonins*—*Opsonic Index*—Variations in disease—Artificial stimulation of opsonin with dead bacteria—Negative and positive phases—Opsonic index in diagnosis—Auto-inoculation—Clinical evidence to replace index—Conclusions.

VACCINE THERAPY is the treatment of bacterial disease with bacteria themselves. It is an attempt to aid Nature in the performance of her ordinary duties.

Before entering upon its explanation, however, it is necessary to remind the reader that all new lines of treatment and all new discoveries, among which vaccine therapy must be classed, hold the field to the exclusion of all others for a certain time after their establishment. Later on they are seen in their true perspective and appreciated at their proper value.

Three cardinal features have to be borne in mind on approaching this subject. In the first place, in spite of the modern tendency to think that the bacterium is the cause of every disease, *all diseases are not bacterial in nature.* Gout, rheumatoid arthritis of the true mono-articular form, diabetes, and numerous other diatheses, are

examples of affections which cannot be placed in the bacterial category.

Secondly, *of the diseases which are due to bacteria, all are not of the same nature:* all the bacteria do not work in the same way. Diphtheria is an example of what might be called an ideal intoxication. This bacterium works by multiplying at the site of infection and pouring into the system toxins: to the effects of these toxins on the heart and tissues the fatal results of diphtheria are due. In contrast to this instance of pure toxæmia is typhoid fever, in which the bacillus multiplies locally in the intestines and lymphoid tissues of the abdomen, giving rise to a bacillæmia. Similarly in staphylococcic and streptococcic infections there exists a condition in which the cocci multiply and are found throughout the system. These are extreme cases, on the one hand, of a pure intoxication, and, on the other, of a bacteriæmia. It ought to be pointed out that even a pure bacillæmia is associated with some amount of intoxication, but to pursue that point would lead us too far from the subject of this chapter. Nor need we do more than mention that we have intermediate types between these two infections. It is sufficient to show that the different bacteria exercise their influence in different ways, and hence must be combated in different ways.

The group of bacteria which produce toxins falls within the scope of serum therapy, whereas it is more particularly in connection with those bacteria

that multiply in the system and work like the staphylococci and the B. coli that vaccine therapy deals.

Thirdly, *bacteria may exist associated with some diseased state and yet not be pathogenic.* That, perhaps, is the most important principle to bear in mind in connection with the technique of bacteriotherapy. We have bacteria upon us, within us, and around us, many of which are harmless, and some of which are useful, and benevolent; some even are of assistance in metabolism. A few—comparatively a small number—are pathogenic, and have been definitely proved to produce infective diseases.

With these three preliminary factors in mind, we may proceed to discuss the relation of the small group of pathogenic bacteria to disease, and the resistance of the organism to infection by them. The resistance to infection has been variously ascribed to two properties. First of all, and for a long time, it was put down to the polymorphonuclear leucocytes which preponderate in the blood stream. These are the so-called phagocytes. For twenty-five years or more Metchnikoff exploited this fascinating theory. In its live state the amœboid leucocyte can be seen to engulf bacilli and to destroy them. But that is not the whole of the question. Some years ago it was found that the blood serum was of itself bactericidal. It was observed that blood could stand in a warm laboratory for several days and yet not putrefy. Since that time various bactericidal agents have

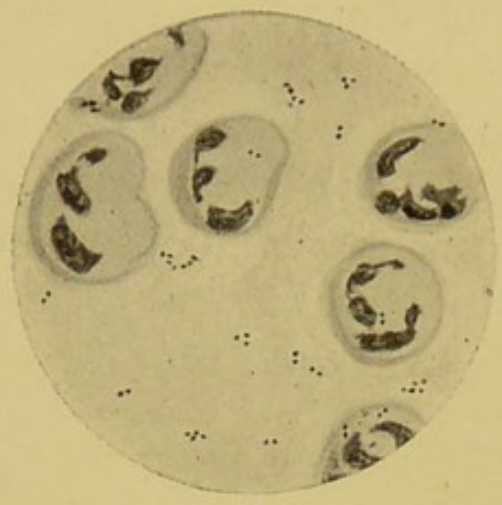
been found, and at the present day a large number of antagonistic bodies—the so-called antibodies—can be demonstrated in the blood stream. These have been already described in Chap. VII, so that here it is only necessary to mention the opsonins, described by Sir Almroth Wright, to whose originality the practice of vaccine therapy is entirely due.

Opsonins

The opsonins are antibodies which are present in the blood stream and which aid in the process of destroying the bacteria. Put briefly, they assist phagocytosis. It does not matter for our purpose whether they act by stimulating the phagocytes, or, by first affecting the bacteria in some way which reduces their virulence and facilitates phagocytosis. For practical work it is enough to know that opsonins exist and that their presence can be demonstrated.

Opsonins in Phagocytosis

Opsonins can be identified by their activity and their existence can be demonstrated by a simple experiment. For this three things are needed: leucocytes, centrifuged from the blood and washed free from all serum; serum removed from blood, and an emulsion of bacteria. Leucocytes are mixed with bacteria alone and again with bacteria and blood serum, and the mixtures incubated for a definite period. At the end of this time films are made from the mixtures and stained. In these the polymorphonuclear leucocytes (phago-



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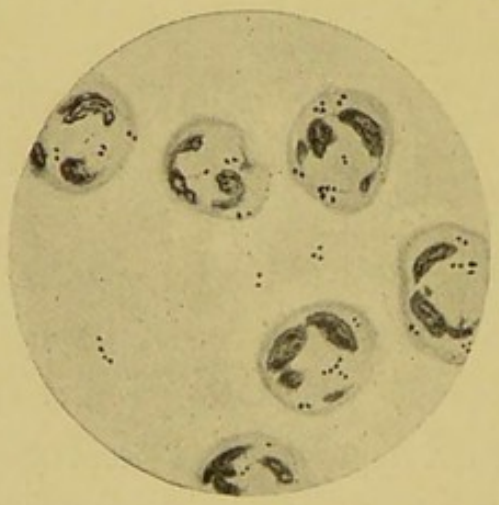

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FIG. 12.—To show from above downwards phagocytosis (1) without serum, (2) with serum of infected patient, (3) with serum of normal person.

cytes) can be readily found under the microscope and be seen to have ingested the bacteria in varying numbers (Fig. 12). Now, whereas the leucocytes unaided by serum will have only ingested a very few bacteria, the leucocytes aided by the addition of serum will have taken up considerably greater numbers, and a numerical comparison will prove that the addition of serum strongly aids in the process of phagocytosis. The factor which is present in the serum is what is known as opsonin. The amount of this body is constant in health, and little variation will be produced in the numerical result if the experiment be repeated with different sera from healthy people. The amount of opsonin present in health is taken as the standard for comparison, and the relation to this of the amount in

sera of infected persons constitutes what is called the *opsonic index.*

The recognition of the presence of opsonins in the blood led up to the work upon their quantitative variations. It was shown that the *opsonins vary in health and in disease,* and, moreover, that they can be artificially altered in the direction either of increase or of diminution. Furthermore, it was noted that the resistance to some bacterial infections depends upon the increase or decrease of the opsonins. The total amount of opsonins present becomes thus a matter of importance. In any ordinary infection—for example, a case of boils—the opsonins are as a rule diminished. In order to discover whether, in a given case, the opsonins vary from the normal, the experiment detailed above is carried out with a normal serum and a parallel experiment with the serum of the infected person. The ratio of activity of the respective sera, as instanced by the average number of cocci ingested by a leucocyte in each case, gives the opsonic index. This index we have already said is the relation between the abnormal and the normal opsonin content.

With the serum of a healthy individual, for example, each phagocyte may perhaps ingest twelve cocci, while with the serum of a person affected with boils the figure may be eight, or six, or less (Fig. 12). If the serum of the patient differs from the serum of the normal individual in that it contains only half the amount of opsonin, the expression of that relationship will furnish the

opsonic index. Thus it would be $\frac{8}{12} = 0{\cdot}66$ or $\frac{6}{12} = 0{\cdot}5$.

Opsonins in Infective Processes

Having evolved a means of determining the

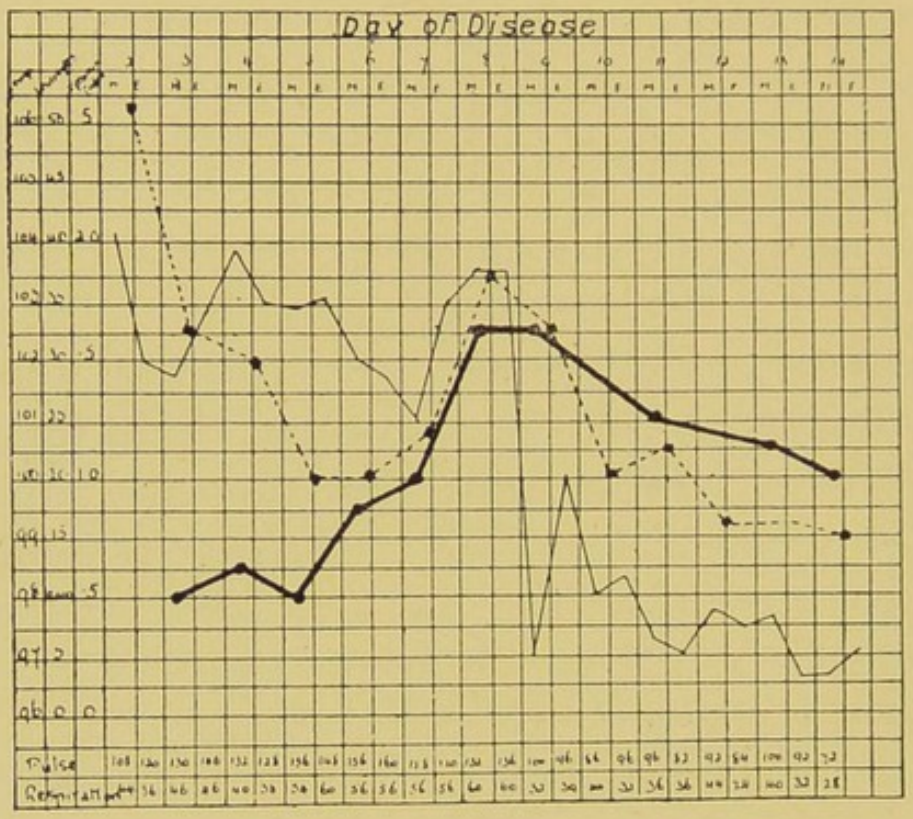


FIG. 13.—Case of pneumonia terminating by crisis. (*Eyre.*)
— = Temperature. •—• = Opsonic index. •····• = Leucocytes.

opsonic index, it is possible to determine how the amount of opsonin varies in disease. In the case of a staphylococcic infection it will be noticed that the opsonic index is below the normal, and if the disease progresses, the opsonic index tends to fall. If, on the other hand, the patient improves, with or without bacterial treatment, the opsonic index gradually rises to normal. In the case of pneumonia (staphylococci being replaced by pneumococci in the technique) the opsonic index will

give a different picture according to the resistance of the patient. In an ordinary pneumonia which runs its course in five or six days and ends by crisis, the opsonic index, starting low, slowly rises to normal, and perhaps after the fifth day reaching higher than normal, returns later to normal, and remains there (Fig. 13). Such a picture is a demonstration that the body is strongly

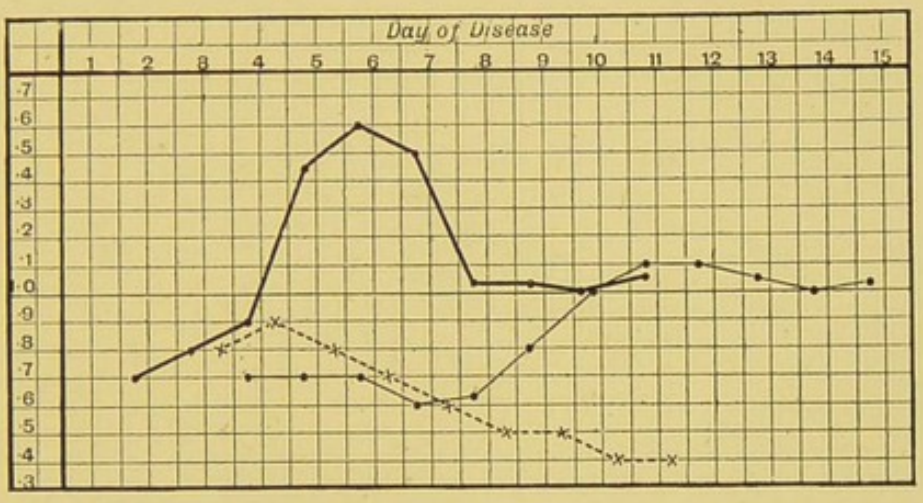


FIG. 14.—Opsonic Index in Pneumococcic Infections. (*Eyre.*)
— = Ordinary type, terminating by crisis. •—• = Delayed lysis.
×···× = Fatal type.

resisting infection, and that the antibodies, or opsonins, are increasing in such number that they are overcoming the attack of the cocci; the acme of opsonin production marks the height of the struggle, and is followed by the crisis and recovery.

In a case of pneumonia which drags on for some long time the index is below normal. It may perhaps reach the normal by the eighth day and even go slightly above it, and finally continue at about normal as the case ends by lysis (Fig. 14).

Pneumonias in which there is no reaction at all, such as those of the alcoholic and asthenic types, show a curve which is always below the normal, and which sinks each day until the fatal termination (Fig. 15). The opsonins are progressively lowered until finally the infection meets with no resistance.

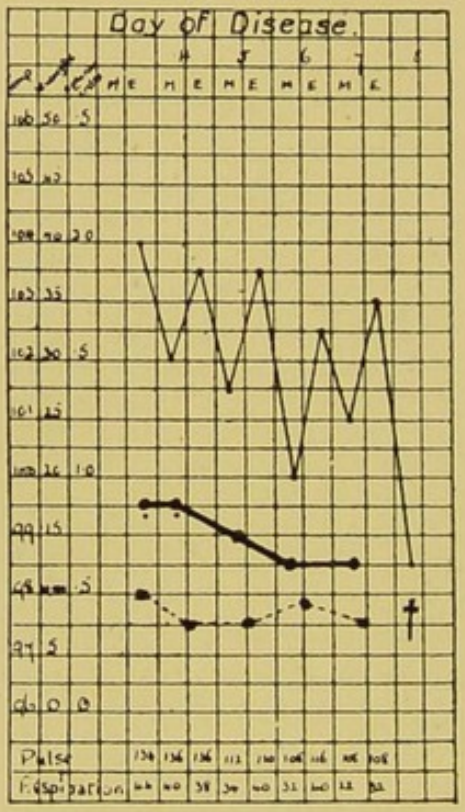


Fig. 15.—Fatal case of Pneumococcic septicæmia. (*Eyre.*)
— = Temperature. •—• = Opsonic index. •····• = Leucocytes.

Artificial Stimulation of Opsonins

It is also possible to demonstrate that artificial aids can be applied to vary the amount of opsonins. For that purpose the first means that would suggest itself is the use of the organism in question. The opsonins are to a considerable extent specific. Those which resist the pneumococcus, for example, will not avail much in defending the system against other bacteria. This

statement, however, must be taken with some amount of reserve, for perhaps the immunity mechanism can be stimulated by many bacteria, though with the specific organism the opsonin production is most marked. Taking their partial specificity for granted, is it possible to vary them by bacterial agents? Let us take the case of a person whose opsonic index is low—a patient who is subject to recurrent outbreaks of boils. His

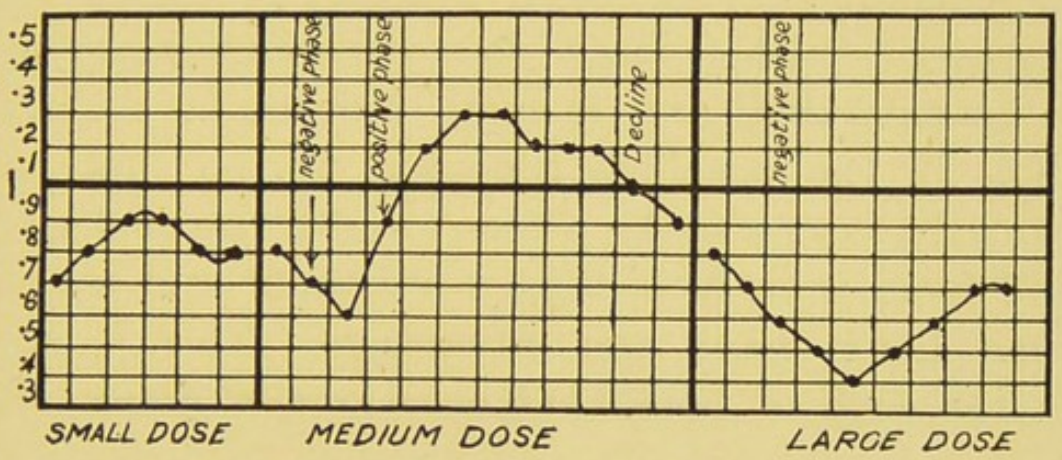


FIG. 16.—To show variation in opsonic index according to dose.

opsonic index to staphylococci at the first examination may be 0·8. He is given an injection of dead staphylococci, and his opsonic index is taken every few hours (Fig. 16). The opsonic index at first falls, perhaps from 0·8 to 0·6. Later it begins to rise and approach the normal, or even go beyond this; so that in a few days it may be at 1·1 or 1·2. From this point it gradually falls.

The first thing that happens, then, after an injection of dead bacteria is a fall in the opsonic index, denoting a diminution in the opsonin content, which is called the negative phase. This may be taken to signify that the first result of injecting staphylococci into the system is that these find

waiting for them a certain amount of natural staphylococcic opsonin with which they combine; hence occurs a diminution in the amount of opsonin. Next the vital processes start their mysterious activities and a new formation of opsonin is stimulated. The increased formation produces a rise in the index; this is called the positive phase. Each chart, of course, varies with the dosage. With a small dosage the preliminary fall is slight, and the subsequent rise, although definite, is not so well marked. With a large dose the preliminary fall is considerable, and it may, indeed, be so large that all the opsonins are used up, so that any bacteria that may be present in a focus of disease will meet with little if any resistance and for the time being have the advantage. This is seen in the crop of boils that occasionally breaks out after an injection of too large a preliminary dose of staphylococcic vaccine. The negative phase increases with the size of the dose, and, later, the positive phase also.

If the dose is repeated during the negative phase a few hours after the first dose, the result is an increased negative phase which is again followed by a rise. The dose repeated during the positive phase results in only a slight negative phase, and a rise also follows. Hence it is found that by interspacing the dose so as to coincide with the positive phase each time, a rising index is obtained which ultimately reaches considerably above the normal figure. It may even go up to twice the normal, by inoculating at every positive phase. The index has to be taken frequently in

order to discover the most suitable time at which to make the injection. With small doses the subsequent effect is very slight, and therefore if, instead of beginning with a thousand million staphylococci as a minimum, we begin with ten millions, we do away with the risks attendant upon a repetition of the negative phase. The danger of the negative phase has been instanced in the case of a patient affected with boils; in such a generalised outbreak of pustules may occur if too large doses are given or if the doses are repeated at too short intervals.

The conclusion of the whole matter is that it is possible by proper doses given at proper times to raise the opsonic content, and so raise a patient's resistance to infection. During this process we find that the patient has been cured. This is the artificial way of bringing about what Nature herself tries to bring about in the cure of disease.

Opsonic Index in Diagnosis

In what further ways does this appreciation of the opsonic index help us ? We have taken the reader to the threshold of its therapeutic importance. The opsonic index has been used in times past and is still occasionally used as a diagnostic agent. In dealing with internal infections, the nature of which is only suspected, such as perhaps tuberculosis of the joints and of the lungs, the opsonic index has been used, and in some hands its use continues, in diagnosis. In tuberculous people the opsonic index is considerably different from the normal. Here we get extremes. The

opsonic index to tubercle bacilli of normal healthy people may, indeed, vary considerably, between 0·8 and 1·2, but below the former figure and above the latter there may well be suspicion of tuberculosis. The reason of the variation in opsonic index in an ordinary untreated case of tuberculosis, or in any case of bacterial infection is to be found in the phenomenon of *auto-inoculation*. While the patient is the seat of an infection the bacteria or their products are constantly getting into the blood stream, and if they get there by a natural process or are put there artificially they will produce the same changes as already described. The result will be a negative phase followed by a positive phase. Some tuberculous patients may have at one time an index of 2 or over, and at another it may be 0·5 or 0·2. Of more value is the artificial production of auto-inoculation. On submitting a patient to massage, or increasing his exercises, and so forth, it may often be found that the opsonic index rises to 1·5 or to 2 or even higher. This variation in the opsonic index as a result of exercise or exertion denotes an auto-inoculation, and hence the presence of the bacterium in question.

Clinical Manifestations

All this is perhaps the laboratory part of the opsonic index, and the question remains as to whether we have any clinical appearances which will save us from carrying out this most tedious method of investigation. Is there anything that can be told us clinically as to whether a phase is

negative or positive? When a patient is given a large injection of vaccine he feels very ill at first, and has much malaise, and when the positive phase makes its appearance he grows better and livelier, and the disease improves. In the negative phase the boils look more angry, and fresh outbreaks may appear. From clinical manifestations such as these it is possible to judge almost as well as from the laboratory findings. We can also overcome the difficulty and danger of marked negative phases by giving smaller doses, thus producing very slight negative results. By so doing the doses may be given and increased much more frequently.

Furthermore, since this method was introduced we have gained much empirical knowledge and know approximately what doses to give. We know, for instance, that staphylococci must be given in their hundreds of millions and streptococci in their single millions, and that has permitted us to deal with a case more courageously.

To sum up: in the past the opsonic index has proved of inestimable value as a means of drawing attention to the effects of bacterial infection; it has cleared the way for vaccine therapy, and it has allowed us to go bravely ahead and build up a vast amount of experimental and empirical knowledge. But now, though fully recognising its importance, we can lay it aside on the shelf of medical history, while we advance in the art of bacteriotherapy. Doubtless in the hands of the skilled technician it can still serve a purpose in diagnosis as well as in therapeutics.

CHAPTER IX

BACTERIOTHERAPY (*continued*)

Acute and chronic infections—Preparation of vaccines—Contaminating germs—Stock vaccines—Autogenous vaccines—Methods of administration—Results of inoculation—Staphylococci—Streptococci—B. pyocyaneus—Pneumococcus—Gonococcus and infections of urethra—B. coli group—Bacteria of respiratory tract—B. tuberculosis—Infective arthritis—Pyorrhœa alveolaris.

We have seen that vaccine therapy is an attempt to produce active immunity of a more or less temporary nature in order that the body may overcome certain infections.

We have now to discuss the organisms that cause these infections, their isolation from the respective lesions, and the building of them up into vaccines. At the outset it is necessary to distinguish between acute and chronic infections. In the case of acute infections it might be said at once that the blood is swarming with micro-organisms, and therefore it would seem useless to pour into the blood stream more micro-organisms in the form of vaccines in order to produce some immunity. There is little information available on vaccine therapy as applied to the cure of septicæmias and the like, and so far as experience goes its value is very uncertain.

But in those conditions in which the bacteria

are localised and sometimes partly shut off from the general system, vaccine therapy is in many cases of real benefit.

The object of vaccine therapy is to raise the *opsonin content* in the blood stream, and to bring this increased amount of opsonin to the site of infection, at which site the opsonins have been shown by experiment to be considerably diminished or entirely absent. Such a condition occurs in a chronic abscess.

Preparation of Vaccine

In considering the preparation of a vaccine, we have in the first place to determine what is the infecting organism. It is necessary to bear in mind that there are innumerable organisms scattered about the body, and that only a few of these are pathogenic.

It is not sufficient to find an organism associated with any diseased state and proceed to make this into a vaccine and then to expect good results from the use of this. If the materials be not carefully collected, there is sure to be contamination with saprophytic germs from the skin or other region, or from the vessel or tube into which the material has been collected. Hence it is important to guard against this; but still more important to be able to decide on the causal relationship of the organism to the disease: this necessitates clinical as well as bacteriological knowledge. Much bad therapy has resulted from neglect of these factors.

In local lesions such as boils and abscesses before these discharge; in internal lesions, such as cystitis, before secondary infection is produced; in pyelitis, pyelonephritis, and other closed infections, which are usually uncontaminated, bacteria can often be found and readily obtained in pure culture. Hence it may be concluded that the bacterium is associated with the etiology of the condition.

In open wounds, in ulcers, in lesions of the alimentary tract, where there are always numerous saprophytic organisms, the isolation of the organism becomes very difficult. In these open areas there are so many organisms normally present, and these, often, so prolific, that it is exceedingly difficult and sometimes impossible to isolate the specific organism from the contaminating flora. For instance, in pyorrhœa there may occur streptococci, yeasts, and a large number of other organisms; in lesions of the lungs, such as chronic bronchitis, a host of contaminating organisms can also be found.

When, however, the process is very acute the specific organism often has the upper hand at the expense of the contaminating saprophytic organisms, as, for example, in acute pneumonia, where the sputum may contain pneumococci solely.

The problem is to isolate the organism and to identify it as the cause of infection. The first thing upon which the successful issue of such a piece of work depends is experience—appreciation of the organisms which are normally found in the

part. It depends in the next place upon various cultural methods, media being used which are specially prepared to facilitate the growth of the organism whose presence is suspected, and to inhibit the various saprophytic organisms; such as blood serum for diphtheria, human blood-agar for gonococci, bile salt media for B. coli, etc.

A sufficient amount of bacteria having been obtained in pure culture, the whole is then transferred to normal saline, shaken for a time to produce an evenly distributed suspension, counted to determine the concentration, diluted appropriately, and dosed out so as to have the requisite series of increasing doses, each in a volume of 1 c.c. of saline. These are then sterilised at 56° C. for half-an-hour, incubated for some hours, again sterilised and after incubation finally sterilised, and are then ready for use. Some prefer to kill the bacteria and also to preserve the vaccines in 0·5 per cent. lysol, under the impression that heating destroys or weakens the activity of the vaccines. Having isolated the organisms they must be dosed out and prepared for injection.

Stock Vaccines

The question may be raised as to whether the vaccines must come from the patient (*i. e.* autogenous), or whether stock vaccines are as efficacious as the autogenous product. *Stock vaccines* consist of bacterial preparations of known organisms, such as the staphylococcus, the bacillus coli, the bacillus typhosus, etc. But when it is appreci-

ated that often an organism is found in so many different forms and in so many different stages of virulence, it will be realised that the autogenous vaccine is the most suitable for the patient. Some organisms, however, do not vary as much as others. The bacillus coli, on the one hand, varies very widely. There are a large number of varieties of coli infection, and although vaccines of typical bacillus coli can be obtained and may give good results, it is better, if possible, to use bacilli obtained from the patient. The stock vaccine of the staphylococcus, on the other hand, is very useful, although there is some objection on the part of patients to having foreign bacteria injected into them. When the autogenous vaccines cannot be obtained, it is advisable to use the stock vaccine. Stock vaccines are made in large amounts either from cultures from recent foci of infection which are still virulent or from subcultures which have been carried on for many generations, under which conditions the virulence of the germ is considerably diminished or lost. Furthermore, the vaccines appear to lose their virulence by keeping, at any rate this has been shown to be the case with typhoid bacilli. So that with stock vaccine it is impossible to appreciate what would constitute a satisfactory dose and in some cases it may be doubtful whether any dose will be efficacious. Generally speaking stock vaccines must be administered in larger doses than autogenous ones.

Method of Administration

Vaccines are administered by different workers either subcutaneously, or by the mouth or rectum, or intravenously. If it be appreciated that the the object of administering the vaccine is to get some local reaction of the blood tissues in the part affected, so as to produce the responsive antibodies which we call opsonins, it will be seen at once that the best and most suitable means of administering such vaccines is the subcutaneous. This is, indeed, the most widely adopted procedure. The administration by the mouth, and still more so by the rectum, has many disadvantages; amongst them is the fact that the gastric juice can attack toxins and can perhaps destroy their activity altogether. Just as the suggestion to give diphtheria antitoxin by the mouth and by the rectum has not met with general acceptance, so it is probable that the administration of vaccines by the mouth and rectum may also be discarded. In a few cases, generally of old people, who refused to suffer the inconvenience of a hypodermic needle, the bacillus coli vaccine administered by the mouth seems to have done good, and favourable results have been reported with tuberculin given in the same way on an empty stomach. The intravenous injection would appear to be futile. The administrative method of preference, therefore, is subcutaneous.

The part chosen for the subcutaneous inocula-

tion varies. The lax tissues of the chest may be chosen, or the loin or back, and occasionally the arm or the shoulder. The dose is generally made up in a convenient bulk of 1 c.c. normal saline.

Results of Inoculation

The result of the inoculation depends upon the dose. It is both local and general. If the dose is large, as it used to be in the early days, a marked local reaction around the site of the inoculation occurs in the course of a few hours. Together with this there is much malaise and discomfort. Around the lesions in the case of boils—and staphylococcic infections offer the best example of the efficacy of vaccine therapy—there appears, if the dose is large, a marked inflammatory reaction. Even boils which may have been fairly quiescent will, in the course of a few hours or a day, become alarmingly active, highly inflamed, and pour out large quantities of pus. Small groups of boils may break out elsewhere than in the inoculated region. This is significant of the negative phase of the reaction. If the dose is smaller these results may be absent or be very slight, but a gradual and often rapid improvement sets in.

The constitutional disturbances include malaise, headache, pyrexia, etc. Then, in a few days, even after the large doses, the inflammation subsides, the malaise disappears, and there is a marked and rapid improvement in the local condition, which may even go on to complete recovery,

and the general reaction gives way to a feeling of well being. In the course of a few days results may be obtained which appear to be almost magical.

Experience has taught that the ideal treatment is to give doses that produce little general and local reaction and to repeat them at closer intervals, instead of giving the larger doses which sometimes necessitate the confinement of the patient to bed, and which can only be repeated at intervals of ten days or a fortnight. Seeing that the effective dosage varies in different people, and even in different people of the same age, it is better to begin with minute doses and rapidly to work up by doubling the doses until some general reaction is obtained. It is not possible to be more than approximate in the matter of dosage, and therefore by starting in this manner with small doses and progressively increasing them, the treatment can be carried out with much greater safety.

But a point of great importance must be accentuated, in order that vaccine therapy should not cause unnecessary disappointment. In the case of the infections which will now be discussed, while it is true that the vaccines will most certainly result in cure for a time, unless the underlying conditions be removed, the lesion will often recur. Two factors are always concerned in every bacterial disease. One is the resistance of the patient, which bacteriotherapy will raise temporarily; the other is the soil, upon which bacteriotherapy will have no effect whatever.

Thus we have the explanation of boils which are cured after one or two injections, but which recur as soon as the injections are stopped. Hence also the tendency for the trouble to return in those cases of B. coli infection in the kidney and urinary tract in old people of low vitality.

Vaccine therapy, therefore, must be regarded as an aid to therapeutics, and to be used judiciously by the clinician himself. In due time it will take its proper place in medicine as one means of combating *some* infections due to certain bacteria.

We propose to go step by step through the different infections, to give some of the results that have been obtained, and to formulate some broad principles on which to dose individual conditions.

Staphylococci

The *staphylococci* are organisms which produce various manifestations according to the virulence of the organism and the resistance of the patient. A simple pustule, such as the acne pustule, may be obtained, or, where resistance is diminished, a boil or carbuncle; or the organism may get into the blood stream and produce pyæmia, and be eliminated at the various terminals of the blood vessels, giving rise to pyæmic abscesses; or empyema, peritonitis and meningitis may result. Other local lesions of importance are sycosis and acne and acute inflammation of bone. Remembering that, broadly speaking, it is only in the chronic lesions that vaccine therapy does

good, it may be said that the effect of such treatment in staphylococcic infections is to produce an undoubted cure of the existing lesions.

Boils may disappear in a few days. A carbuncle covering an extensive area will grow rapidly smaller and smaller, until in the course of a few weeks it will have healed altogether.

Staphylococci are given in initial doses which average from 25 million to 50 million. The latter would be considered by some to be a moderately small dose, but personally the author prefers to start with a dose of 25 million, even in the case of healthy and vigorous people, while in people of less vigour he would start with 10 million. As the treatment proceeds the dose is doubled each time—from 25 million to 50 million and then to 100 million at intervals of three or four days, noting, of course, the general results. One may, if necessary, even proceed to 500 million. The boils disappear rapidly.

Sycosis, even where it has lasted for many years, has rapidly yielded to inoculations with the staphylococcus pyogenes aureus. The vaccine is obtained by inseminating the root of a diseased hair into a tube of culture media.

Acne, the vaccine treatment of which is lauded by some, depends upon some metabolic error, but it is frequently complicated by the presence of staphylococci, which cause the pustular outbreak. In addition, an acne bacillus is also described with a special predilection for media and tissues containing oleic acid. With a staphylococcic

vaccine the pustules of acne will disappear like any pustular lesion elsewhere, but the true papules of acne will still be troublesome. The acne bacillus, which is said to be of some use, is given in doses of 5 million.

In chronic suppurations in any part of the body due to the staphylococcus equally good results are obtained. In compound fractures where the wound refuses to heal and suppuration continues, good results are noted, as also in osteomyelitis, while in pyæmia this line of treatment is worth attempting. Where large abscesses have accumulated and become encapsulated so that the circulating lymph is impeded, it is necessary to resort to surgical interference to drain the pus, which cannot be absorbed by any amount of vaccines.

Occasionally the *Micrococcus tetragenus* is found to be the cause of an abscess, and this can be isolated and used in the same way as staphylococcus.

Streptococci

The *streptococci* also produce divers lesions according to the resistance of the patient and the virulence of the organism, such as a locally spreading erysipelas, a more diffuse lymphangitis, or a generalised septicæmia, which may be acute and rapidly fatal, or chronic. The streptococcus is also associated with scarlet fever, and with acute nephritis,—perhaps obtaining entry to the circulation by the tonsil. A large variety of

streptococci are found normally in the mouth and alimentary tract (*S. buccalis* and *S. fæcalis*), and these appear to be capable of acquiring some degree of virulence under certain conditions, such as in chronic endocarditis, where they implant themselves on the diseased valves and set up a state of infective endocarditis. The many varieties of the streptococcus which are described are probably one and the same organism modified by its environment.

In erysipelas moderately good results have been obtained with streptococcus vaccine. In acute septicæmia no definite results whatever have been obtained, and it is a little difficult to imagine how in an acute septicæmia, where the blood is swarming with organisms, it is possible to do any good by inoculating a comparatively few bacteria. But in more chronic varieties of septicæmia in which local abscesses form—*e. g.* in arthritis—better results can be anticipated from vaccine therapy. In several cases of puerperal septicæmia associated with septic arthritis, etc., much success has accompanied the administration of vaccines prepared from streptococci isolated from the local lesions. The streptococci can be isolated in pure culture, from the edge of the erysipelatous patch, or from the seropurulent discharge of a cellulitis, or from the sputum in a streptococcic pneumonia, or from the blood in septicæmia (*vide* Blood cultures). In acute infections of marked virulence they grow very readily, but in chronic lesions some days elapse before a suitable growth is obtained.

The initial dose of streptococci is 5 million, to be repeated after three or four days in a dose of 10 million, and later in a dose of 20 million. With a recently isolated virulent strain it is not often necessary to exceed this. In more serious cases a start may be made with 1 million and the dose may go on to 5 million, but the variations in virulence of stock vaccines and also of the different autogenous vaccines make it such that the only clue to the limitation of the dose is the effect of each dose.

B. pyocyaneus

Another pyogenic organism is that which produces blue pus and is known as the *bacillus pyocyaneus*. This is found either alone or mixed with other organisms in lesions of the skin, bladder, rectum, etc. It is not an uncommon cause of cystitis and often complicates compound fractures. It often spreads throughout a ward and is recognised readily by the greenish or bluish colour of the pus at the edge of the wounds, and by the marked colour of the cultures. The treatment in conditions in which this organism is at work is similar to that employed in the case of the staphylococcus. A start is made with doses of 10 million. It would seem that the B. pyocyaneus produces a marked toxæmia, so care must be exercised in its administration.

It is practically impossible to isolate other organisms from a culture containing B. pyocyaneus, and as suppuration is often maintained

by such, *e. g.* staphyloccocus and B. coli, it is advisable to make a mixed vaccine from the culture and treat with this. Sometimes the B. pyocyaneus can be first removed by the use of its vaccine and then a fresh vaccine made from the remaining organisms.

Pneumococcus

The *pneomucoccus* produces numerous lesions. Under normal conditions of health it is found in the mouth and communicating cavities: many children have a pneumococcus in the middle ear in an avirulent condition (see Chap. XXII), which can at times be exalted into virulence and produce middle-ear disease, meningitis, etc. The pneumococcus in adults produces pneumonia, empyema, pericarditis, otitis, and meningitis, and occasionally arthritis and peritonitis. Most frequently in children it produces otitis media and associated lesions, pneumonia,—either of the lobar or lobular type,—etc. Occasionally catarrh of the upper air passages alone exists, and one has seen large abscesses in the neck result from the pneumococcus; also laryngitis and tonsillitis of a somewhat epidemic type. In more fatal cases it may give rise to actual septicæmia, and sometimes to pyæmia.

The pneumococcus may be classed with the streptococcus, and the vaccine made accordingly. An average dose of the pneumococcus to start with would be 5 million, but with a freshly

prepared autogenous vaccine 1 million would suffice as an initial dose.

In chronic abscesses due to the pneumococcus good results can be obtained. In lobar pneumonia it is debatable as to whether the vaccine does any good or not. There are, however, statistics which show that the pneumococcus, given in the early stages, produces an abortive crisis. In the late stages there are no definite results. The pneumococcic vaccine can be prepared within thirty-six hours from an acute case; in this condition the sputum swarms with the pneumococcus and a pure culture can be readily obtained. In a chronic or unresolved form of pneumonia the story is different. Some pneumonias do not go on to resolution, but drag on with pyrexia and a persistence of consolidation. These appear occasionally to resolve under pneumococcus vaccine given in slightly larger doses, beginning with 5 million and going on to 10 million and so on to 100 million of the patient's own pneumococcus, which under these chronic conditions is never highly virulent. The virulence of pneumococci rapidly deteriorates in artificial cultures, so that where 1 million of a freshly prepared autogenous vaccine will be all powerful, considerably larger doses of an old culture or a stock vaccine may be quite inefficacious to produce any reaction whatever.

In otitis media of children, where an organism is obtained which is morphologically identical with the pneumococcus, but which does not seem to be very virulent, marked results follow from the

pneumococcic vaccine. It is easy to get the pus uncontaminated in middle-ear disease, and to get a pure growth of colonies of pneumococci.

In dealing with empyema, if the culture is obtained immediately it is opened, a pure pneumococcus may be obtained; in the course of a short time it is likely to become contaminated with other organisms, which will outgrow the pneumococci in cultures. It is sometimes useful to treat these secondary infections with appropriate vaccines.

A characteristic feature of pneumococcic infections is the marked toxæmia often accompanied by great weakness and prostration. In the pneumococcal catarrhal conditions, not only has improvement been noted, but the toxæmic symptoms appear to be much allayed.

Gonococcus

The lesions due to the gonococcus vary from a simple localised urethritis to a general septicæmia. The urethritis may be superficial and readily heal, or it may spread to the follicles and lacunæ of the urethral mucosa or the glands and set up a chronic gleet. The other lesions include ascending cystitis or pyelitis or pyelonephritis, acute or chronic prostatitis in the male, and vaginitis, cervicitis, metritis and salpingitis and even peritonitis in the female, all spreading by direct continuity; generalised infections producing commonly, inflammations of the joints and synovial sheaths and, rarely, general septicæmia with occasional localised manifestations of an

infective endocarditis; and finally conjunctivitis by direct inoculation.

The gonococcus is readily killed, and in fact dies shortly after removal from the body. But the chronicity of infection is due to the impossibility of attacking it directly when it has worked its way into the follicles and glands of the urethra or the cervix. Local applications fail to reach it, and it slowly proliferates until it reaches the surface, when it may set up an acute urethritis again, or merely manifest itself as a chronic gleet.

Furthermore, in the chronic stage, not infrequently other bacteria are superadded to the infection, generally obtaining access from without, *e. g.* staphylococci, B. coli, B. pyocyaneus, etc. (see Chap. XIX), and these either share in the production of the chronic inflammation or perhaps outgrow the gonococci entirely and maintain the urethritis by themselves.

Vaccine therapy is undoubtedly of value in chronic cases, and more especially where the inflammation is being maintained by other organisms than the gonococci. In acute cases its value is less definite, but in them it is of great use to prepare an autogenous vaccine whilst the discharge is profuse in case the disease enters into the more chronic stage.

The vaccine is difficult of preparation, and failure is often encountered. The gonococcus is best grown on human blood-agar; some recommend ascitic-agar and others rabbit blood-agar. Where there is a profuse discharge it is perhaps easier,

but in the long-standing cases where only a few threads appear in the urine, it is often impossible. In these it is better to obtain the first morning urine, which should be collected in three tubes after washing the meatus, in the manner described on p. 225. The sediment should be rapidly obtained by centrifugalising, and inseminated on to the blood-agar and the tubes immediately put to incubate. In all cases the cultures must be started immediately, for the gonococci rapidly die unless kept at body temperature.

Occasionally the chronic gleet may be incited to activity, and hence to a more plentiful discharge by administering a dose of stock gonococcus vaccine of about 10 million the night before the specimens are to be taken. If no gonococci are obtained or if the cultures be mixed, a vaccine can be prepared from all the organisms and used with good results and often complete and rapid cure.

The remarks regarding stock vaccines apply particularly to gonococci, and the variation in virulence of such, resulting from long preservation or many generations of sub-cultures, will account for the varying results reported and the varying dosage recommended.

As to dosage, the gonococcus is treated like the streptococcus. A virulent vaccine made from a case of recent infection can be used in an initial dose of 1 million and continued at intervals of a few days in doses of 5, 10, 20, 25 millions, and if necessary even higher. Evidence of activity is

often obtained in the form of a localised inflammation around the site of infection and an increase in urethral discharge.

In inflammation of the joints and bursæ due to the gonococcus or leucorrhœal discharges of different bacterial origin, vaccine can be prepared from the discharges and used with satisfactory results, but often there is no urethritis at the time of the joint exacerbation, and then it may be necessary to employ a stock gonococcal vaccine in the specific cases.

In the present state of our knowledge it is, moreover, unwise to rely solely on the vaccine treatment of gonococcal infections.

Other Infections of the Urethra

With regard to the urethra, some organisms that produce a urethritis have already been mentioned. These include the *gonococcus*, the *bacillus coli*, and the *staphylococcus*.

When a urine from a bladder is obtained swarming with organisms, it is not always permissible to deduce that these organisms are the cause of the bladder condition, they may be only the result. Many of them will only disappear when the bladder is drained, and treated by surgical methods.

B. coli group

Another important group of infective micro-organisms is the so-called *colon group*, which includes the B. coli, the B. typhosus, and

various dysentery bacilli. Of these, the colon organism has been the most fully worked out. The B. coli, normally present in the body, can set up pathological processes when circumstances are suitable. It can, for example, produce cystitis, pyelitis, pyelo-nephritis, appendicitis and peritonitis, inflammation of the gall-bladder, and sub-phrenic abscess. In other conditions the bacillus enters the urethral tract, and can even spread up into the bladder, to result in a cystitis. In this latter case a severe pyrexia, with occasional rigors, is associated with highly acid urine, frequent micturition, and sometimes pus in the urine. The urine is turbid with bacilli, which can be readily cultivated on suitable media. In children, especially, this condition must be borne in mind in cases of acute illness with pyrexia. A vaccine can be made and dosed out in a manner comparable with the staphylococci. A coli bacilluria can be rapidly cleared up by the use of vaccines. In the acute cases, especially in children, the bacilli disappear from the urine and do not return. In children and in enfeebled or old patients, a start is made with a dose of 5 million, in adults with 25 million.

An infection of the kidney, probably of hæmic origin, is occasionally found associated with pregnancy—a condition described as *pyelonephritis of pregnancy*—or the puerperium, and is characterised by a condition of acid pyuria. This is due to the B. coli and is amenable to vaccine treatment. But the chronic cases, though they

respond rapidly to vaccine treatment, often recur when the treatment is stopped, and hence it is necessary to give prophylactic doses at intervals of a few months, especially in old people (Fig. 46).

Urethritis due to *B. coli* is not uncommon and is often mistaken for gonorrhœa.

The question of bacteriotherapy in typhoid infection is one that has received much attention, more from the prophylactic aspect than from any other, but up to the present this line of treatment has not served to cure cases of typhoid carriers.

It is necessary, in dealing with the question of vaccination with B. coli, again to emphasise the importance of autogenous vaccines. It is possible to obtain stock vaccines which may do good, but it is better to cultivate the patient's own bacillus. Mucous colitis and ulcerative colitis have been treated with B. coli vaccine, but though the latter offers more hope of success, the former hardly comes into the category of bacterial diseases.

Bacteria of the Respiratory Tract

Vaccines of all sorts have been prepared to treat bad colds, pneumonia, bronchitis, bronchiectasis and similar conditions. Of the organisms found, the *micrococcus catarrhalis* is the common cause of repeated nasal catarrhs. The micrococcus catarrhalis vaccine can prevent the recurring colds from which so many people suffer during the autumn and winter. It will also prevent attacks of acute bronchitis that accompany chronic

emphysema or any chronic pulmonary condition. In acute nasal catarrh and acute bronchitic attacks it is quite easy to isolate the rapidly growing micrococcus catarrhalis and make a vaccine. This should be given in an initial dose of 10 million, and then at intervals of six or seven days, in increasing doses. Occasionally severe malaise results from even small doses; if so the same or a smaller dose should be given and the intervals prolonged.

Friedlander's bacillus occasionally is found in nasal catarrhs and in chronic bronchitics during exacerbations. Good results accrue from a vaccine of this in initial doses of 10 million. In a recent case of sub-acute multiple arthritis in a young girl, this organism was isolated from a chronic nasal discharge which also existed, and after the first few doses there was a marked improvement in the joints which had been getting steadily worse for several years.

Bacillus influenzæ has also been isolated, but the results of treatment are indefinite.

Pneumococcus is occasionally the predominating organism, found during the exacerbations of bronchitis, though it is apparently of low virulence. It has been used with success as a prophylactic vaccine during the winter months.

In bronchiectasis vaccines may occasionally prevent the mischief which arises from secondary infections, but no treatment can repair the structural changes that characterise this diseased state.

Staphylococci and streptococci are occasionally found in pulmonary infections, and vaccine therapy is occasionally of benefit.

Vaccination has been suggested in asthma. But the true neurotic type of asthma is most likely not due to bacteria at all, and the bronchitic asthma has been already mentioned.

B. tuberculosis

With regard to the lesions resulting from the tubercle bacillus it need only be said here that in localised chronic tuberculosis of glands, bones and joints, and in lupus, and in genito-urinary diseases, tuberculin has done a remarkable amount of good, whilst in picked cases of pulmonary tuberculosis equally good results can be obtained. The tuberculin treatment will be specially dealt with in Chap. XXVIII.

Infective Conditions of Joints

Arthritis is the result of many conditions. The gonorrhœal and leucorrhœal varieties have been already mentioned. Subacute arthritis and some varieties of so-called rheumatoid arthritis are often associated with distinct bacterial lesions elsewhere in the body, as, for example, in the case cited above, in which a chronic rhinitis with Friedlander's bacillus existed. Occasionally, there is a suppurative process in the sinuses of the nose and cranium, or a septic condition of the naso- or buccal-pharynx, or a chronic catarrh

of the cervix uteri. The bacteria in these cases include: staphylococcus pyogenes aureus, streptococci, B. coli, etc., and they can be isolated and used as vaccines with very satisfactory results. Often a condition of pyorrhœa alveolaris is found and isolation of an organism from this may result in a satisfactory vaccine being obtained. But in cases of chronic sinusitis, or suppuration in an antrum, or of pyorrhœa, the treatment is only palliative and should be accompanied by local treatment, where such is indicated. In an article recently published a medical writer, suffering from chronic arthritis, describes the good, though palliative results of constantly vaccinating himself with a staphylococcus obtained from a nasal discharge. In another case a course of streptococcus vaccine obtained from a culture from the throat produced complete cure of the joint affection.

Where no definite focus of infection can be found, as occasionally occurs in young married women, recourse may be had to a bacteriological investigation of the fæces and occasionally from them an organism may be isolated and used tentatively, and sometimes with satisfactory results. Nevertheless, there still remains a series of cases, often in younger adults, which run their crippling course, despite all treatment.

In the long-standing cases of chronic arthritis either of the monarticular variety or the multiple variety, in all of which there is much crippling from the growth of osteophytes, little if any good can be expected from vaccine therapy, and indeed,

it is impossible to locate any source of infection. It is natural to suppose, and most probable, that these cases are the result of long continued intoxication, perhaps of intestinal origin. In these, vaccine therapy can merely be advocated as a means of varying the treatment to benefit the patient by suggestion.

Pyorrhœa Alveolaris

This is also a condition that has come into the sphere of the bacteriotherapist. Here, however, it is most probable that there is an underlying caries or periostitis to which has been superadded an infection with pyogenic organisms. Though we do not think that the condition can be cured when it exists to any degree, nevertheless, much good can be done by attacking the pyogenic organisms with vaccines. The difficulty lies in isolating a specific bacterium from the prolific flora that abounds in the discharges. By using special media, based on the observation that the reaction of the buccal secretion becomes acid under these conditions, the author has succeeded in isolating a streptococcus which grows readily, and when made into a vaccine has been used with much success (see p. 275).

Sensitised Vaccines. Recently there has been advocated the use of vaccines which have been *sensitised* by admixture with the corresponding anti-serum, where such can be obtained.

CHAPTER X

BACTERIOTHERAPY (*continued*)

Prophylactic vaccination—Smallpox—Rabies—Typhoid fever —Plague—Coley's fluid—Lactic acid bacilli.

THUS far we have discussed the use of bacteria in the treatment of disease only in connection with curative therapeutics. But the use of vaccines as prophylactic agents was in vogue long prior to this.

In some cases even, *e. g.* smallpox, in which the causal agent has not yet been isolated, material from an infected person or animal, which contains the virus, was, and even at the present day is, used to produce a condition of immunity in healthy persons. It is known that in infected cases the virus of smallpox is contained in the vesicles, and that of rabies in the spinal-cord, so that inoculation of material from these parts will produce the disease experimentally.

Prophylactic vaccination is employed at the present day against smallpox, rabies, typhoid fever, plague and cholera in man, and against anthrax, pleuropneumonia, distemper, etc., in animals. In all cases an attenuated virus is employed.

The variation in virulence of the virus or

bacterium is brought about in many ways. In smallpox the virus of cowpox is used for vaccination, and it is almost certain that this is indeed a modified form of smallpox. This latter has been transmitted to calves and converted into typical cowpox, the lesions from which have given a virus for human inoculation.

In rabies attenuation of the virus results from desiccation of the spinal-cord of a rabbit. The treatment of a suspected case is begun by injecting material from a cord that has been dried for fourteen days, and rapidly followed by injections of increasing virulence until a cord that has been dried for only three days is employed; during this process the patient has become highly immune to rabies. The whole process occupies from two to three weeks, which is within the limits of the incubation period of the disease.

Anthrax vaccines are attenuated by keeping the bacilli at a temperature of 42° C., and are only used in animals.

Prophylactic vaccines in man are always made from dead bacteria: typhoid and plague perhaps have shown most successful results.

Typhoid Fever

Vaccination against typhoid fever is advocated in the case of emigrants or troops or travellers to India and Africa, and other places where typhoid fever is endemic. Bacilli killed at a temperature of 60° C. are injected deep into the subcutaneous tissues of the flank or chest

in a dose of 1,000 million. The injection is repeated in ten to fourteen days with 2,000 million bacilli. The immediate reaction varies with the dose and consists of local tenderness with slight pyrexia and malaise lasting twenty-four hours; in more severe cases marked tenderness or local inflammation with severe malaise, sickness and pyrexia lasting for several days.

Statistics as derived from the army records tend to prove that this line of treatment results in a decided reduction in incidence, in severity, and in mortality of typhoid fever.

Plague

Prophylactic vaccination has produced better results than curative antiserum described on p. 136. Haffkine's vaccine, which consists of killed broth cultures of the B. pestis, produces an undoubted immunity. The injections also produce local inflammation and general malaise and pyrexia; they are to be repeated two or three times. Most favourable results have been reported in India with this line of treatment.

Vaccines have also been used against cholera and dysentery with doubtful results.

An important point is the duration of the immunity to infection produced by these vaccines. This is very variable. It is thought at present that with smallpox the duration of immunity is about seven years; with typhoid vaccines about two or three years, and with plague several years.

Coley's Fluid

Under the heading of bacteriotherapy must also be discussed other attempts to treat disease by means of bacteria.

It was known long ago that an attack of erysipelas altered considerably the progress of a new growth, which sometimes, indeed, disappeared. As a result of this, an attempt has been made to treat tumours by means of what is known as Coley's fluid, consisting of a mixture of the streptococcus erysipelatis and the bacillus prodigiosus, both having been killed at 60° C. In cases of inoperable tumour the method is worth trying. At first the mixture is given to the amount of a quarter of a minim into the neighbourhood of the growth; if the patient is weak, one-sixteenth of a minim will suffice. If the temperature should rise the next dose must be delayed until it falls to normal; in the absence of such the injection is to be repeated next day; the amount given is increased at each dose by a quarter of a minim, and the treatment is continued until there are signs of improvement. After each injection there should be a reactionary rise in temperature. From one-sixteenth of a minim the dose may be increased gradually to six or eight minims, or occasionally to as much as twenty minims. An improvement should be noticed after three or four weeks, otherwise the treatment should be stopped. Good results have been obtained in sarcomatous tumours.

Lactic Acid Bacilli

A word may be said finally about the actual bacterial treatment of disease, which is an attempt to oust bacteria from the position they may have taken up by means of other more prolific bacteria. The lactic acid bacillus, for example, may be made to proliferate in the intestinal canal at the expense of the saprophytic germs which set up putrefaction and consequent toxæmia. Lactic acid bacilli are given in milk, in which media they grow rapidly, and produce clotting. In the course of a few days after administration they practically form the bulk of the organisms found in the stools and the intestines. Lactic acid bacilli are also used in the treatment of chronic fistulæ and diseases of the mucous membranes.

Numerous other organisms produce coagulation of milk; hence the varied preparations on the market are more or less under suspicion, more especially the dried preparations which contain other organisms, such as streptococci and the like. Therefore it is always better to use liquid cultures themselves contained in the clotted milk. It seems highly probable that this line of treatment is very efficacious in counteracting the simple putrefactive changes in the intestine, but of little use in dealing with the more severe pathogenic bacteria such as in typhoid fever. It is, at least, in the former condition that the author has found it the more useful.

CHAPTER XI

SERUM THERAPY

Definition—Normal sera—Antitoxic sera—Antibacterial sera—Toxins; elective activity of diphtheria and tetanus—Endotoxins—Serum sickness—Anaphylaxis—Antitoxic sera; diphtheria; tetanus. Antibacterial sera; streptococcus, meningococcus, pneumococcus, anthrax, plague. Antivenoms—Normal serum.

SERUM THERAPY concerns itself with the use of blood serum in the treatment of disease. Already we have seen that serum of normal animals contains various specific antibodies which can counteract various infections, and that also it is possible to stimulate an increased production of these by means of artificial injections of bacteria.

These antibodies can be formed in normal animals, the serum of which ultimately containing copious antibodies can be collected and stored for immediate use against the infective conditions produced by these toxins. Or, if time permits of delay, as in the more chronic infections, they can be formed in a patient himself, and used in increasing the defensive property—this is described under the vaccine therapy. Or, finally, with certain infections, if a modified virus can be obtained with a lessened inoculation period it is possible even after the start of the infection to induce an immunity which will inhibit the develop-

ment of the disease. In rabies and smallpox this latter method is employed. In rabies a virus so modified that its incubation period is reduced from weeks to days is inoculated in increasing doses into a patient, so that a condition of immunity to virulent doses is produced before hydrophobia has time to develop, necessitating, as it does, an incubation period of some weeks. The case is similar in smallpox. Cowpox—a modified form of smallpox—can be inoculated into a patient, even after he has acquired smallpox, and by virtue of its slightly reduced incubation period it can produce a degree of immunity which either inhibits the disease or considerably modifies it.

The application of serum containing natural or artificially induced antibodies constitutes what is called serum therapy. Such treatment is really an attempt to produce passive immunity, which has to be sharply distinguished from the active immunity produced in the patient himself by the injection of dead bacteria, as in vaccine therapy, or by the injection of a modified virus, as in the treatment of rabies and smallpox.

Under the heading of serum therapy must be discussed—

(1) Normal serum.
(2) Antitoxic sera.
(3) Antibacterial sera.

It has already been said that normal serum contains various antibodies. A true appreciation

of the bactericidal power of normal serum would suggest its use as a therapeutic aid in infective conditions. Only in recent years have attempts been made to employ the natural antibodies in various diseases; for this purpose horse serum is used.

But the antagonistic power of normal serum is slight as compared with the sera in which the production of immune bodies has been artificially stimulated; so that it will be more useful to discuss, in the first place, these latter.

Toxins and Antitoxins

Before entering into a discussion of true serum therapy, it is necessary to say a few words about toxins and antitoxins. Some bacteria produce toxins outside themselves which are called exo-toxins; of these the toxins concerned in diphtheria and tetanus are among the best examples. Other bacteria produce no toxins outside their bodies, but it is thought that they have in their protoplasm endo-toxins which are only liberated when the bacteria die: to this group belong the organisms in typhoid and plague, the streptococcus, the staphylococcus, and a large number of others. In a third group, which includes B. tuberculosis and B. mallei, there are produced both exo-toxins and endo-toxins: this group will be described in the section which treats of the utility of tuberculin.

The term "toxin" is best applied to any substance which when inoculated into animals produces

definite antitoxin, so that at the present time this would restrict us to the so-called "exo-toxins." Toxins may be either bacterial, animal or plant in origin. The bacterial toxins are soluble bodies produced in the surrounding medium by certain bacteria growing therein, which when injected into animals are capable of producing symptoms like those resulting from the bacteria themselves. These include the products of activity of the bacilli of diphtheria, tetanus and botulinus. The animal toxins include snake-venom, eel-venom, etc.; the plant toxins are those of ricin, abrin and croton.

These toxins are extremely potent. The most minute application of a culture of tetanus is fatal to animals. They are unstable to heat and light, and a temperature of 60° C. will rapidly kill them. After injection there follows a variable period, resembling an incubation period, before their activity is exerted. Furthermore, these toxins have a peculiar elective method of working in that they fix upon different tissues and exert their influence by virtue of this combination. For example, the tetanus toxin, soon after its administration, works its way up the nerve sheaths, and combines with the motor cells of the anterior cornu, and hence there results the marked symptoms of stimulation of the motor regions. The tetanus toxin, indeed, forms so firm a combination with the cells of the brain and spinal cord that it may be impossible to separate it during life. The importance of this is that, when dealing with the antitoxic treatment of these infections, the

longer the delay in treatment the firmer will be the combination of the toxin with its selective cell and the more difficult will it be to break down that combination. This is the explanation of the hopelessness of injecting antitoxins when the disease is considerably advanced. Tetanus toxin and its antitoxin, mixed together outside the body, will produce when injected into the body no symptoms whatever. But if the antitoxin of tetanus be injected shortly after the toxin it will require a larger amount to counteract the effect than when they were mixed outside the body. And if the administration of the antitoxin be delayed until the cerebral and motor cells have formed a firm union with the toxin, no quantity of antitoxin will break down that combination or stop the progress of the disease.

When injected into animals in small or non-virulent doses these toxins produce a condition of increasing immunity, which after repeated and increasing doses becomes so marked that the animal acquires a complete immunity to the toxin; the serum of the animal so treated constitutes an antitoxic serum which is very potent in counteracting the effect of the specific toxin. But the antitoxic serums themselves will not counteract the action of the bacteria. On the contrary, the diphtheria antitoxin rather stimulates the growth of diphtheria bacilli than otherwise. Therefore it is useless to employ the diphtheria antitoxin as a local application to the throat.

It will be seen that toxins differ essentially from true alkaloidal poisons such as strychnine. These latter exert an immediate toxic activity, though often exhibiting an elective combination with certain tissues such as the anterior cornua cells. They never produce antitoxins.

Antibacterial sera

In addition to the antitoxic serum, there is prepared from the bacteria that produce no toxins outside themselves an antibacterial or bactericidal serum by injecting bacteria; these contain the endo-toxins, and so differ from the filtered cultures containing the toxins. Antibacterial sera are sera containing antibodies that counteract and sometimes destroy, sometimes even dissolve, the bacteria themselves. The serum of an animal immunised to cholera bacilli, for example, will cause a rapid solution of cholera bacilli when brought into contact with them. It is hoped that these sera are of use against those bacteria that do not form definite toxins in their surrounding media, but rapidly proliferate and spread throughout the body. These include, as already stated, the organisms of typhoid, dysentery, cholera and plague, and the streptococcus and staphylococcus. These sera are far from being as efficacious as the antitoxic sera which are produced in response to infection of definitely known toxins which can be isolated apart from the bacteria. The endo-toxins are more indefinite bodies, supposed to be formed within the bacteria

themselves and only liberated from them after the death of the organism. They have a greater resistance to heat, etc., and in many ways their behaviour differs from that of the true toxins. The difficulty of obtaining these so-called endo-toxins is great. Attempts have been made to obtain them by maceration of the bacteria, or, as they are not altered by low temperatures, by crushing the bacteria at the temperature of liquid air. But it is evident that the endo-toxins are not of the same nature as, and, therefore, are not exactly comparable with, the ordinary toxins.

Serum Sickness

All these antitoxins or antibacterial substances are administered in media of horse serum, from which, indeed, many of them have not yet been isolated. It seems that the administration of these antibodies is perfectly harmless, but in the administration of horse serum itself there lies a danger. Many peculiar sequelæ of serum treatment which have been observed ever since its introduction are now known to be due to the effect of a serum from a different species of animal. Some patients who had been treated with anti-toxic serums were observed, after a certain latent period, to show sequelæ such as rashes, urticaria, pains in the joints and pyrexia; occasionally the symptoms were even more marked. According to some workers, one-third of the patients who were treated with antitoxic serum suffered from this " serum sickness," though as a rule only of a

mild type. This has been shown to be due to the horse serum itself and not to the antitoxin. The serum of an animal inoculated into another of a different species is liable to produce serum sickness.

Concentrated antitoxic sera are now produced by a process of precipitation, and the use of these appears to do away with many of the concomitant symptoms classed under the heading of "serum sickness." The efficacy of these sera is at least equal to the ordinary varieties.

Anaphylaxis

But there is a more important and more fascinating point. Animals which have been treated with an injection of serum—even horse serum itself—when reinoculated with a much smaller dose of the same serum after an interval of twelve days or more, are affected with symptoms that vary from mild vomiting, mild cardiac disturbance and slight pyrexia, up to severe respiratory disturbances, suffocation, collapse, rigor and convulsions, followed sometimes by death. This phenomenon, which points to an increased susceptibility where from the earlier work on the subject an increasing immunity would have been expected, is known as *anaphylaxis* or hyper-sensitiveness. So severe is the reaction in some cases that experimental guinea-pigs, inoculated with a small dose of horse serum, have died instantly when reinoculated a fortnight later with a much smaller dose of the same serum. That is an extreme example of anaphyl-

axis. This same condition is met with when dealing with repeated inoculations of antitoxin in human beings. Thus, whereas previously we had looked for an increasing immunity with successive inoculations we now have to bear in mind the possibility of an increasing susceptibility, rendering our use of sera a very difficult and troublesome problem.

As soon as the new work on this subject was put forward, asylum superintendents, who were accustomed to use largely diphtheria antitoxin, adduced clinical evidence in support. They had frequently observed that patients who had had a prophylactic or full dose of diphtheria antitoxin at some time in their lives, and who some years later acquired diphtheria and were reinoculated, showed symptoms of anaphylaxis after a curative dose, and occasionally died.

Anaphylaxis can be produced against serum, or milk injections or bacterial extracts and various foreign protein materials, or against egg-albumin, always accompanied by the same series of events as that just mentioned. But the protein material must be one foreign to the experimental animal. It is not possible to obtain anaphylaxis by inoculating the serum of one animal into an animal of the same species. Furthermore, the production of anaphylaxis necessitates an interval of twelve days or more between the two injections. The condition can be produced by feeding the animal with the serum or protein in question as well as by injecting it. The symptoms include slight

irritation, slight cutaneous trouble, more severe cardiac and respiratory disturbances, collapse, paralysis, convulsions and sometimes death. The condition of anaphylaxis can be produced in a passive way by inoculating into an animal the serum of another animal that has already had one injection. There is, further, a condition of congenital anaphylaxis. If a pregnant woman has had an injection of serum, the child subsequently born may, after another injection, present symptoms of anaphylaxis.

It is interesting to note that anti-anaphylaxis can be produced. A guinea-pig which has been given injections of small doses of serum daily for ten days or more becomes refractory and no longer gives evidence of anaphylaxis.

The period during which it is possible to obtain anaphylaxis by reinoculation is an important point to the clinician, but it is widely variable. From a period of twelve days it may last up to a few years, and probably in some cases for life. The importance of the condition in these days of widespread antitoxic treatment will be obvious. The facts are not sufficient to help us, and at present we do not seem to have any method of combating it, or of determining whether a patient, requiring a second course of treatment with antitoxin, will or will not develop these symptoms. But so many injections have been made, and so much serum has been used with so few fatal results that for the present it is legitimate and advisable to continue using anti-serum as before.

We may say in passing that the phenomenon of anaphylaxis may in some way be closely connected with such diseases as hay fever, urticaria, etc.

At the present day many anti-sera are on the market, and as so many of these are useless in that they are not formed on scientific principles, it follows that the value of the antitoxin treatment is belittled. Nevertheless, in some infections *antitoxic* sera offer the only justifiable means of treatment. Especially is this so in the treatment of diphtheria, which is now so well understood that one need not even touch upon its absolute superiority to all other lines of bacterial treatment against any infection.

The respective sera are specially prepared, dosed out in units according to their capacity for counteracting the lethal dose of toxin, and supplied in sterilised phials. The injections have to be given either subcutaneously or, in cases of emergency, where it is necessary that the antitoxin should come into immediate contact with the toxin, intravenously; or, when it is required to get it into direct contact with certain parts of the body, as in the case of tetanus, the injection may be made into the cerebro-spinal canal or directly into the brain. There are no dangers in antitoxic injections, beyond anaphylaxis; hence the antitoxin, counteracting as it does the toxin itself in definite quantities, must be given in sufficiently large doses to produce any good result. Probably some of the poor results that have accompanied the administration of antitoxins are due to too small doses.

Diphtheria antitoxic serum

It will be necessary to bring a few of the antitoxins separately to the consideration of the reader.

The *diphtheria antitoxin*, as is well known, is absolutely curative. The toxin of diphtheria in its elective attack on certain cells sets up marked degenerative changes, and therefore the longer that the treatment is delayed the more difficult it becomes to free the toxin from its combination. Hence, as soon as the condition is suspected, a dose of at least 2000 units for a child, and one of 5000 units for an adult should be injected. The result is rapid. There is marked improvement, and the membrane separates and may even disappear in the course of the following day. If there is great improvement the dose can be repeated, especially if in the meantime the diagnosis has been corroborated by the bacteriologist, and in severe cases with marked toxæmia even 20,000 units may be given, again subcutaneously. Although the diphtheria antitoxin is not antibacterial, yet a few days after the administration the membrane may have separated, and bacteria may no longer be found in the throat. This is a very important point in diagnosing cases of diphtheria after treatment. Swabs taken from the throat a few days after treatment with antitoxins frequently do not show any bacteria in culture. But despite the antitoxic treatment there are cases in which bacilli remain in the

throat for weeks or months after the patient is well. This class of patient forms the dangerous group of diphtheria carriers, and cannot be treated by means of antitoxins. Diphtheria carriers do seem to be rendered harmless by means of vaccine therapy directed towards increasing the patient's resistance to the bacteria themselves. There is also supplied an antibacterial serum which may have some direct effect in destroying the bacteria.

Diphtheria antitoxin is equally efficacious in other lesions resulting from infection with the B. diphtheriæ, such as ulcers of the skin, conjunctivitis, and in cases of vulvitis, which are not uncommon in children. As a prophylactic, in those who have been exposed to infection, it is also valuable, given in doses of about 500 units. But there is, perhaps, an additional danger in giving a prophylactic dose in that, years afterwards, the patient may acquire diphtheria, and on reinoculation suffer from anaphylactic manifestations.

Tetanus antitoxic serum

Tetanus is another example of a pure intoxication, resulting in a more or less firm combination of the tetanus toxin with the motor nerve cells—a combination which does not destroy the activity of the toxin, for after the death of the animal on maceration of the spinal cord or brain the tetanus toxin can be again obtained in a virulent condition. Experimentally the inoculation of a lethal dose of tetanus toxin previously mixed with

a definite amount of antitoxin produces no bad effects. The same dose of toxin injected alone and followed by the same dose of antitoxin is not so harmless, and the longer the interval between the two injections the larger must be the dose of antitoxin to counteract; indeed, when the interval is so prolonged that symptoms have already set in, it is often impossible to break down with any quantity of antitoxin the combination of toxin and the elected cells. Hence in the treatment of tetanus the antitoxin ought to be given in large doses as early as possible. The toxin apparently spreads slowly up the nerve trunk. This is supported by the experimental evidence that excision of a portion of the main nerve of the limb even some time after infection prevents the spread of the intoxication; also injection of the antitoxin into the nerve sheath produces similar inhibition. When the spasms and definite clinical manifestations of tetanus appear, it is evidence that the combination is firm and it is too late, or almost so, to treat with an antitoxin. It is advisable to bring the antitoxin into the neighbourhood of the toxin in as large a quantity and as rapid a manner as possible. Hence the injection may be made beneath the skin, into the veins, into the cerebro-spinal canal, or, if possible, through a trephine wound into the lateral ventricles of the brain itself. The cases of tetanus that the author has seen recover were treated with large doses of antitoxin given hourly in every possible way—subcutaneously, intravenously and intraspinally.

The prophylactic use of the antitoxin is of importance. In view of the fact that tetanus cannot be diagnosed definitely until the symptoms develop, when, perhaps, the original wound has healed up, it is advisable in districts where tetanus is rife to treat every case of wounds which are contaminated with soil—especially crushed wounds—with prophylactic doses of anti-tetanic serum. A dose of 20 c.c. should be given at the time the wound is treated. The incidence has been greatly diminished by this method, especially in horses.

From these two classic examples of antitoxic treatment one passes to more debatable territory. The antitoxic sera can be accurately standardised against the lethal dose of the toxin, but the anti-bacterial sera cannot be so standardised.

Anti-streptococcus serum

Streptococci do not produce toxins to any marked degree in culture media. Consequently the anti-serum is produced by inoculating the cocci themselves into horses: it is, therefore, antibacterial in nature. Between the harmless organisms that inhabit the mouth and intestines (*S. salivarius* and *S. fæcalis*) and the highly virulent cocci of puerperal fever and acute septic-æmia there are streptococci which exhibit all grades of virulence. Hence it is customary to employ cocci from these different sources, and the resulting sera are named polyvalent; puerperal, erysipelas or scarlatina.

There are cases in which the injection of an

anti-streptococcic serum has produced immediate and permanent relief, but there are a greater number in which it has not affected the progress of the disease in the slightest. If the one variety of serum does not prove efficacious it is well to try the others, but, as in other serum-treatment, the longer the delay the less chance there is of doing any good. If there is the slightest improvement, a fall of temperature, an improvement in the pulse, or in the patient's general condition, the dose should be repeated in a few hours, and, if there is further improvement, repeated again. If there is no change, a different variety of anti-streptococcic serum may occasionally produce a fall of temperature and lead to improvement. The cases which have yielded best to such treatment are those of puerperal septicæmia. If the streptococcic infection is more chronic, as in a spreading case of erysipelas, attention can be turned to the production of the patient's own immune bodies by means of vaccine therapy, or the production of an antibacterial serum by treating an animal with the specific bacteria.[1]

Anti-staphylococcus sera are upon the market,

[1] Recently there has been published a case of chronic infective endocarditis due to the *streptococcus fæcalis* which, after resisting for months all treatment with autogenous vaccines and heterogeneous serum, responded markedly to an autogenous antistreptococcus serum prepared by inoculating horses with the cocci obtained from the patient herself. The writer has seen this lady, and there seems no doubt that she has recovered from the infective condition, and in all probability this was due to the autogenous serum (see *Lancet*, 1913).

but they have not proved of much service up to the present.

The *pneumococcus* no doubt produces its result by means of toxins, most of which are true endo-toxins derived from the bodies of disintegrating cocci, though there is some evidence pointing to the production of a true exo-toxin. These give rise to a marked intoxication, and it seems probable, therefore, that the satisfactory treatment of this disease will be in the form of an anti-pneumococcic serum. The difficulty, however, in preparing such a serum lies in the difficulty of obtaining the true intracellular toxin. More satisfactory results have accrued from using toxins expressed from the cocci at a temperature of liquid air. This does not destroy the cocci, and a toxin of extraordinary virulence is thus obtained. Up to the present many sera have been produced, but none are absolutely reliable. Flexner has recently produced a pneumococcus antitoxin for which good results are claimed.

Anti-meningococcus serum

The *meningococcus* is the organism concerned in cerebro-spinal fever. It is both sporadic and epidemic, producing either the posterior basic type of meningitis, or the acute "spotted fever." An *anti-meningococcus serum* is to be obtained. The statistics of the recent epidemics in America and in various parts of Europe show that the use of this serum has diminished the mortality considerably. There are two sera on the market,

one made in America by Flexner, and the other in Germany by Kolle and Wassermann. Of the two Flexner's has, perhaps, produced the better results. The important point is that the serum is bactericidal and must be brought closely into relationship with the bacteria. The injection is made into the cerebro-spinal canal. Seeing that the infection leads to a purulent exudate over the base of the brain, which of itself can bring about permanent mechanical effects that are worse than death, such as hydrocephalus, it is necessary to counteract the infection before the inflammation has advanced to such a degree. Hence the need for diagnosing the meningitis at the earliest stage possible becomes obvious. An injection is given into the spinal canal of 20 c.c. of anti-meningococcus serum, previously withdrawing some cerebro-spinal fluid. It is repeated, if there is improvement, in the course of a few hours, or even more frequently. In children 10 c.c. will suffice for each injection.

It has been shown that the serum from cases convalescent from this type of meningitis is bactericidal, and good results are recorded from the injection of such serum. In epidemics, this method is readily applicable as the serum can be obtained from blisters artificially produced.

For *dysentery* also there is an anti-serum which is said to be useful.

To combat the *bacillus coli* there is an anti-colon serum, which, however, has not been widely accepted.

Anthrax—Sclavo's serum

Anthrax, which is fortunately rare in this country, but which may be met with more frequently in other countries, produces a marked bacillæmia, in which organisms multiply in the blood stream. A serum is obtained by inoculating animals first with dead bacilli, then with increasing doses of live bacilli, until ultimately the animal becomes immune to virulent doses of anthrax. The serum of animals thus prepared constitutes the anti-anthrax serum, known as Sclavo's serum. It is antibacterial, and 30 or 40 c.c. of this ought to be given as soon as the malignant pustule is diagnosed; rapid improvement is seen in twenty-four or forty-eight hours. In cases of generalised anthrax or splenic fever it is necessary to inject this serum into the blood stream in large quantities Though it is doubtful whether any good can be done in these cases, there seems plenty of evidence that in localised anthrax the serum is itself sufficient to counteract the disease without surgical interference. The early diagnosis is again an important point, as the infection remains localised in the malignant pustule for many days before becoming generalised.

Plague—Yersin's serum

Plague has been treated by curative serum, known as Yersin's serum; this is produced by inoculating horses, sometimes for considerable periods, with dead and then with living plague

bacilli. The anti-plague serum has to be used in large doses of 150 to 200 c.c. There is evidence of slight diminution in mortality from the use of the serum, but it is not very gratifying.

Anti-typhoid serum, referring only to the anti-bacterial serum used as a curative measure in typhoid fever, is not hopeful enough to discuss; but it must not be confused with the prophylactic treatment of typhoid fever by typhoid vaccines.

A few of the other infections which are treated by antitoxins must be mentioned. Hay fever is now supposed to be due, not so much to the mechanical irritation of the pollen, as to toxic substances in the pollen cells themselves. Good results are reported in hay fever from an application of a powdered anti-serum in the form of snuff, or put into the eye in the form of drops, in the early stages of the condition, but there is not sufficient evidence to make more definite statements.

Antivenom sera

Comparable with the bacterial toxins are the snake venoms. Antivenoms can be formed against venoms exactly as antibacterial serums can be formed against bacteria. These antivenoms are absolutely antagonistic to the venoms themselves, but unfortunately they are to a great extent specific; the antivenom of one species, for example, is different from that of other snakes. This necessitates the production of antivenoms

against the local venomous snakes in each district, but it is perhaps better to prepare an antivenom of a polyvalent type against the numerous venoms found in the district. The toxins in snake venoms have a markedly toxic action, which is hæmolytic, dissolving the red blood corpuscles; leucolytic, dissolving the leucocytes; hæmorrhagic, interfering with the coagulability of the blood; neurotoxic, affecting the nerve cells; and cytolytic, dissolving the various tissue cells.

Lasting power of sera

A point of practical importance is concerned with the duration of potency of these anti-sera, especially as they have to be sent to remote parts of the world and often stocked for some time. Only a very slight depreciation in potency occurs, and this in the course of years. Some manufacturers allow for this in their dosage and append tables showing the maximum of depreciation, and by adding a little to each phial, accurate dosage, at least with the antitoxic sera, can be carried out.

Normal serum

A few words ought to be said about the use of normal serum itself in diseased conditions. This has been advocated very widely by Hort, who claims excellent results from the application of horse serum to various ulcers, both external and gastric; some hopeful results have been described in conditions of hæmophilia, after using 30 to

40 c.c. of serum. The serum is usually preserved after heating to 56° C., which does not appear to affect its power; in some places it is possible to obtain fresh serum collected in as aseptic a manner as possible, though absolute sterility cannot be guaranteed. This can be given by the mouth in repeated doses. Local ulcers can be bathed with horse serum, and good results follow. Horse serum can also be given internally as a food, and for weeks patients have been kept nourished by this means. From 30 to 50 c.c. are advocated for children, and from 100 to 150 c.c. for adults. Hort himself has given 30 c.c. daily by the mouth for many weeks.

As a continuation of what has been said about the use of normal serum with its antibodies for the specific purposes of counteracting the infection, the reader ought to be reminded that Bier's treatment for chronic joint infections and chronic inflammations depends upon the fact that the part is flooded with a large amount of blood serum; this produces much the same effect as bathing the parts with a foreign serum, with the additional advantage that the patient's own antibodies are being employed.

CHAPTER XII

COMPLEMENT-FIXATION METHOD OF DIAGNOSIS

Wassermann reaction—Rationale—*Technique*—Typhoid fever—Glanders—Echinococcus disease—Infective diseases of unknown origin—Reactions in cerebro-spinal fluid in syphilis of central nervous system—Diagnostic import—Partial reactions—Para-syphilis—Congenital syphilis—Syphilis and abortion—Latent syphilis—Efficacy of treatment—Modifications of test—Conclusions.

THE Wassermann reaction is the popular name for the method of diagnosis known as complement-fixation or complement-deviation. It depends upon the observation that injection of the living system with certain bodies of proteid nature—cells, bacteria, vegetable poisons, etc.—results in the formation by the animal system of certain antagonistic bodies, called antibodies. The demonstration of the presence of these antibodies in the system gives specific proof of infection.

The bodies that are inoculated in order to produce antibodies are known as "antigens." We have seen that some of these antibodies, such as the agglutinins and the precipitins, act directly on the specific agent producing them, but others, as the cytolysins and the hæmolysins, will only act in the presence of a body which is called complement. It is with the infective agents that produce antibodies allied to this latter

group that we are concerned in this chapter. The two antigens that are concerned in the Wassermann reaction are the syphilitic virus and the blood corpuscles of the sheep.

Complement is a body which is common to all animal sera, and which in virtue of certain activities, and only in virtue of such, becomes obvious. Whereas these antibodies are specific for their antigens (for example hæmolysin is specific for the corpuscles, and antisyphilitic body is specific for the virus of syphilis), complement is common to all sera and is found in varying amounts in them. It is destroyed at a temperature of 56° C. rapidly, or at normal temperature in the course of twenty-four hours, or at most in two or three days. Though it cannot be isolated it can be utilised in the media of animal serum; for this purpose guinea-pig's serum, freshly obtained, is employed.

Infection with syphilis produces an antibody in the body fluids; this will combine with the syphilitic virus *in vitro* in the presence of a certain amount of complement which is absorbed or otherwise used up in the process.

Similarly in infections with typhoid bacilli or glanders bacilli antibodies are formed in the blood of the infected persons, which will combine *in vitro* with the specific bacteria and use up a certain amount of complement.

If, now, it can be demonstrated that this combination occurs when the three bodies are brought into contact it would be possible in the known presence of two, such as complement and antigen,

to test for the presence of the third or antisyphilitic body in a serum suspected of having come from a syphilitic patient, and hence diagnose the presence or absence of infection.

But there is no naked eye or microscopic changes resulting from such a combination of this class of antibody with antigen, and so no means of determining directly the change. Recourse is had, therefore, to another group of antibodies, which work in the way just mentioned, namely

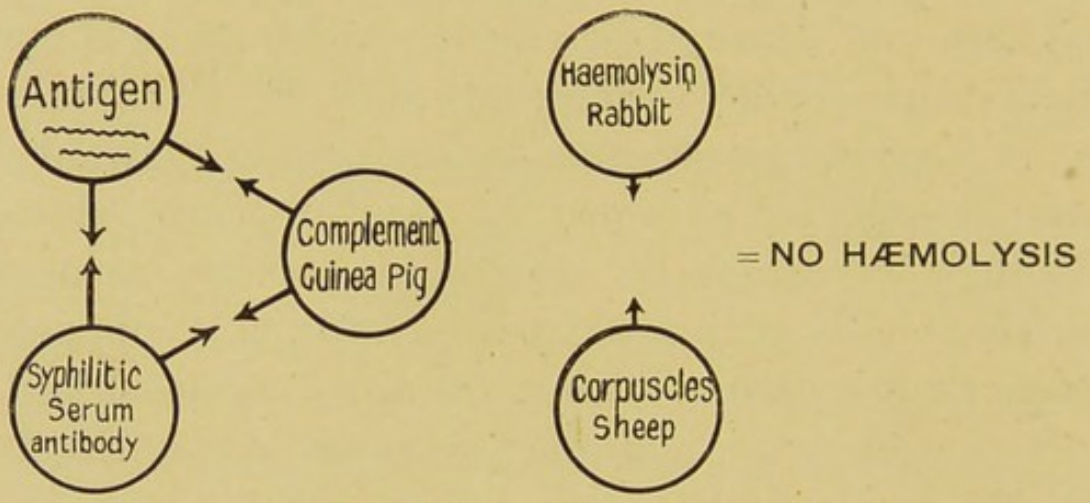


FIG. 17.—Scheme of positive reaction

the hæmolysins. A hæmolysin (contained in a serum) combines with the specific corpuscles that have incited its formation, using up in the process a definite amount of complement and results in a solution of the blood corpuscles so that the fluid mixture becomes red and transparent. In the absence of complement no hæmolysis occurs and the corpuscles sink to the bottom of the tube, leaving a clear supernatant fluid (Plate 5).

So that with the naked eye the activity of the hæmolysins can be determined. It is evident hat if hæmolysin and corpuscles are known to be

present in a mixture, it will be possible to test for the presence or absence of complement, which will be indicated by the resulting hæmolysis or sedimentation of the corpuscles respectively.

So, then, inasmuch as this hæmolytic system can be used to test for the presence of complement in a mixture, it can be used as an indicator of the combination or otherwise of antisyphilitic body, with syphilitic antigen in the presence of complement.

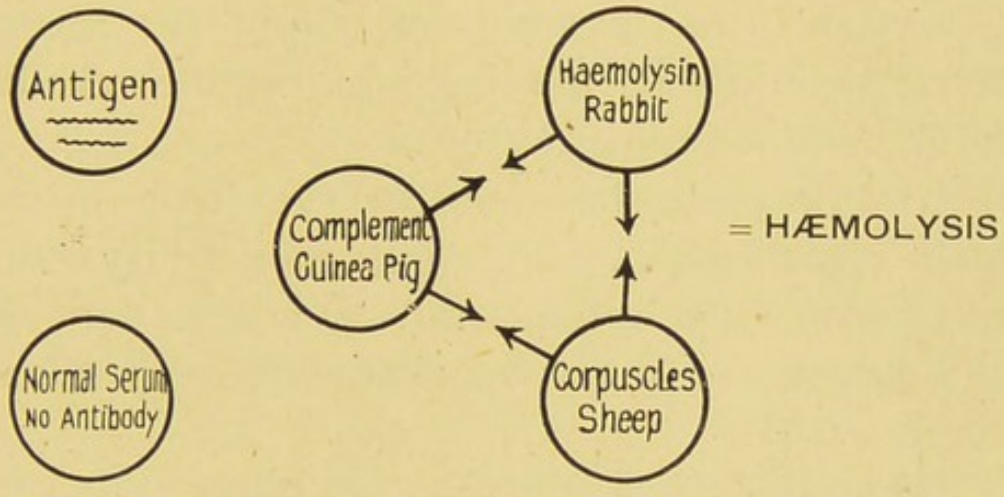


FIG. 18.—Scheme of negative reaction.

Starting with known antigen and complement the presence of antisyphilitic body in a serum to be tested will result in combination and fixation of the complement, so that on subsequently adding hæmolysin and corpuscles, no complement remaining, no hæmolysis occurs. And the serum to be tested must therefore have come from a syphilitic patient, for in him alone would anti-syphilitic body have been produced (Fig. 17).

On the other hand, starting again with antigen and complement, the addition of a normal serum will cause no change, so that on the subsequent

addition of hæmolysin and corpuscles the unaffected complement will be used up in producing hæmolysis; this demonstrates the absence of antisyphilitic body and hence the absence of infection (Fig. 18).

In short, given antigen, complement, hæmolysin and corpuscles, it is possible readily to determine the presence of the only variant factor, namely the antisyphilitic body, in a serum of an infected person.

The reagents requisite for the test are—

(1) Antigen, an extract of syphilitic virus, obtained generally by making an alcoholic extract of the liver of a syphilitic fœtus.

(2) Complement, contained in the fresh blood serum of a guinea-pig. This loses its activity after removal from the animal and in a few days is quite inactive, so must be obtained fresh when required.

(3) Hæmolysin, contained in the blood serum of a rabbit that has been treated for several weeks with a weekly injection of washed red corpuscles of a sheep into the peritoneal cavity. The serum is withdrawn in an aseptic manner, heated to 56° C. to destroy all complement and preserved in the cold. This can be made to hæmolyse sheep's corpuscles in a dilution of 800 or 1000 fold, or even greater, provided that complement be also added.

(4) Sheep's corpuscles, obtained from the abattoir; the blood is immediately defibrinated by whipping and then washed repeatedly with

normal saline to remove any traces of sheep's serum.

(2), (3), (4), in admixture, should result in complete solution of the corpuscles, and the reagents are titrated to determine the dilution necessary to obtain complete union of these three elements.

(5) Sera from a normal and a syphilitic patient, obtained in a wide-bored tube by capillary action from pricking the lobe of an ear, are used as controls. Sufficient serum can be obtained by this means, so it is unnecessary to puncture a large vein (Fig. 41). The sera are heated to 56° C. for half-an-hour to destroy all the natural complement. The reagents are all standardised to produce a complete reaction with the known syphilitic serum, but it is unnecessary here to dwell on the minutiæ of technique, which indeed are only acquired by long practice.

A preliminary control test is carried out with the known syphilitic and non-syphilitic sera.

The procedure followed in making a test may be recapitulated. In the first place the patient's serum is taken, and heated to 56° C. in order to destroy the natural complement it contains. Two tubes are used for testing each serum and into each is placed a volume of serum. In one tube is placed a volume of syphilitic antigen; in the other the antigen is replaced by a volume of saline. The volume in each tube is the same, and to each is added a volume of complement. The contents of the tubes are then mixed and put in the incubator. The result is as follows:—

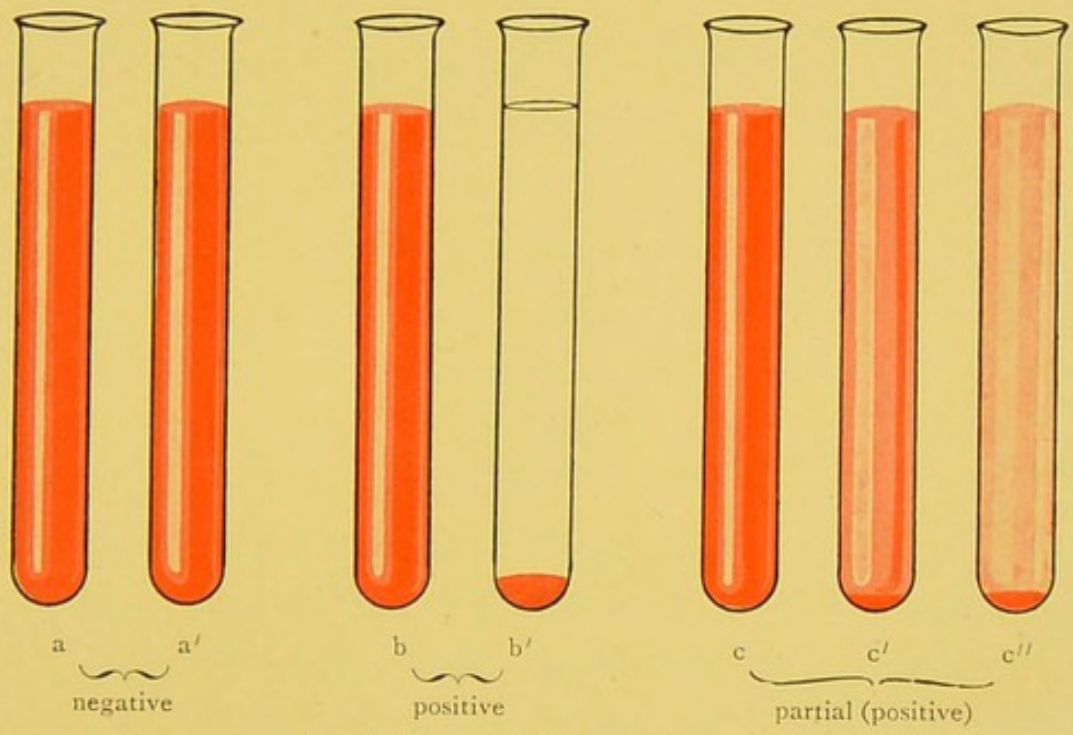
Saline + serum of the syphilitic + complement = no change.
Antigen + serum of the syphilitic + complement = complement fixation.

At the end of half-an-hour into each of these tubes is mixed an equal volume of hæmolysin and an equal volume of corpuscles.

Saline + syphilitic serum + complement + hæmolysin + corpuscles = hæmolysis.
Antigen + syphilitic serum + complement + hæmolysin + corpuscles = no hæmolysis.

In the tube in which the syphilitic serum has been mixed with complement no antibody has been put in to complete the system, so that no combination occurs and the complement is free to combine with the hæmolysin and the corpuscles. Hence we have hæmolysis. In the other case, the antigen, antibody and complement all being present, combination takes place, and therefore, the hæmolysin being unable to combine with the corpuscles, no hæmolysis is obtained. That is the positive syphilitic reaction. The purpose of the parallel experiment in which no antigen is put in to complete the system is merely to control the test. If, as sometimes happens, the patient's serum alone can deviate the complement, then the experiment is null and void. In another tube or series of tubes we repeat exactly the same experiment, but the syphilitic serum is replaced by normal serum, and in both cases complete hæmolysis ought to occur as the complement is not used in completing a syphilitic antigen system.

Syphilitic serum, therefore, ultimately results



"WASSERMANN" REACTION.

a b c = Control tubes with normal saline instead of antigen.
$a^{/}$ $b^{/}$ $c^{/}$ $c^{//}$ = Complete test
$c^{//}$ = Complete test with double strength of serum.

PLATE 5.

in inhibition of hæmolysis; normal serum results in complete hæmolysis.

The inconstant factor or variant is the anti-syphilitic body. If that body is present the syphilitic antigen system is closed and the hæmolytic system cannot be completed owing to the complement having been deviated.

Typhoid fever, Glanders, Echinococcus disease

The Wassermann reaction relates primarily to syphilis diagnosis, but it must be pointed out that with any organisms that behave like that of syphilis and produce a similarly reacting antibody, the same reaction can be obtained by testing for the combination of antigen and antibody, provided that in each case the specific antigen in question be taken. In typhoid infection, for instance, the examination can be made in the same way by using typhoid bacilli and testing the blood serum for antityphoid material. In glanders the complement-fixation method of diagnosis can be carried out by using B. mallei as an antigen and testing for the antimallei product in the blood serum. In hydatid disease, likewise, the complement-fixation method of diagnosis has been used with success, the antigen in these cases being an extract of the echinococcus cyst wall.

Still more important is it to know that in those evidently infectious diseases in which the specific virus is not known, it is possible to carry out this method of diagnosis by using as antigen an ex-

tract of the viscera which are suspected to contain infective material. In syphilis, for instance, one need not necessarily have a pure extract of spirochæta. It is sufficient to take an extract of a syphilitic liver, for even yet there is not complete scientific proof of the etiological relationship of spirochæta pallida to syphilis; nor indeed can the spirochæta be obtained in culture, so that it is necessary to employ the viscera. Possibly in smallpox the test for the antibody could be made by using an antigen consisting of an extract of the emulsion of the diseased viscera.

There are thus a number of diseases which can be diagnosed by means of the complement-fixation test. But owing to the fact that it is so elaborate—and the details of the preparation and standardisation of the various media have here been omitted—and that it has to be delayed until sufficient antibodies are formed in response to the infection, which may be a matter of days or weeks, it is not always the readiest means of diagnosis. Although, for example, it can be employed in typhoid fever, the agglutinin reaction can be obtained earlier and by simpler means. But like agglutination, it is a general means of diagnosis of *some* infections; for, as already stated, different bacteria work in different ways, and just as some produce agglutinins which will cause clumping of the specific bacteria, others produce antibodies which have the power of combining with their specific antigen, *i. e.* the infecting organism, and deviating complement.

Reactions in the Cerebro-spinal fluid

It must be added that an antibody is found, not only in the blood, but also in other fluids, particularly the cerebro-spinal fluid. In many cases of chronic infections of the central nervous system, the reaction may be obtained in the cerebro-spinal fluid, even if it is not obtained in the blood: this is found in cases of cerebral syphilis, locomotor ataxia in the progressive stage, general paralysis, gummatous meningitis.

Diagnostic import of test

The value of the Wassermann test depends, of course, upon its accuracy. This may be summed up in the statement that a positive Wassermann reaction denotes invariably syphilitic infections in this country. There are a few conditions which give similar reactions: acute malaria, for instance, occasionally does so. As explanatory of this, it is necessary to keep in mind the fact that the Spirochæta pallida is, like the malaria parasite, a protozoon, and just as group reactions appear in the agglutination phenomena, so apparently group reactions may occur in the complement-fixation phenomena. The protozoa which are closely allied may produce similar antibodies. The reaction is sometimes obtained in tubercular leprosy, and it has been described in yaws. Otherwise it is not obtained in any other disease, according to the results of a large series of

examinations. Therefore, with the reservation that the reaction is sometimes obtainable in malaria, and sometimes in tubercular leprosy and in yaws, it may be stated that it is absolutely diagnostic of syphilis.

Statistics seem to show, however, that ten per cent. of those known to be syphilitic fail to give the reaction. Thus a positive reaction is certain and diagnostic, while a negative reaction is a little uncertain and has to be taken with some reservation. The writer's own experience of many thousands of cases, however, is that the number of failures does not represent anything like ten per cent. The few failures that have been obtained occurred in very chronic cases of tertiary syphilitic lesions in which it is probable that the lesion has been so encapsulated that there has been little resistance in the tissue and little or no formation of antibody.

Certain other factors have to be considered in any estimate of the precise value of the reaction. It is not found in the early days of infection, but only when this becomes generalised and the system has responded. In the primary stage of syphilis, therefore, the reaction is not of much use. It appears towards the end of the primary stage, just when the glands are beginning to enlarge and a little before the appearance of the rash. With a careful quantitative method it is possible to obtain earlier evidence of the production of antibody and to get what is known as a partial positive reaction (Plate 5).

Partial reactions

The partial reactions are of great importance. In long standing cases of infection, in disappearing infection, and in the early days of onset when the infection is just becoming generalised, as well as in many cases of congenital infection, the quantity of antibody present in the blood is by no means as great as that in a well-marked case of syphilis, such as would be used to supply the control positive serum and to standardise the reagents. Hence often in these cases there is insufficient antibody to completely combine with the antigen and fix all the complement, so that some remains free and allows of partial action of the hæmolysin and solution of part only of the corpuscles. By a quantitative use of more concentrated serum or of double volumes a more marked or complete reaction is obtained. But in all cases the partial reaction is significant of infection. During the early stages of infection the reaction becomes more and more marked week after week, until a complete positive result obtains. Likewise on cessation of mercury treatment in the uncured cases the reaction gradually appears until it becomes completely positive in four to six weeks.

The fact that the reaction is not obtained in the first stage is not of much importance, because a quicker means of diagnosing is the immediate finding of the spirochæta pallida in the lesions. In the second stage the reaction is practically always obtained, as it is also in the tertiary stage

while active. In the tertiary stage, however, it is only the positive results which are of value; negative results may be obtained even when the syphilis is latent.

Para-syphilis

Certain para-syphilitic infections may now be considered. In general paralysis of the insane the reaction has been found in a large number of cases, and also in tabes dorsalis. It has also been found in a large number of cases of aneurysm, a condition which is undoubtedly of syphilitic origin, and in more indefinite syphilitic infections, in which there are severe headaches and slight meningeal symptoms. When any of these para-syphilitic conditions are active the reaction is probably obtained, but when dealing with the result of damage caused by syphilis which has healed there is no reason why a positive reaction should occur. A person with aneurysm of the aorta, which is the result of syphilis, may give no reaction; such is only obtained in the earlier cases of aneurysm of the aorta or of aortitis in which the syphilis is still active. In the active stages of tabes where the lesion is spreading, the syphilitic reaction is found, as also in general paralysis of the insane. Finally, in some para-syphilitic infections in which the reaction is not obtained in the blood, it may be obtained in the cerebro-spinal fluid.

Congenital Syphilis

The test in cases of congenital syphilis is

of special interest. A positive reaction can be obtained in a large number of cases and also frequently in the mother or some near collateral. It is often a partial one but nevertheless definite. For the past few years the author has been in the habit of examining the blood of the many children sent from the out-patients' department with a diagnosis of congenital syphilis. In the majority of cases a positive reaction was obtained, and also with the blood of mothers or other members of the family.

An investigation on similar lines of a series of cases from eight to ten years old suffering with interstitial keratitis, iritis, cyclitis and other eye diseases, gave equally good results : in this series, all cases which were definitely syphilitic gave a positive reaction, and also those who were suggestively syphilitic, whilst a similar reaction was obtained in some of the remainder in whom there was no reason to suspect syphilis.

A series of cases from the children's hospital, consisting of patients between the ages of three and eleven suffering from diseases of the joints or bones, gave serological corroboration of the specific diagnosis.

In congenital syphilitics who present lesions at later stages of life, as in one case of tabes dorsalis in a girl of sixteen, and in a case of general paralysis of the insane in another girl of about the same age, the positive reaction has been forthcoming.

Syphilis and Abortion

A positive reaction has also been obtained in the blood of women who have miscarried repeatedly, though not in every case. In cases which have been diagnosed as syphilitic by this method, antisyphilitic treatment has resulted in the birth of full term children; these in a few cases that have been kept under observation were free from infection.

Latent Syphilis

Finally, an investigation into the occurrence of syphilis amongst the ordinary out-patients of general hospitals carried out on an extensive scale in Sydney and on a lesser scale by the writer, has resulted in a surprisingly large number of cases of latent syphilis being discovered. Amongst these must be included indefinite manifestations, such as headache, nervousness, neurasthenia, etc., occurring in about middle life.

Control of Treatment

The Wassermann reaction can also be used as an index of treatment and a means of prognosis. In considering the question of treatment it is necessary to remember that while the patient is under mercury the reaction is not obtained. Until the mercury disappears from the system the reaction remains negative. It is a question of practical importance as to how long it is necessary to wait after the administration of

mercury before performing the test. The time is uncertain. Occasionally when the patient is not completely under mercury there may be a positive reaction; in other cases it is necessary to wait three or four, and occasionally six or eight, weeks after the cessation of the mercury treatment. During this period of waiting, however, it may be possible to obtain a partial positive reaction.

It may be taken that in those cases that were originally positive the *permanent* disappearance of the reaction indicates complete cure. Hence the test offers an index of the efficacy of any line of treatment. In the case of mercurial treatment statistics show that of those syphilitics who had been thoroughly treated with mercury and who were supposed to be completely cured, 80 per cent. were actually cured, while 20 per cent. still gave a positive reaction. Of course, it has to be remembered that these statistics can be but merely approximately accurate. Of cases partially treated, but still well treated, 50 per cent. only gave a negative reaction, and of those who were only treated for a short time until the symptoms disappeared not more than 20 per cent. gave a negative reaction.

Conclusions

The opinions as to the value of the Wassermann test have been biassed by the discrepancies in the results, obtained occasionally with the same specimen by different observers. This necessitates

explanation. The test, as described above, is the original reaction based on scientific premises and logical deductions, but numerous modifications, all having as their object simplification of the technique, have been introduced, which cannot be said to have so firm a foundation. It is true that the test can also be carried out when the specific antigen (containing extract of syphilitic tissue) is replaced by extract of normal heart or other viscus or even by an extract of cholesterin and lecithin.

But notwithstanding this discovery, which places the test rather in the light of a fortunate accident than a true scientific principle, statistics show that even on an empirical basis its value is none the less great.

There is little doubt also that the original method of performing the test with the employment of specific antigen to combine with the antibody is not only the most scientific, but the least liable to error, and, though a little more elaborate and necessitating much experience to understand the pitfalls, its universal adoption would be productive of more convincing and unanimous results.

The pitfalls are numerous, the details of technique wearying and exacting, and on the whole it must be evident that the reaction can only be carried out satisfactorily by those who are constantly practising it.

The Wassermann test for syphilis, therefore, has its uses in diagnosis, in treatment, in prognosis,

in life assurance work, and, in some cases, in forensic medicine. It avails also to pick out latent syphilis in persons who may be ignorant of the fact that they ever have had it. And it has obvious uses in the case of wives and children of syphilitic men, and fathers of large families, who may have had syphilis before being married and in whom it has been latent ever since, without infecting any of their children; also in the case of such children themselves.

CHAPTER XIII

CYTOLOGY

Cerebro-spinal fluid—Polymorphonuclear cells; lymphocytes —Meningitis: tuberculous; syphilitic; epidemic and posterior-basic; pyogenic—Lumbar puncture; variations in acute and chronic inflammations — Wassermann reaction—Treatment in intracranial pressure and in uræmia —*Pleural and peritoneal fluid*—tuberculosis, acute inflammations, cancer, *chylous fluid*—*cystic fluid*—pancreatic, renal, hydatid—*Joint fluid*—toxic arthritis—bacterial arthritis; staphylococcus, streptococcus, gonococcus, pneumococcus.

The investigation of the cells present in various fluids, that may be found in the serous sacs, such as the cerebro-spinal canal, the joints, the peritoneum and the pleural sac, often produces evidence of assistance in diagnosis, and constitutes at present a most important method of examination. The fluids can be obtained by direct puncture, though only from the cerebro-spinal canal can any fluid be obtained under ordinary conditions of health. And perhaps cytology is more helpful in connection with diseases of the central nervous system than elsewhere.

Cerebro-spinal fluid—lumbar puncture

The cerebro-spinal fluid bathes the surface of the brain and cord and communicates directly

with the fluid in the lateral ventricles. It can be obtained with safety from the arachnoid space below the termination of the spinal cord; this in adults is at the level of the upper border of the second lumbar vertebra. But in children it extends much lower according to age, and in infants it goes on for the entire length of the vertebral column.

In performing a lumbar puncture a needle is used having a medium bore, measuring from three to four inches in length, with a stilette filling the lumen and completing the bevel at the needle-point. The needle must be perfectly clean and free from rust and have a sharp point and a straight bevel, and, needless to say, must be sterilised before using. Such simple precautions make all the difference between a satisfactory and painless operation and the unsatisfactory blundering which fails to produce any fluid whatsoever.

The patient can be made to sit up, the best position being that of bending over to rest on his knees, in order to separate the laminæ as far as possible. If this is not feasible, however, he should lie on his side with the legs coiled and the body bent so that the head and knees approach. In cases of meningitis with rigidity it is often impossible to get a satisfactory position, and a little patience is needed to direct the needle into the cerebro-spinal canal. A local anæsthetic is not as a rule necessary, and a general anæsthetic is only indicated in a very few cases of obstreperous children and delirious adults.

The needle is inserted either in the middle line or laterally between the third and fourth or fourth and fifth lumbar vertebræ, at a point a little below the level of the line joining the crests of the ilia. It is pushed steadily towards the middle line until it either slips upwards and inwards through the inter-laminal space, or else meets the vertebral arch itself, in which case by gently moving the needle the space is found, and the needle slips through into the canal to perforate the theca and enter the arachnoid space. If the needle point is blunt the dura is often pushed before it, and no fluid is obtained. In other cases it may even perforate one of the smaller veins. If it has successfully entered the arachnoid space, on withdrawing the stilette the fluid exudes at a greater or lesser pressure, and can be collected in sterilised tubes. It is seldom necessary to use a syringe, as the fluid either drips from the end of the needle, or else, as in cases of meningitis, gushes out under great pressure; but in some cases of advanced purulent meningitis the exudate is too thick to escape through the needle. The first fluid may be a little bloodstained, so that a series of tubes should be used, and the contents of the second or third tube will be the uncontaminated cerebro-spinal fluid. The distance to which the needle enters is always much greater than one would anticipate, even in children, while in big adults a four-inch needle is desirable.

The normal fluid is clear, but that from a purulent meningitis is turbid, and may be too purulent

and too thick to enter through the needle. All degrees of turbidity are met with, and fluids that appear to be clear often show on microscopic examination marked pathological changes. These are examined after centrifuging for five minutes at a high rate, decanting off the fluid, and then

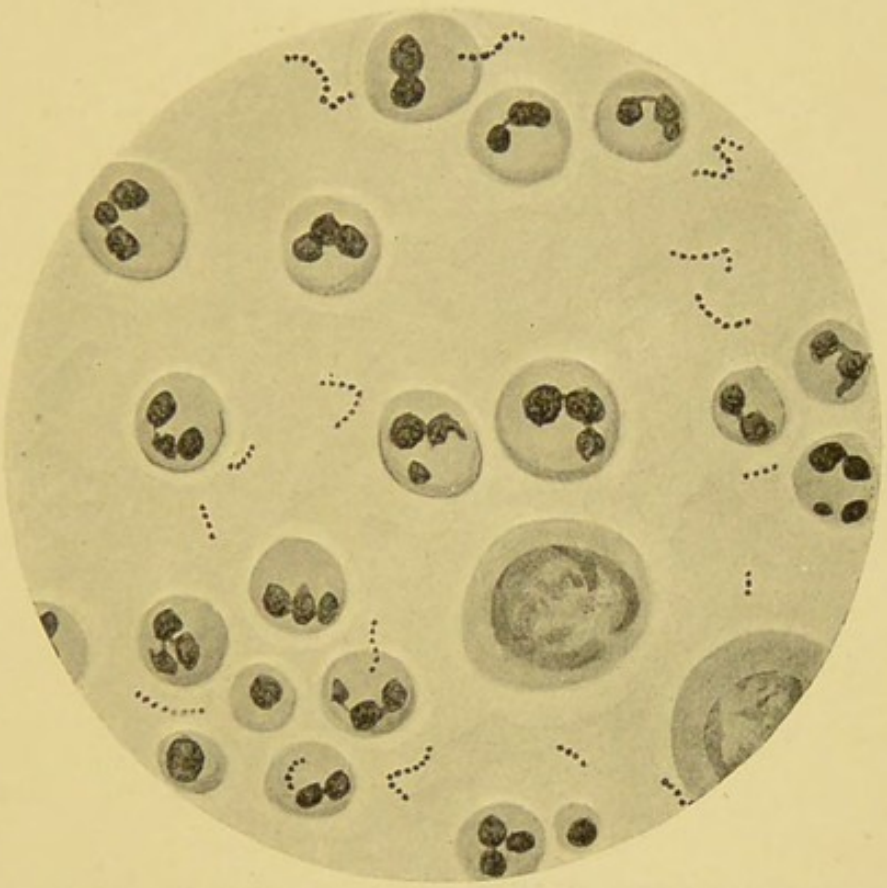


FIG. 19.—Acute Meningitis, showing polymorphonuclear cells, and streptococci. The two larger cells are desquamated endothelium (× 1000.)

preparing a slide from the deposit by allowing a drop to dry without spreading, and suitably staining.

A normal fluid contains practically no cells, though an occasional lymphocyte may be found. Pathological fluids contain varying quantities of lymphocytes (monomorphonuclear cells) or polymorphonuclear elements.

Acute Meningitis

The polymorphonuclear cells denote acute inflammation, such as posterior basic meningitis, or an acute epidemic cerebro-spinal fever, or pyogenic meningitis following middle-ear disease, or

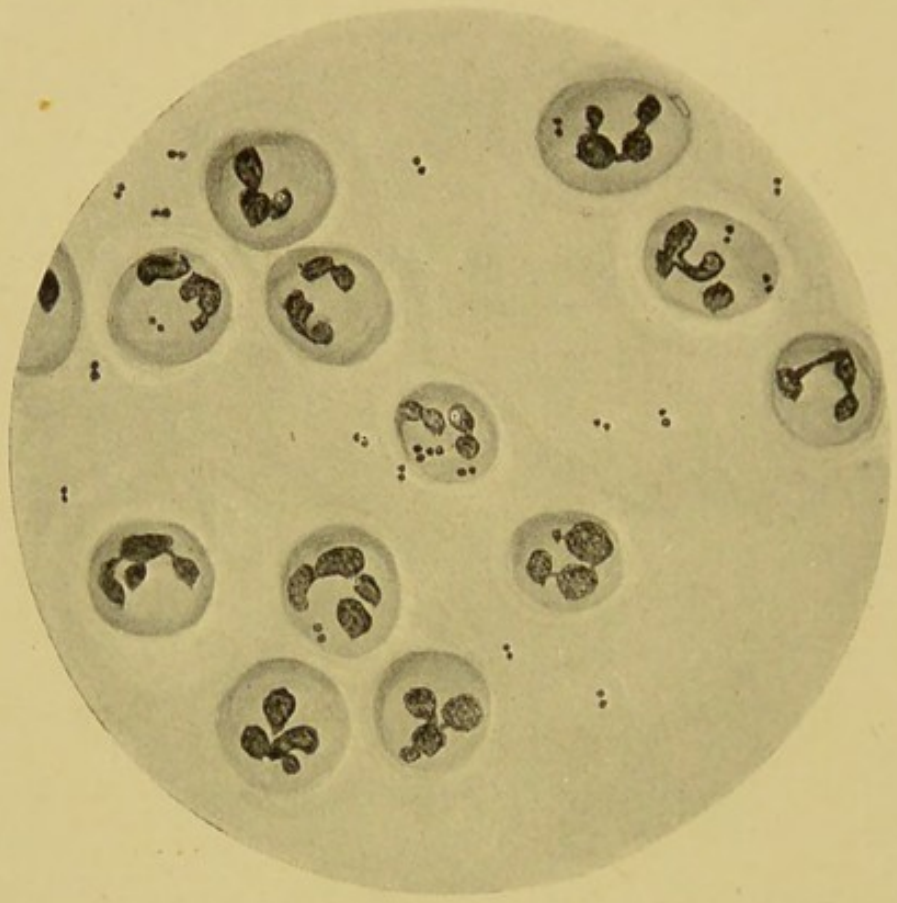


FIG. 20.—Cerebro-spinal fluid from Posterior Basic Meningitis, showing polymorphonuclear leucocytes and meningococci, many of which are intracellular. (The same appearances are seen in acute epidemic meningitis.) (× 1000.)

pneumococcic infection, etc. Even in the early stages of these infections the polymorphonuclear cells are found by this method in great excess, and, indeed, even before there is sufficient exudate to cause symptoms of irritation. The specific cause of infection, and hence the type of meningitis, can be readily determined on the same films by observing the characteristic organism (Figs. 19–21).

Chronic Meningitis—Syphilis; Tuberculosis

Lymphocytes in excess (lymphocytosis) are indicative of chronic inflammations, though a few lymphocytes can be found in poliomyelitis, and in myelitis. In one recent case of acute poliomyelitis the lymphocytes reached fifty to the

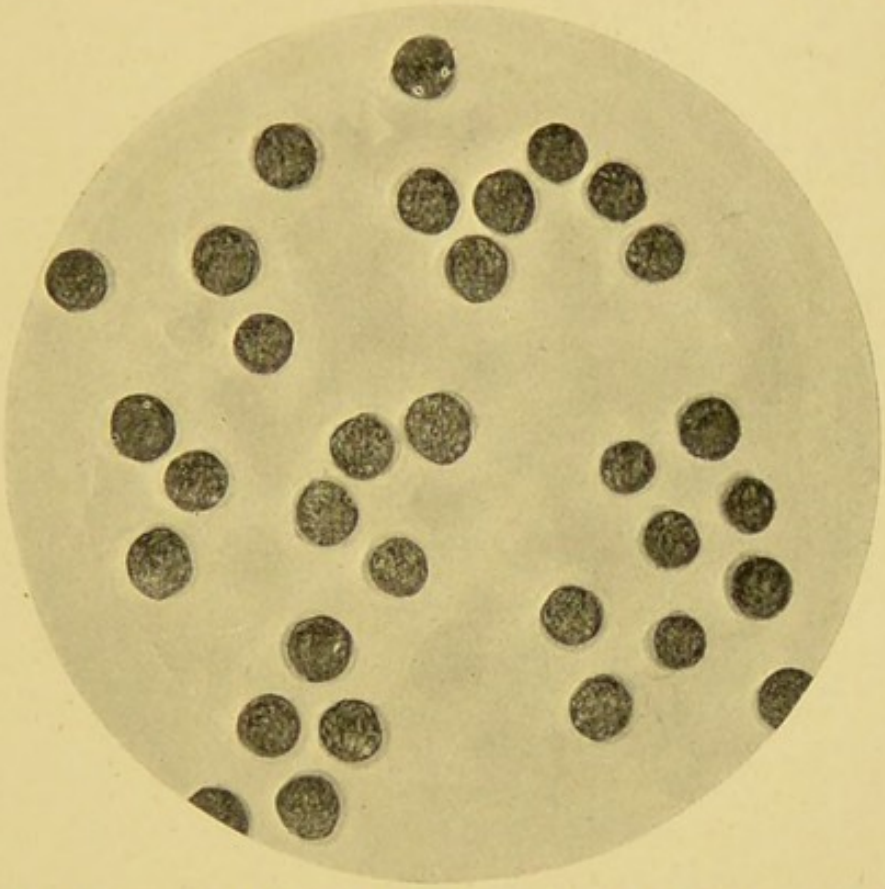


FIG. 21.—Cerebro-spinal fluid from case of Tabes dorsalis, showing lymphocytosis (× 1000). The same findings are regarded as typical of tuberculosis, but see Fig. 22.

field—an unusual finding. A marked lymphocytosis is diagnostic of tuberculosis or syphilis (Fig. 21), and between these the clinical distinction is easy. In tabes dorsalis each field of the microscope may contain twenty, forty, or even a hundred or more lymphocytes; the same occurs in gummatous meningitis, general para-

lysis of the insane, and other syphilitic lesions. Lymphocytosis is also present in the late stages of chronic posterior basic meningitis.

Occasionally in tuberculous meningitis an increase of polymorphonuclear cells is noted (Fig. 22), just as in some cases of chronic posterior

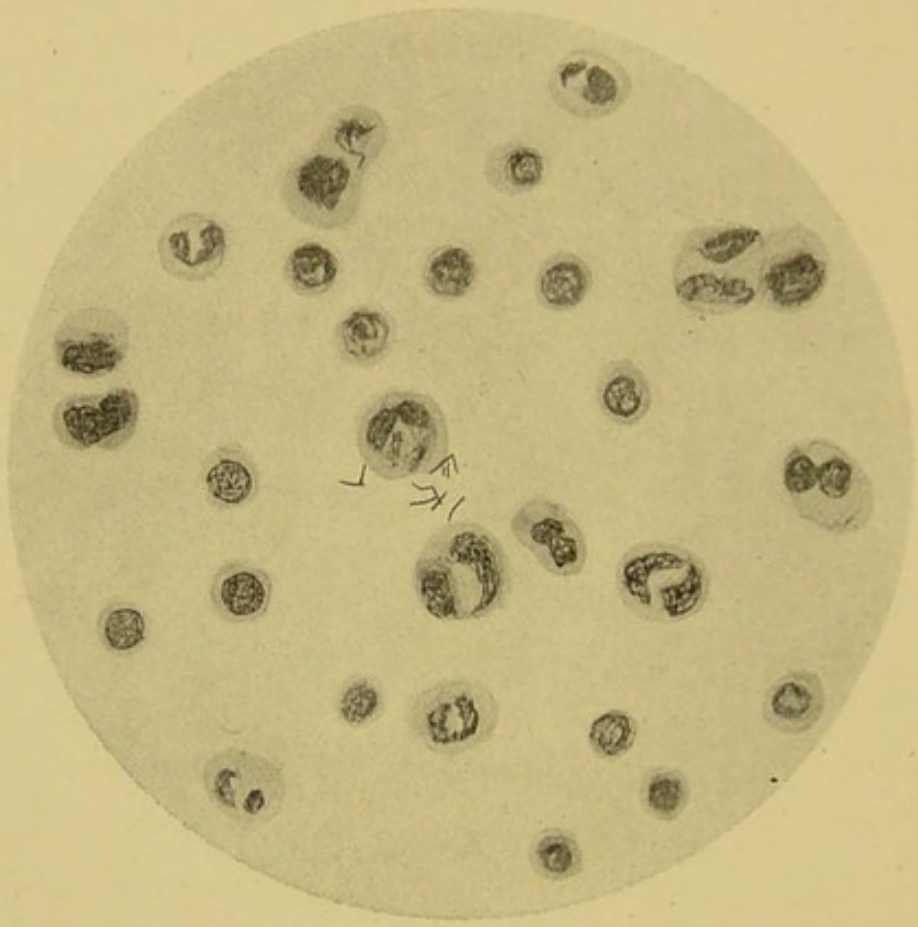


FIG. 22.—Cerebro-spinal fluid from tuberculous meningitis showing tubercle bacilli. Though a lymphocytosis is regarded as occurring in tuberculosis a varying number of polymorphonuclear cells often occurs.

basic meningitis a lymphocytic excess is found. But then tuberculous meningitis is often complicated by secondary infections and the polymorphonuclear cell is merely an indication of the acuteness of the inflammatory process, whilst the lymphocyte is the cell of chronic inflammations.

Tuberculosis can be further distinguished when

necessary by the finding, even on the same slide properly stained, of the specific bacillus. On several occasions in cases of tuberculous meningitis in which there were at the time no localising features, we have found this suggestive lymphocytosis, and in consequence the specific bacilli. (Fig. 22).

In syphilis, corroboration can be obtained by the finding of a positive Wassermann reaction in the cerebro-spinal fluid. In early general paralysis of the insane, in locomotor ataxia especially of the anomalous type, and in true syphilitic lesions of the central nervous system we have frequently obtained this cytological evidence of infection and corroborated by the serological test (Wassermann reaction). It is an interesting fact that occasionally in cases of parasyphilis in which a negative Wassermann reaction obtains in the blood, a positive reaction can be obtained in the cerebro-spinal fluid.

The importance of early diagnosis in meningitis lies in the fact that the earlier that treatment is begun the greater certainty is there of escaping secondary effects of pressure from the accumulation of exudate, such as chronic hydrocephalus.

In the case of meningitis due to the meningococcus, the antibacterial serum that is being used with some amount of success has a much more evident action in the early stages of the disease. In those cases of meningitis for which we have as yet no treatment, beneficial results are obtained by repeated lumbar punctures and relief

of pressure, and much success has been recorded in relieving intra-cranial pressure accompanying tumours, also in some conditions of coma.

In uræmia, where the urea contents of the cerebro-spinal fluid is sometimes found to be as much as 0·4 per cent., palliative results are ob-

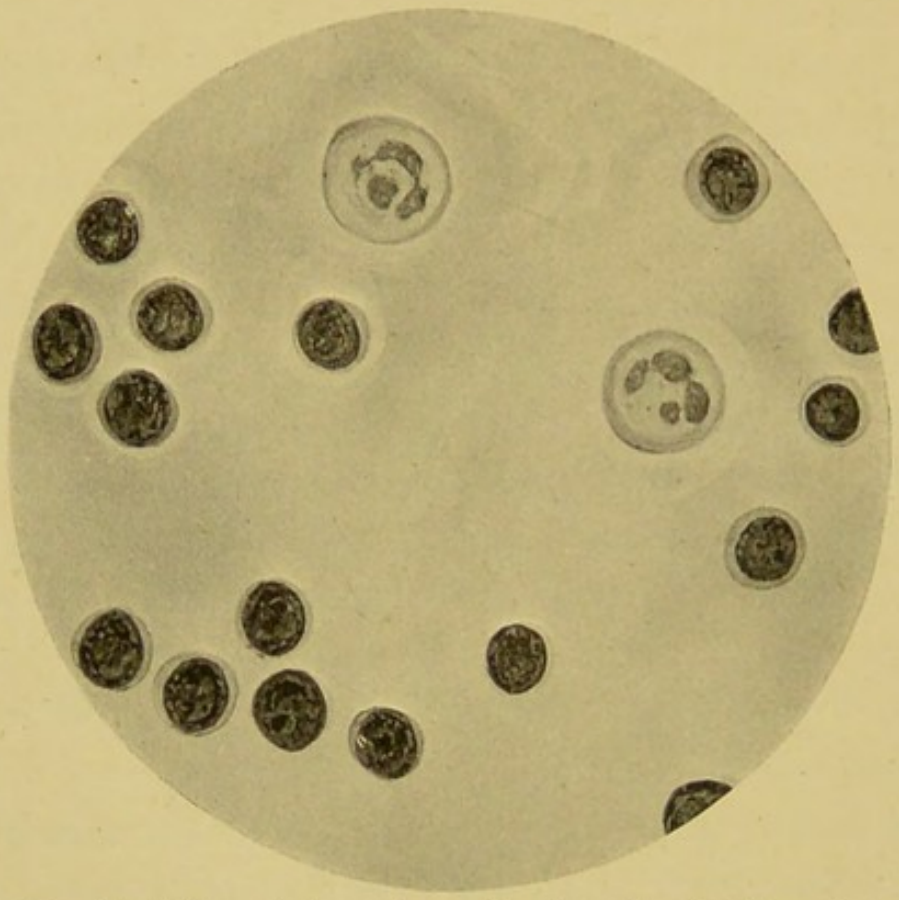


Fig. 23.—Fluid from tuberculous pleurisy, showing lymphocytosis. Two polymorphonuclear cells are seen (× 1000).

tained from lumbar puncture, and occasionally good results in eclampsia.

Finally, in sleeping sickness trypanosomes have been readily found in the cerebro-spinal fluid.

Pleural and Peritoneal Exudates

The same generalisations which relate to the cerebro-spinal fluid can be applied to the inflam-

matory exudates in the peritoneum and pleura. It is unnecessary to detail the mode of obtaining these fluids by puncture. Acute peritonitis and acute pleuritis reveal fluids rich in polymorphonuclear cells and even in pus. Tuberculous pleurisy (Fig. 23) or tuberculous peritonitis often produces a serous exudate which shows a marked accumulation of lymphocytes. It is extremely rare to find by ordinary bacterioscopical methods tubercle bacilli in the pleural effusion, and it is rather rare to find them in the peritoneal exudate. If corroboration be necessary recourse must be had to animal inoculation, a satisfactory though delayed proof.

Fluids that have transuded into the serous sacs, as in passive congestion of cardiac disease, and cirrhosis of the liver, contain numbers of large endothelial cells derived from the serous membranes themselves, and these larger cells are readily distinguished from the type of cell described in inflammatory exudates. Inflammatory exudates differ essentially from transudates in the quantity of albuminous bodies that they contain, and this is sometimes used as a distinguishing feature.

It was hoped in the early days of cytology that neoplasms of the abdominal cavity could be diagnosed from an examination of the fluids that often accompanied them. But this has not proved to be the case. The large cells that are sometimes found in these fluids may be either cells of a new growth or may be cells lining the serous sacs, as

is found in cirrhosis of the liver, in which condition diagnosis from cancer sometimes becomes important. It is true that sometimes large cells are found in masses and sometimes with cell inclusions, but these again are only suggestive and not diagnostic (Fig. 24). Occasionally in

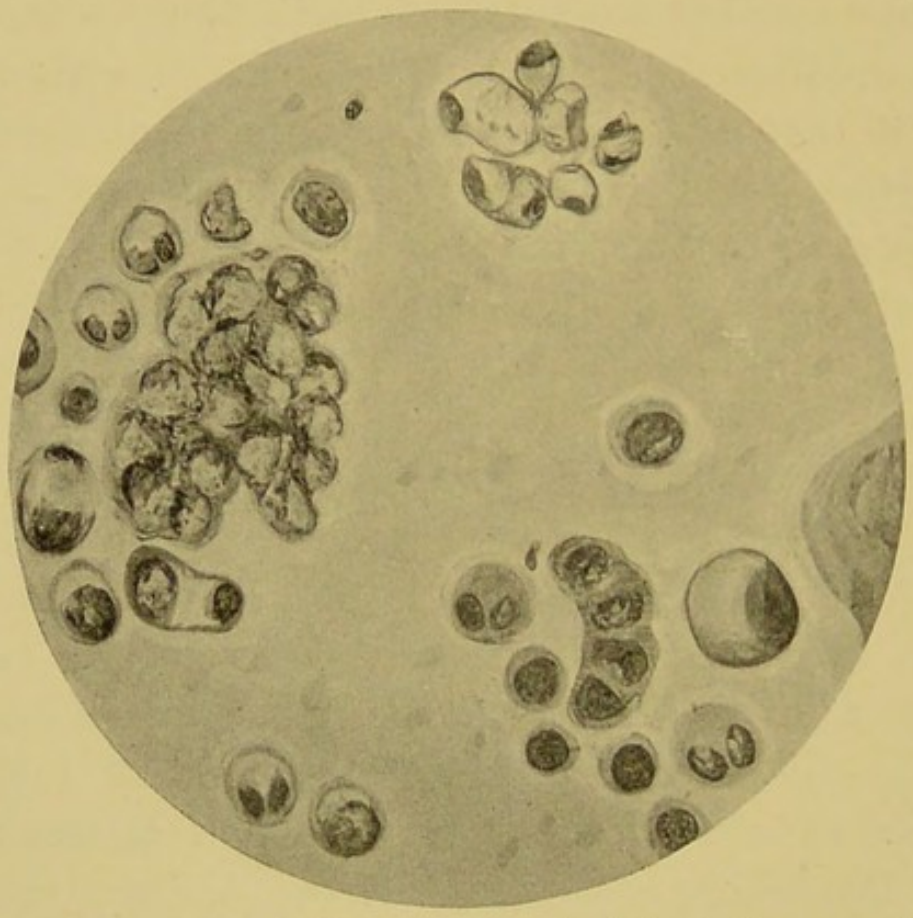


FIG. 24.—Peritoneal fluid from a case of abdominal cancer (from a preparation by Dr. R. G. Hebb) × 750.

melanotic sarcoma of the omentum or liver, large cells are found filled with black melanin, which is definitely diagnostic.

Of the milky fluids that are obtained from the abdominal cavity, the true chylous fluid which has exuded from the chyle vessels is the only one in which cells are found; these are considerably degenerated and contain fatty globules. In the

chyliform fluid, which is formed probably by changes in the albumen, only fine granular debris is found.

A slight eosinophilia is described in tuberculous pleurisy, and in acute pleurisy there is sometimes an enormous increase, which by some is taken to denote a good prognosis.

In the fluids obtained by puncture in the tunica vaginalis, cytological investigation reveals little of note in simple hydrocele, spermatozoa in large numbers in encysted hydrocele, and blood in traumatic cases. In one case a true chylous fluid was obtained. It has the same significance as in ascites.

Puncture of Solid Viscera

Various solid viscera have been subjected to puncture in order to obtain material for investigation.

Lung puncture has been at times strongly advocated as a means of obtaining from an inflamed or pneumonic area the causal bacteria, and in careful hands it is of some use, though it is, of course, fraught with some danger. It has the advantage that the organisms are obtained in pure form from the site of infection instead of, as is otherwise the case, from the sputum, where they must be contaminated by the prolific flora of the mouth and upper air passages; or perhaps not at all in children and in other cases without sputum. Horder is a strong advocate of this

method of diagnosis, and has published illustrative cases which tend to support its value.

Spleen puncture is seldom performed in this country, but has distinct advantages. By its aid Leishman was able to isolate the protozoan body associated with kala azar—the Leishman-Donovan body. In the early stages of typhoid fever the bacilli can be readily obtained from the spleen, though this is not a method often employed. There can be no doubt that in investigating the cases of splenomegaly that are met with in this country spleen puncture should be used, and would probably add much to our knowledge of these diseases.

Fluids from Cysts

Occasionally other fluids are obtained from fistulæ or cysts in the abdomen or from the joints, and certain distinguishing features allow of a diagnosis being made.

Pancreatic cysts often give a fluid containing pancreatic ferments, the demonstration of which is easy. Trypsin will digest egg albumin in alkaline solution, diastase will invert starch, and the amylopsin will convert fats into fatty acids. In some cases of long standing, when probably the cyst has got shut off from the pancreas, these ferments are not found, so it is only a positive finding which is of real value in diagnosis.

Renal cysts, which often reach a large size, and fistulæ connected with the kidney, produce

a fluid which contains urea to the extent of 0·4 per cent. or more, whilst other secretions contain at the most only a trace. Ovarian cysts contain neither ferments nor urea, and often glisten from the presence of a large amount of cholesterin, which is readily demonstrable under the microscope.

Hydatid cysts can only be diagnosed with certainty by the finding of hooklets in their contents, but occasionally these are not found.

Simple cysts of the abdomen, arising in the liver or the mesentery, have merely negative characters, and often are only determined definitely by exploratory operation.

Joint Fluid

Fluid in or around a joint offers difficulties of investigation. From a distended joint the fluid can often be obtained by simple puncture with a rather wide bored needle, but not infrequently a swollen joint gives no fluid on puncture. This latter is the case where a periarthritis exists, and is not uncommon in gonorrhœal arthritis.

The fluid varies with the type of arthritis, and is either serous, seropurulent, or purulent.

In investigating the etiology it must be remembered that though many cases of arthritis appear to be of an infective nature, bacteria are not always found in the joints themselves. Arthritis of toxic origin has probably its etiological source in a focus of infection in some other part

of the body, as, for example, in a septic throat or a suppurating sinus in the nose or neighbourhood, or even in the intestine or uterus; though occasionally no such focus can be identified even when a toxic origin is highly probable.

Cases of arthritis in which the bacteria themselves are in the joint and its exudate can be identified by the demonstration of the causal microbes. Staphylococcus pyogenes aureus is found in the purulent exudate in pyæmia; streptococcus in the seropurulent and sometimes purulent exudate in septicæmia and frequently in the puerperal type; pneumococcus in the plastic purofibrinous exudate which is present in this type of arthritis, which may be primary or secondary to a lobar pneumonia. Gonococcus, though a frequent cause of arthritis and periarthritis, is rarely demonstrable in the exudates which are serous or seropurulent. The writer has only obtained it on a few occasions and then in very scanty numbers.

From tuberculous arthritis sometimes a fluid can be obtained, but rarely can the bacilli be identified; though the cytological appearances are the same as described above, and a marked lymphocytosis is present.

CHAPTER XIV

THE URINE

Introductory — Selective activity of kidneys — Excess of normal blood constituents excreted — Foreign proteids excreted—Albumosuria—Salts—Permanent disturbance of metabolism—Impairment of renal epithelium, transitory or permanent — Functional Albuminuria — Diseased kidney fails to excrete toxic bodies from blood—Changes in urine after leaving kidneys—Classification of urinary findings.

The urine is a fluid separated from the blood by the kidneys by a process of what must be called selective activity. There is much yet to be learned as to the nature of this process. We are, however, certain that the urine is not really a product of filtration, and for the following reasons: the urine contains only a few of the constituents of the blood, and these in different proportion from that in which they are found in the blood itself—indeed, in the urine they are often found in a more concentrated form. Under normal conditions of health the albuminous elements and the carbohydrates are not passed from the blood into the urine. The urea, which is only present in the blood to the extent of 0·03 per cent. to 0·1 per cent., is found in the urine to the extent of 2 per cent. The salts, namely, the chlorides, phosphates, etc., occur in the urine

in almost the same amount as in the blood, with the exception of the sulphates, which are in excess. The reaction of the two fluids is different, the blood being alkaline, the urine acid. None of the structural blood elements, such as the corpuscles or hæmoglobin, are passed through the kidney, though certain bodies allied to hæmoglobin, and formed from its products as a result of intestinal activity, appear in the urine as definite pigments.

Furthermore, the renal epithelium has the power of differentiating between certain poisons, eliminating some and failing to remove others. It will also remove abnormal products of intestinal activity, such as indican and other putrefactive substances, and will allow to pass through it without damage bacteria circulating in the blood stream, as in bacilluria in typhoid fever, or products of abnormal disintegration of the blood occurring in hæmoglobinuria and hæmatoporphinuria.

Although the kidney has this power of refusing to remove normal constituents of the blood that are useful to the economy, there are limitations to this so-called selective activity. We have said—and for all practical purposes it is true—that the albumins and sugars are not removed from the blood, but when these occur in excessive amount they do appear in the urine, producing the conditions of albuminuria and glycosuria. The essential feature of this latter is an excess of sugar in the blood stream—a condition of *hyperglycæmia.*

These conditions form a variety of physiological or alimentary albuminuria or glycosuria, and must be distinguished from the more permanent varieties that are associated with organic renal disturbances or definite disturbances in the metabolic processes.

The kidney can also discriminate between normal and foreign proteid bodies, so that whereas serum albumin and serum globulin are retained in the circulation, egg albumin is rapidly eliminated; in some cases there occurs such an idiosyncrasy to egg albumin that even when given in very slight amounts it appears unchanged in the urine. Albumoses also, obtaining an entry in the blood stream, whether as a result of subcutaneous or intravenous injection or of rapid destruction of tissues, appear in the urine, so that their identification can be regarded as having a diagnostic significance. *Albumosuria* occurs in suppurative processes or involutions of the uterus, malignant growths breaking down, etc. It has been suggested as a means of diagnosing the occurrence of empyema, but a resolving pneumonia gives the same conditions, and from the same cause. It is also found in febrile conditions with tissue degeneration, in extensive disintegration of the liver, leukæmia and phthisis.

The salts in the urine are kept in solution, but in an unstable condition and with slight variations in reaction they are often deposited. Concentration alone of the urine, such as occurs in excessive elimination of fluid by other channels—

for example, the bowels, or skin, or perhaps the lungs—often results in a heavy deposit of urates. Diminution in acidity, such as occurs in dyspeptic states or after heavy proteid diet, which necessitates a drain on the hydrochloric acid elements of the blood, is often associated with a deposit of phosphates. But here must be mentioned the hypothesis that an increase of hydrochloric acid in the alimentary tract, as occurs in hyperchlorhydria, favours the absorption of oxalates in the food, and so explains the oxalæmia found in this condition.

All this has reference to the transitory changes in the normal subject, but in the same manner in more definite and more permanent disturbances of the metabolic processes in which excess of normal constituents or even abnormal ones occur in the blood, these products appear also in the urine—as, for example, in true diabetes or gout, or in the more acute processes affecting the liver, such as acute yellow atrophy.

In all of these, the abnormal products in the urine offer evidence of the condition, but produce no change in the kidney that can be directly ascribed to them. The kidney need not necessarily be affected, and with the disappearance of the transitory disturbances the normal urine reappears, even in the case of such definite disorders as diabetes and gout, when these are amenable to treatment.

But when the kidney itself is diseased or the epithelium impaired by any means, whether toxic,

as in the infectious fevers [1] or various forms of nephritis, or merely as the result of temporary engorgement as in cardiac disease or pressure on the renal vein, then the discriminating power is likewise impaired, and products normally found in the blood appear in the urine, such as serum albumin and serum globulin.

Transitory impairment of the secretory function is seen also in the so-called phloridzin diabetes—a condition of glycosuria which results from the direct action of a drug—phloridzin—on the renal epithelium. As a result of this, the sugar normally present in the blood stream is eliminated.

In the so-called functional albuminurias, in which large quantities of albumin can appear in the urine even for long periods of time, it is still a moot point as to whether this signifies the existence of definite renal lesions. It is the tendency at the present day to regard this as not the case, and to consider functional albuminuria to be the result of disturbances in blood pressure, or poverty of blood, or special idiosyncrasy against particular albuminous products, all of which are denoted in the various terms applied to this condition, for example, albuminuria of adolescence, cyclic, orthostatic albuminuria, etc. Certainly large quantities of albumin can be found in the urine in cases of movable kidney when the

[1] A distinction must be drawn between the transitory albuminuria of toxic origin in the early stage of scarlet fever and the albuminuria in the later stages which is due to organic renal mischief.

patients are allowed to walk about so as to bring about an interference with the circulation in the renal vein, the albuminuria often disappearing after rest in bed.

But as regards the type of albuminuria described as alimentary, and which is often classed under the heading of functional albuminuria, although this condition improves and may disappear entirely with dieting, it is more than probable that there exists slight but definite changes in the renal epithelium—changes which may have been brought about by the strain of the excessive proteid metabolism.

In all forms of nephritis the albuminous products normally present in the blood appear in the urine, but whilst the diseased kidney permits the passage of some bodies, such as the albumins, it fails often to remove others, and these frequently, the deleterious or at least the unnecessary products of metabolism in sufficient quantities. Thus the accumulation of some of these in the blood leads to conditions of toxæmia, as seen in the various types of uræmia. It is true that at present we do not know the exact nature of these toxic substances, but as the conditions are associated with impaired excretion of the known bodies, this can be used as a premonitory index.

Widal has pointed out that in Bright's disease there may occur retention of chlorides in the blood, met with more particularly in the dropsical varieties; or retention of urea and nitrogenous bodies which is met with in the dry

varieties. Hence the importance of estimating the chloride as well as the nitrogenous excretion, and perhaps also the urea content of the blood itself.

Theoretically, the urine is the fluid as it enters the renal tubules. But on its way to the exterior it must necessarily collect and take with it various products such as result from organic disease in the kidney, and also products of inflammation or organic changes in any part of the urinary tract or the genital tract in as far as these two become common. In passing from the meatus it will further collect much of the prolific saprophytic flora that abounds at the orifice and in the vulva, as well as the more especially pathogenic bacteria that may occur in these parts. The urine also may undergo certain changes in composition after leaving the kidneys, generally of the nature of alkaline fermentation, either as a result of retention in a bladder, the seat of cystitis, or as a result of contamination after collection. In all cases this is the result of bacterial infection: the change in reaction results in a deposit of various salts such as phosphates in combination with the ammonia derived from the urea disintegration.

From this introductory survey it will be seen that the examination of the urine ought to reveal—

Firstly, changes in the metabolic processes, whether transitory or permanent.

Secondly, changes in the kidney structure.

Thirdly, the presence of extraneous matter that may have entered the blood through the intestines,

such as the various putrefactive products and drugs; or from the lower urinary tract, the seat of organic disturbances.

These can now be discussed in detail, but it must be pointed out that although the description may appear dogmatic, our ignorance is such that we can merely regard the given opinions as forming a working basis. Nevertheless, although the theories may continue to change, many of the facts will remain as empirical findings associated with certain conditions.

CHAPTER XV

THE URINE (*continued*)

Evidence of changes in metabolism—*Proteid metabolism*—Urea—Influence of liver—Carbohydrate quota of proteid—Uric acid—Exogenous and endogenous—Cystinuria—Alcaptonuria—Indicanuria—Evidence of intestinal putrefaction, constipation and obstruction—*Carbohydrate metabolism*—Tolerance limit for sugars—Hyperglycæmia—Glycosuria—Diabetes—Acetonuria in carbohydrate starvation—Diacetic acid as prodrome of coma—Urine as index of treatment and severity of condition—*Fat metabolism*—Lipæmia—Chyluria.

In order to accentuate the significance of the urinary findings, it will be necessary to give a brief résumé of the present-day conception of the metabolic processes. There are many gaps in our knowledge, and perhaps many errors in our conception, but a definite association has been made out between certain urinary findings and certain changes in the metabolic processes and viscera more intimately concerned with them. Indeed, these urinary findings form a stage in the building up of our hypotheses.

Proteid digestion in the intestines results in a decomposition and in the production of bodies in a descending scale of complexity until certain amino-bodies remain. These are taken up into the system to be again synthesised, in a manner unknown, but

most probably in the liver, into various proteids, such as serum albumin and serum globulin, nucleo-proteid, etc., which constitute the protoplasm of the body structures.

Katabolic processes associated with activity of the muscles, glands etc., result again in a decomposition of proteid into ammonia and sarcolactic acid, and these are changed in the liver into urea, etc.

The end-products of proteid metabolism form the nitrogen constituent of the urine. This is made up for the most part of urea (85 to 90 per cent.) and a little ammonia, a very small proportion appearing as creatinin or uric acid or its allies.

Urea

For all practical purposes the amount of urea remains fairly constant and can be regarded as an index of the proteid katabolism, which for the most part takes place in the muscles. The amount of urea averages 2 per cent. with a normal excretion of fifty ounces of urine. Under certain conditions, such as the appearance of acids in the blood stream, these combine with the ammonia so that the urea production is diminished, while the ammonia factor in the urine is increased. For more exact working, therefore, it is often necessary to determine the total nitrogenous content of the urine in order to recognise the changes in proteid metabolism. The relation of the urea-nitrogen to the ammonium-nitrogen is often also of great

significance. Diminished proteid metabolism, such as occurs in starvation or chronic wasting disease, results in a corresponding diminution of urea. Excessive proteid metabolism, such as occurs in increased muscular exercise, acute inflammation, including acute fevers, and acute wasting disease, is accompanied by an increase of the urea excretion. In a case of orthostatic albuminuria in an otherwise healthy and very active youth aged twenty, the urea averaged 5 per cent. in the morning specimen, and occasionally 7 per cent., though the twenty-four hours' specimen reduced these high figures to 3 per cent. with an excretion of a normal amount of urine.

It is important always to examine samples from the entire collections in the twenty-four hours.

Proteids can also take a part in the carbohydrate metabolism. In the proteid molecule there exists a carbohydrate quota which under ordinary circumstances is used up in supplying energy and perhaps even in forming glucose itself. In diabetes the proteid can vicariously replace the normal carbohydrate metabolism. In milder cases, where only the carbohydrate of the food cannot be properly dealt with, the carbohydrate quota of the proteid is used up in supplying energy, but in severe cases the liver fails to deal even with this, and glucose continues to appear in the urine, despite the withholding of carbohydrates from the food. In all cases, however, and in the severe types to a greater extent, the demand on the proteids necessitates a greater destruction than normal and

so the urea content of the urine is increased in some cases as much as threefold.

As the liver is the great centre of synthesis of urea from the products of proteid katabolism, it follows that impairment of this liver function will result in a failure of such synthesis, and hence a decrease in the urea formation with a consequent increase in the ammonia and intermediate products, such as leucin, tyrosin, uric acid, and xanthin bodies. This, indeed, is often the case. Though extensive damage must occur in the liver to interfere seriously in the synthesis of urea, in some cases of cirrhosis a diminution of urea has been noted, whilst the ammonium-nitrogen has been increased. But in destructive lesions of liver, such as occur in acute yellow atrophy or phosphorus poisoning, the urea content is considerably diminished, at the same time as the ammonia is correspondingly increased. In these cases the total nitrogen may be considerably increased as a result of the excessive proteid destruction occurring in the liver itself (autolysis). Characteristic products of this self-digestion in the shape of tyrosin and leucin crystals also appear in the urine as highly significant evidence of the grave disturbance.

Uric Acid

In addition to the metabolic processes that result in a splitting up of the proteid molecule into a nitrogenous part which ultimately reaches the urine as urea and a carbohydrate

part which forms energy or can be actually converted into glucose, there remains a further product of proteid katabolism to be considered, namely, that associated with the formation of uric acid. Some of the proteid in the body combines with nucleic acid to form nucleoproteid; this is an important constituent of the nuclei and hence is present in great quantities in the viscera that are markedly parenchymatous, *e. g.* spleen, thymus, testicle, etc. Now nucleic acid is a combination of purin bases with phosphoric acid. As a result of enzyme action, katabolic processes result in the splitting up of the nucleoproteid into its proteid and nucleic acid. This latter is then further split up into the purin bases—xanthin and hypoxanthin—which by a process of oxidation can be converted into uric acid. It is probable, also, that there exist free purin bases in the muscles, which are capable of forming uric acid.

Most of the purin bodies and also the uric acid are transformed in their passage through the liver and perhaps other viscera into urea.

But nevertheless a fairly constant amount of uric acid exists in combination in the urine of a normal individual who is having his normal diet.

In addition to this great source of uric acid —the *endogenous* origin—there is a further supply obtained from the nucleoproteid element of food, and more particularly from thymus, sweetbread, spleen, liver, etc.—the *exogenous* origin.

Consequently an excess of uric acid is present in the urine as a result of an increased supply of

nucleo-proteids. Thus it is met with as a result of ingestion of large amounts of meats, and especially the parenchymatous viscera mentioned and meat extracts; or as a result of excessive tissue katabolism, especially when associated with activity of the leucocytes as in fevers, leucocythæmia, pneumonia, etc.

Now uric acid itself is a highly insoluble product, and is held in solution in the urine by the salts, and in the blood, hypothetically, as a quadriurate salt.

Its deposition in the urine—which often occurs—must not be mistaken for an excessive production, for this is not the case: a highly acid urine of low pigmentation will readily deposit uric acid from its more soluble basic combination, though the uric acid may be present only in normal quantity. The only significance of such a deposit is that if it occur soon after the urine is voided it might be supposed that a similar deposition could occur in the urinary tract, and so tend to the production of calculi.

But the importance of uric acid lies in its relation to gout. We may say at once that though much has been written on the subject by rival schools of theorists, there is little, if any, evidence on which to hypothesise regarding the rôle uric acid plays in the causation of gout—the cryptic pathogenesis of which we have already mentioned.

It is true that a striking manifestation of gout is the deposit of uric acid in the form of insoluble

biurate needles in the joints. This might conceivably be the result of either an increased amount of uric acid in the blood or a diminished alkalinity, such as might result from an excess of sodium salts. As to the former there is never more than a slight increase, and we know little about the alteration in reaction of the blood. In chronic gout there is said to be some increase in uric acid in the blood, but no increase in the urine. Preceding an attack of acute gout there is a diminished excretion of uric acid, but during and for a time subsequent to the attack there is an increase.

Furthermore, uric acid is as devoid of toxicity as is urea. Finally, investigation of nitrogenous excretion shows that there is a marked disturbance of metabolism in gout, so that as far as uric acid is concerned we can only say that it is associated with some of the manifestations of gout. Consequently examination of the urine reveals little that can be of assistance in dealing with gout, at least as far as the gouty diathesis itself is concerned.

Our knowledge, or rather our ignorance, concerning the pathogenesis of gout has been truly summed up in describing it as a "misdirection of the proteids."

Alcaptonuria and Cystinuria

Finally, there is a fascinating group of cases in which the proteid-urea cycle is not completed but results in the appearance of intermediate bodies in the urine, *alcapton* and *cystin*. These

conditions are often hereditary, and have been defined as results of "an inborn error of metabolism" or "a chemical malformation," which, again, defines our ignorance rather than our knowledge of the subject. Cystinuria, from the fact that cystin is passed in a crystalline form, is often associated with the formation of large and sometimes numerous calculi. In alcaptonuria the urine darkens on exposure to air.

Indicanuria

There is a further stage of proteid disintegration occurring in the intestine which, although very common, cannot be regarded as normal. Prolonged retention of the intestinal contents is associated with the production of further decomposition products—the result of bacterial activity. The amino-bodies already mentioned decompose into skatol and indol—putrefactive products always—which are absorbed from the intestines, and after undergoing a preliminary oxidation, combine with sulphuric acid in the liver, and are eliminated in the urine as oxysulphates. Of these the indol derivative, or indoxyl-sulphate, is readily identified in the urine by its marked colour reactions, and so can be regarded as an index of putrefaction whether from simple constipation or from organic obstruction.

The conversion of indol into the indigo-blue compound forms a ready means of testing for it. Rarely, the oxidation into indigo blue is carried on to the end in the body itself, and is

actually passed in the urine as a blue sediment. Indicanuria, which is present in all cases of constipation, becomes very marked in obstruction of the small intestine especially, and to a lesser extent in obstruction of the large intestine; here probably only when stagnation results also in obstruction of the ileum. It is also possible that the indol can be derived from proteid putrefaction elsewhere, such as gangrene and putrid growths, or decomposing retained placenta, or exudates generally. Indol itself is only slightly toxic, though after administration it has been known to produce symptoms such as are associated with chronic constipation, including frontal headache, irritability, insomnia, fatigue. The presence of indicanuria is of great significance in those cases, especially of women, who confess to a daily action of the bowels, but who, nevertheless, are sufferers from chronic constipation. In many cases of purpura a marked indicanuria is found, bearing out the idea of an etiological toxin arising in the alimentary tract.[1]

Thus we see that proteids after ingestion are converted by a process of analysis and synthesis into the human proteids, the katabolic end-products of which appear finally as nitrogenous

[1] The test for indican is: Add to about one inch of urine in a tube an equal quantity of strong hydrochloric acid and then a few drops of a 0·5 per cent. solution of potassium permanganate and warm gently. The urine darkens and on shaking with chloroform the latter sinks to the bottom and becomes more or less blue in colour.

bodies in the urine. The sulphur-content of proteid forms ethereal sulphates in the urine; phosphates are also derived in part from the proteids, whilst abnormal proteid metabolism can result in a compensatory production of glucose and carbohydrates, to replace the failure of the normal carbohydrate metabolism. Foreign proteids, as such, do not enter the blood stream as a rule, but occasionally egg albumin can do so, and albumoses likewise, but these are always rapidly eliminated, and the latter at least is of assistance in diagnosis, as we have already seen.

Glycosuria [1]

Carbohydrates are converted in the intestine by the activity of the ferments in the saliva, pancreatic juice, and succus entericus into soluble sugars, but the capacity for such conversion is limited. In children the capacity for dealing with starch is not developed until teeth and salivary glands appear—an important point to bear in mind in infant feeding. Any soluble starches, etc., which are not converted are excreted by the bowel, just as in the case of the excess of proteid food which is not completely digested. In the form of soluble glucose, carbohydrates enter the blood, probably

[1] No mention is made here of the various "reducing bodies" that can appear in the urine. The carbohydrates here mentioned give the following tests as proof of their nature—

1. Reduction of copper salts.
2. Ferment and then do not reduce.
3. Phenyl-osazone test.

by the portal system, to be dealt with by the liver and the muscles, being stored up as glycogen and circulating as glucose. The carbohydrates are expended in supplying the energy and heat of the body, and their end-products appear in the urine as carbonates and water. Glucose normally is present in the blood in amount not exceeding 0·2 per cent. When, however, this figure is exceeded, the condition of *hyperglycæmia* is produced, and the excess of sugar is then eliminated by the kidneys. This condition of hyperglycæmia is a constant feature in diabetes, but can be brought about as a temporary feature by exhibition of large quantities of glucose. There exists, in health, a *tolerance limit for sugars*, which is reached when 200 grams of glucose are given by the mouth, but the limit for lævulose is lower. Beyond this amount sugar appears as such in the urine. It is possible that the sugar in these cases is absorbed directly into the lacteals of the intestine, and, entering the blood, is excreted unchanged in the urine. There is also an individual tolerance limit which varies considerably in different cases.

In health, no quantity of starch, however great, can produce a glycosuria, as only a certain quantity can be dealt with in the intestine, and the rest passes on unchanged. But a characteristic feature of severe diabetes is the fact that starch diet increases the glycosuria. Dextrose, lævulose, cane sugar or lactose all produce this glycosuria when taken in excess.

The factors that appear to be concerned in the sugar metabolism are the liver, with its capacity for storing up glycogen; the pancreas, with its internal secretion, which gives to the blood its glycolytic function; and to some degree, though as yet but little understood, the various glands with internal secretions, all of which appear to be interdependent; and, perhaps of equal importance, the nervous system itself controlling the various functions. One need only instance the glycosuria that occurs in some cases of exophthalmic goitre, and the diabetes following a severe nervous shock, and perhaps also the association of the posterior lobe of the pituitary body with an intolerance of carbohydrates, as shown by Cushing.

Glycosuria may occur, then, from (1) the excretion of sugar normally present in the blood, (2) excessive ingestion of certain sugars and (3) a true disturbance of the carbohydrate metabolism, this constituting diabetes.

The excretion of the sugar normally present in the blood is seen as a result of the action of phloridzin on the renal epithelium, which has already been described; also from interference with the nervous mechanism, which is seen in cerebral tumours, such as tumours of the cerebellum, generally when the floor of the fourth ventricle is encroached upon, or in epilepsy, or following severe nervous shock. Experimentally there is found a centre in the floor of the fourth ventricle that controls the glycolytic function, perhaps of vasomotor nature.

The glycosuria that follows on excessive intake has already been mentioned. The assimilation limit or tolerance limit described under this head is occasionally impaired in advanced cirrhosis of the liver or in other lesions of the liver that produce destruction of the parenchyma. In these conditions the tolerance limit is considerably reduced, so that frequently the administration of 100 grams of glucose results in glycosuria. This has been recommended as a means of diagnosing cirrhosis of the liver.

The condition of alimentary glycosuria in which administration of moderate quantities of sugar produces the condition, probably forms the connecting link between these artificial glycosurias and the true diabetes.

Diabetes

In diabetes there occurs an abnormal metabolism of carbohydrates, inasmuch as the system is unable to deal with them. This has been described as a "misdirection of the carbohydrates," which, indeed, sums up our knowledge or lack of knowledge of the etiology. It is supposed that as a result of this metabolic disturbance there occurs a condition of hyperglycæmia in which the sugar in the blood may be increased from 0·1 per cent. to 0·3 per cent., or even, in exceptional cases, to 1 per cent., accompanied in all cases, as we have said, by an elimination of the excess of sugar in the urine.

The severity of the condition, and hence the prognosis, depends upon the intensity of the

glycosuria, and its relationship to the various forms of diet, and the ability of the system to maintain the balance of metabolism. Although there is an inability to deal with the carbohydrates of the food, they can be replaced in the economy by the products of decomposition of the proteids and fats, from both of which, indeed, sugar itself can be and is perhaps normally formed (see p. 183). In the milder forms of diabetes, such as occurs in the so-called alimentary glycosuria of middle-aged and well-fed patients, the glycosuria only appears on a carbohydrate diet, disappearing on withholding carbohydrates from the food. Even when glucose is not tolerated by the system, but is passed unchanged in the urine, lævulose may be tolerated by some diabetics. In the more severe types the power of dealing with sugar is still further diminished, so that when given in the food it appears in the urine, whilst the destruction of proteids increases to meet the tissue demands for carbohydrates. In the later stages still, the glucose of proteid origin fails to be dealt with by the liver and even in the absence of carbohydrate diet the glycosuria remains or even increases. We have seen that as a consequence of this increase of nitrogenous metabolism the urea in the urine is present in marked excess. In the true diabetic the administration of starch foods likewise increases the glycosuria.

Acetone Bodies

In meeting the demand of the tissues for carbo-

hydrates the vicarious metabolism of the fats results in the formation of various intermediate products. As the disease progresses the power of dealing with these substances is diminished also, and so incompletely oxidised products appear in the blood and in the urine. These offer marked evidence of the severity of the condition, and frequently are danger signals pointing to the onset of coma. To these belong the acetone bodies, which include *β-oxybutyric acid*, *diacetic acid* and *acetone*. Acetone is the harmless product of oxidation of the acids, but these accumulate in the blood, either from excessive production as a result of excessive and compensatory fat metabolism, or failure of this oxidising power. Though not of themselves toxic, they probably interfere with tissue-respiratory changes to such an extent as to produce air-hunger and coma. They combine with ammonia and the mineral bases, and impede the removal of carbon dioxide from the tissues (see p. 10), so that the ammonium combinations of nitrogen are increased in the urine, whilst the urea quota is diminished. We have already pointed out, however, that in advanced cases of diabetes the entire nitrogenous content of the urine is markedly increased, so that here the important estimation must be the ratio of urea to ammonium nitrogen.

In milder cases of diabetes no diacetic acid appears in the urine, though traces of acetone occur, as they do likewise in the expired air from the lungs in all cases. But when the metabolic

equilibrium is not maintained, and especially where there is much wasting, diacetic acid and β-oxybutyric acid are easily identified in the urine, and their presence can be regarded as an indication of a grave state. When present in quantity they signify the onset of coma. In many cases they can be made to disappear from the urine by the administration of alkalis, either by the mouth or, in the more severe stages, by the blood stream; this is, indeed, the usual treatment.

Acetonuria is found also in other conditions associated with metabolic disturbances. Just as in diabetes we have regarded it as indicative of failure of carbohydrate metabolism, we also find it in conditions of carbohydrate starvation from actual insufficiency of these in the system as in acidosis in children, starvation, vomiting of pregnancy and a host of other conditions when looked for. But a distinction must be drawn between the milder and remediable forms of acetonuria and the ominous condition of diaceturia associated with a grave disturbance of metabolism.

Mild intestinal disturbances also result in interference with the carbohydrate digestion. So that in conditions of stasis, such as dilatation of the stomach, fermentation occurs, with a production of lactic acid and gases which render the stools highly acid and result in irritation of the perinæum: oxalic acid produced from this fermentation is excreted in the urine and appears in excess.

Summary

We have seen, then, that normally the products of carbohydrate metabolism which appear in the urine are the carbonates, but excessive ingestion of sugar can lead to glycosuria. Inability to cope with the sugars leads to a permanent diabetes with concomitant findings in the urine, denoting the attempts of the proteids and fats to compensate for the impaired metabolism.

Thus, the investigation of the urine is of the utmost importance in conditions of glycosuria to determine the severity, the extent to which the condition can be controlled by suitable diet, and hence the prognosis, and also to forestall the appearance of the coma. Also, in conditions of coma associated with acidosis, the acetonuria gives the clue to diagnosis and points the line of treatment with glucose.

In milder cases of diabetes by reducing (gradually) the carbohydrates in the food until none is exhibited, glycosuria often ceases and then by slowly giving increasing amounts of carbohydrates we can find what amount can be dealt with without producing glycosuria. A restricted diet containing less than this amount of carbohydrate produces after some time a certain adaptability of the metabolic functions and larger quantities can then be administered and assimilated.

In more severe cases no such adaptability is possible, though a certain amount of carbohydrate must be dealt with. It is a familiar

observation that these cases rapidly become comatose if a rigid carbohydrate diet be given, and, like milder cases, can be changed to a more serious stage by such a diet.

Metabolism of Fats

Fats are split up in the intestine into fatty acids and glycerine, and under ordinary circumstances they do not influence the urine. But when the pancreatic juice is absent from the intestine, from disturbance of the pancreas or of the ducts, this decomposition does not take place.

We have already mentioned that the fats can in part compensate for the carbohydrates, and that in diabetes intermediate products of oxidation, such as β-oxybutyric acid and acetone, may appear in the urine, with ominous significance. Occasionally there is such marked interference with the oxidising processes that fats actually appear unchanged in the blood, constituting the condition known as *lipæmia*.

Here also might be mentioned the condition of *chyluria*, in which the contents of the lymph lacteals enter the bladder, as occurs in obstruction of the duct by filaria ova. The typical milky appearance of the urine leaves no room for mistaking the condition.

CHAPTER XVI

URINE (*continued*)

Influence of Changes in the kidney—Functional capacity of healthy and diseased kidney—ALBUMINURIA in transitory and prolonged lesions—*Latent nephritis* with contracted kidney—Functional and organic albuminuria—NEPHRITIS, varieties of, significance of albumin and of urea—CASTS—Disease of renal pelvis and parts below—Pigments and products of blood degeneration—Volume and specific gravity.

CHANGES in the renal structure itself may produce either alterations in the urine owing to disturbance of the secretory activity, or else by the addition of inflammatory products after the urine has been secreted. Both kidneys may be affected simultaneously, as occurs in various types of nephritis, in which condition the urine that passes from the bladder will be of itself significant; or else one kidney may be affected, as is seen in hydronephrosis, or pyonephrosis, or other sequelæ of obstructive lesions; or else both kidneys may be affected to an unequal extent. Occasionally, also, one kidney may be entirely absent, a condition described as asymmetrical or unilateral kidney. In view of the fact that there is a marked capacity for compensation in the healthy kidney in unilateral disease, or in the unilateral asymmetrical kidney, little evidence of the functional capacity of the

kidneys can be obtained from an examination of the urine collected in the normal way.

Functional Activity of Kidneys

For this reason, then, in order to determine the extent of mischief, or the functional capacity of one kidney where the other is known to be seriously damaged from disease, it is necessary to collect the urine directly from each side; this, of course, necessitates ureteral catheterisation by those specially skilled in the technique.

The points of importance in the determination of the functional capacity are—

The amount of urine and its specific gravity.
The total amount of urea.
The presence or absence of adventitious materials.

The functional activity also of the affected kidney in unilateral disease can be determined in the same way, and the question decided as to whether it is advisable, if possible, to leave portions of the kidney. In infective conditions also it is sometimes necessary to decide whether one kidney alone is infected, and obtain bacteria in pure culture, in order to proceed, if necessary, to the preparation of a vaccine.

Other methods of testing the functional capacity of each kidney are—

(*a*) *Phloridzin Test.*—This glucoside is given by the mouth, preparatory to ureteral catheterisation, and the subsequent glycosuria in each specimen

tested. The diseased kidney will pass less sugar than the healthy one or none at all.

(*b*) *Methylene Blue Test.*—This, given in the form of a pill, will result in a blue urine being passed from the healthy kidney, but a colourless or very slightly coloured fluid from the diseased kidney.

(*c*) *Polyuria Test.*—Polyuria may be associated with a diseased kidney which often secretes a large amount of urine of low specific gravity and low urea content. But if a diuretic (*e. g.* Contrexeville water) be given in such a condition then the healthy kidney will pass a largely increased amount of urine whilst the diseased one will pass an unchanged or only slightly increased amount.

Albuminuria

It might be said broadly that transitory disturbances of the renal epithelium are associated with temporary albuminuria, whereas the severe inflammations are associated with albuminuria and casts. The renal epithelium is temporarily impaired as a result of disturbances in the circulation. It is consequently met with in the venous congestion of cardiac disease or in movable kidney, where the dragging kidney impedes the circulation, or in pressure of new growths or glands on the renal vein; also in toxic conditions as seen in febrile states.

Where an albuminuria exists, therefore, it is of extreme importance to determine the nature of the underlying process at work. It must be remembered that there are types of very chronic

nephritis which often date back to a scarlatina or perhaps other infectious disease of childhood. In these there may be no suspicion of such change nor any reason to suggest an examination of the urine until attention is directed thereto by a sudden onset of uræmia in any of its protean manifestations, or of cerebral hæmorrhage, or of cardiac failure following on the hypertrophy that accompanies this condition. These latent cases are by no means uncommon, and constitute a type of irregular, distorted and contracted kidney which has many features in common with the "small white kidney."

Seeing that albuminuria can be due to a variety of conditions, the important point is to determine whether there exist any organic renal disturbance. We have already mentioned the conditions of functional albuminuria and of alimentary albuminuria, and there can be no doubt that many of these are of only a transitory nature and may truly be described as adolescent, cyclic, orthostatic or postural, etc. All these may be associated with a certain amount of anæmia or with an excessive ingestion of proteid foods, as seen more especially in the egg albuminuria already mentioned; or perhaps may follow severe exercises, as is not uncommon in athletes; or may follow chills, when it may be due to a slight toxic derangement of the renal epithelium; or may follow temporary derangement of blood pressure. Nevertheless, it is often impossible to state definitely a favourable prognosis for

some of these so-called functional cases. Even large quantities of albumin can occur in the urine under these conditions, and such cases have been known ultimately to recover.

Perhaps the most distinctive feature by which a discrimination may be made between these so-called functional albuminurias and true organic renal disturbances is to be found in the absence of casts in the former and in the fact that the urea excretion is not impaired. That many of them are due to the erect posture is shown by the fact that some patients when kept in bed have no albuminuria, which reappears immediately on rising. A similar disappearance is noted in some cases of movable kidney when the patient is kept in the recumbent position.

Nephritis itself, however, is of toxic nature, and there must be mild cases of toxic derangement of the epithelium which are on the borderland between the transitory albuminurias and the more permanent albuminurias of extensive organic disease. The etiology of nephritis is as yet a closed book. It is true that we can divide the better known types into—

(1) Acute inflammation, which is often associated with some infective condition elsewhere, as, for example, tonsillitis, scarlatina or diphtheria;

(2) Subacute cases, which are of insidious onset, perhaps corresponding with the large white kidney, in which there is less evidence of bacterial association;

(3) A very chronic inflammation associated with

marked interstitial changes in the kidney and cardio-vascular system which extends over many years and results in the so-called red granular kidney: in this there is no evidence of true bacterial origin, though possibly it may result from a chronic toxæmia originating in the intestines, and indirectly, therefore, of bacterial origin.

Pathological investigation of an acute nephritis, therefore, should be directed to the finding of a focus of infection, despite the fact that we have little knowledge at present upon which to work. The streptococcus might be isolated from the throat or the diphtheria bacillus from the mouth, although often these have disappeared by the time the nephritis is manifested. Attempts might also be made to cultivate organisms from the urine, withdrawn in a sterile fashion. Streptococci have on some occasions been so isolated.

Significance of Amount of Albumin

There is no true relationship between the amount of albuminuria and the severity of the complaint, beyond the fact that in acute nephritis the albumin, for the time being, is in great excess. Sometimes, traces only are found in chronic interstitial nephritis with uræmia. It is necessary to compare the percentage of albumin with the total amount of urine. It must also be pointed out that the total output of albumin is seldom great, and is insufficient to account for the marked anæmia which accompanies this condition; this, indeed, is most probably due to the same toxin that is

causing the nephritis. Hence little good can be done by attempting to control the albuminuria by means of a rigid diet. In fact it has been shown that after the acute stage is over a more liberal diet improves the condition.

It is as well, however, in following out a case of Bright's disease to have daily estimations of the quantity of albumin, as well as the total amount of urine and of urea eliminated in order to obtain some idea of the state of metabolism and perhaps also the influence of various foods. But it must be said that the proteid foods produce, as a matter of fact, little variation in albuminuria. Nor is there any diminution of albumin excretion on a purely milk diet, which, indeed, in many cases is liable to be accompanied by severe and serious results. But in nephritis, egg albumin is especially bad, seeing that it is excreted in the urine unchanged as egg albumin. The amount of albumin is generally below 1 per cent., though occasionally it reaches 2 per cent., and exceptionally has been found much above that figure. The proteid consists of serum albumin and globulin, and attempts have been made to obtain a definite relationship between these two substances so as to get what has been called the "proteid quotient." Little, however, can be learned from this. It is true that in advanced Bright's disease, especially in the case of the large white kidney, the serum globulin is increased in amount, and a marked and persistent increase is an unfavourable sign.

Casts

It has already been remarked that a great significance attaches to the presence of casts in the urine, and though occasionally the hyaline variety can be found in conditions of passive congestion, it may still be asserted that casts are diagnostic of true nephritis. Whilst in acute and subacute nephritis they are readily found, in the chronic interstitial variety, it is often just as difficult to find the characteristic hyaline casts as it is to find the occasional traces of albumin that are present.

It will not be out of place here to give a brief summary of the nature and significance of casts.

Casts are of three distinct types—

(1) The *hyaline cast*, which is nothing more than albuminous coagulum formed in the lumen of the renal tubules.

(2) The *cell cast*, which consists of a groundwork of hyaline material on which is superimposed nucleated round cells.

(3) The *blood cast*, composed of the same hyaline matrix, with closely packed red blood corpuscles superimposed.

As subdivisions of the second variety of cast, there is found in the subacute and more chronic cases a degeneration of the cell elements, producing either a *granular cast* or a fatty degeneration of protoplasm, forming the *fatty cast*.

These are the main varieties that are met with. Occasionally the *amyloid cast* occurs—a large homogeneous cast, bigger and broader than the

hyaline cast, at one time supposed to be the product of amyloid disease of the kidney, but now observed in other diseases as well.

Casts can be simulated by various hyaline or mucous elements which are found in the urine and which come from the lower parts of the urinary tract; also by small hyaline casts originating in the urethral ducts. These, however, are easily distinguished from the more definitely formed renal casts, as are also the elongated and sometimes tortuous mucous cylindroids.

The names of the casts furnish some idea as to their structure. They are all formed on a hyaline matrix. The blood cast explains itself. Concerning the cell cast there has been most discussion. In the early days of pathological investigation these were called epithelial casts, and at the present day many persist in carrying on the term, regardless of the fact that it denotes a definite etiology which has never been proved, signifying that epithelial cells of the urinary tubules have been shed into the lumina of the tubules. This designation arose from the fact that the early histologists, having to cut their sections by hand, noticed that some tubules were lined by epithelium while others were empty; from the fact that these empty tubules were associated with nephritis, they concluded that the cell casts were the result of shed epithelium. But at the present day, with improved methods, no section is ever obtained showing a lumen devoid of epithelium, nor is there any evidence that this

can shed itself. The other explanation is that leucocytes wander through the epithelium and aggregate in the lumen, just as in bronchitis the leucocytes wander through the mucous membrane and accumulate in the lumen of the bronchus. Hence many are of the opinion that these are true leucocytic casts, and in the light of present knowledge the term "cell casts" is perhaps the most suitable.

Their relationship to the diseased condition is the main factor. In acute nephritis every variety of cast is found. The acute changes in the kidney result in engorgement and pouring out of blood and cells, just as occurs in any other inflammatory area. In subacute nephritis, or in acute nephritis that is subsiding, hyaline casts are found, and cell casts in various stages of degeneration. In granular kidney only the hyaline cast occurs. The blood cast only appears in subacute and chronic nephritis when acute inflammation is superadded.

Here might also be mentioned the condition of syphilitic albuminuria, which is sometimes excessive in amount, and is associated with secondary syphilis.

The estimation of urea has been suggested as a means of determining the process at work in nephritis, but here again little can be learned. It is true that uræmia was originally supposed to be due to a retention of urea in the blood. Occasionally the urea is diminished previously to an attack of uræmia or of eclampsia, and if the patient

recovers it is increased in convalescence. But this is by no means a constant feature, and often there are no such variations of urea in nephritis. It is now known also that urea is by no means toxic, nor, in all probability, are the products that are usually excreted in the urine in health. This latter statement is borne out by the fact that the anuria following excision of unilateral kidney or complete obstruction from a calculus or any other cause, may result in death in a matter of a few days—occasionally even two or three weeks—without any of the symptoms of intoxication that characterise uræmia. Perhaps uræmia might be regarded as a toxæmic state due to the accumulation of the same toxins in the blood stream that are causing the nephritis. Nevertheless, the estimation of the urea gives some index of the processes of metabolism. It has been suggested that more important evidence can be obtained from an investigation of the urea-content of the blood. This, together with the question of estimating the chlorides in the urine, has already been mentioned.

In discussing albuminuria we must insist upon the importance of distinguishing the varieties just described from those resulting from the mixture of the urine with adventitious products arising from inflammation of the urinary tract or, in the case of females, from leucorrhœal discharge.

Disease of Renal-pelvis and Urinary Passages

An examination of the urine will also adduce evidence of disease of the kidney or of the parts

below, such as pyuria in tuberculosis and calculus, or bacterial infections of the kidney or of the pelvis or bladder (see Chap. XVIII). The same applies to hæmaturia, such as is associated with tuberculosis of the kidney, or growths in the bladder, or bilharziosis of the bladder. It must be remembered that tuberculous lesions, or calculi, can produce intermittent symptoms with normal intervals, and that tuberculosis can be associated with severe hæmorrhage, often when the lesion is only slight.

We need only mention here the broad distinction between acid urine in lesions of the kidney and alkaline urine in cystitis. Occasionally, however, as we shall see, a *Bacillus coli* infection of the bladder is associated with an acid urine. More particularly in testing for this latter group of abnormalities, is it necessary to have carefully collected specimens of the urine, uncontaminated by vaginal or preputial discharges. This, indeed, is applicable to all accurate urine work. The necessary conditions can be fulfilled by obtaining catheter specimens, or, in the case of the male, by collecting the specimens directly into a sterilised vessel, after discarding the first washings of the urethra. In all cases, however, it is important to remember that the vessel must be scrupulously clean, even when absolute sterility is not demanded. Extraneous products, such as arise from unclean urine glasses, etc., are likely to obscure the examination.

Extraneous Bodies entering via the Blood and Intestines

The presence of an excess of bile in the blood, as occurs in jaundice, results in the condition of *bilinuria*. Bile pigments, however, must not be mistaken for the normal urinary pigments which are sometimes present in a less concentrated form, though, of course, they are closely allied in composition. The normal pigments are *urochrome*, which is the iron-free product of the blood, producing the normal yellow colour of the urine; and *urobilin*, which is derived from the hydrobilirubin, and so indirectly from the bile pigments in the intestines. Urobilin, which gives the dark colour to the urine, occurs in excess in conditions of intestinal putrefaction and obstruction, and also in hæmorrhages into the intestine and elsewhere. It is increased, also, in pernicious anæmia, where there is excessive destruction of blood corpuscles with a consequent increase of hæmoglobin in circulation; and as a result of blood destruction from various blood poisons, such as antipyrin, sulphonal and antifebrin.

Hæmoglobin itself may be set free in the blood stream and appear in the urine. *Hæmoglobinuria* results from the effects of various poisons on the red blood corpuscles, for example, potassium chlorate and quinine. Occasionally drugs lead to the destruction of hæmoglobin, which is relieved of its iron in the liver, so that the iron-free quota is eliminated, thus producing the condition of

hæmatoporphinuria. These urines are sometimes reddish in colour, but the colour is often masked by the effects of the drug. Sulphonal and trional are particularly potent in producing this condition.

Drugs given by the intestine are frequently present in some form or some derivative in the urine, occasionally in characteristic findings. It is only necessary to mention the urine passed after the administration of salol, the derivative of which in the urine gives a characteristic colour with ferric chloride; this is used as a test for the motility of the stomach; the darkening urine after absorption of phenol; purgen, which sometimes gives a red colour; methylene blue, as mentioned above; asparagus and turpentine, which produce their characteristic odours in the urine, and various drugs, such as lead, arsenic, alcohol, potassium iodide, the finding of which is often of great assistance in diagnosis. Arsenic can be found in the urine in cases of arsenical poisoning.

Volume and Specific Gravity

No description of the urine would be complete without some mention of the volume and the specific gravity—two factors which, under ordinary conditions of life, are fairly constant. Fluids are excreted from the body by other channels, —namely, the skin, the bowels, and the lungs, so that when any of these are functioning in excess the others are less active. In addition, the volume of the urine depends on the vascular supply, the

nervous control, and the constitution of the urine itself.

The nervous control is no inconsiderable factor, as shown by the excess of urine in neuroses and under stress of excitement, and, more particularly, in lesions affecting the centre (probably vaso-motor) in the floor of the fourth ventricle, such as tumours and experimental punctures, and in diabetes insipidus. In all these conditions the specific gravity will vary inversely as the volume of the urine.

In chronic interstitial nephritis and arteriosclerosis there is a characteristic increase in volume, but whether the polyuria is due to a renal change or to a change in the vascular system is uncertain. In glycosuria there is also a large increase in volume of urine, which is pale and watery, as in the other conditions, but has, as its distinguishing feature, a high specific gravity. Occasionally, however, cases of diabetic polyuria are met with having a low specific gravity (in one instance 1,007), which would be deceptive unless the total quantity of sugar passed in the twenty-four hours were estimated. The possible association of lesions such as chronic interstitial nephritis and diabetes must be borne in mind in interpreting such anomalous results.

The specific gravity of the urine depends on the urea and salts and its concentration; from the specific gravity a rough calculation of the quantity of the urea can be made—a method which is often adopted in order to determine the percentage of sugar excreted.

The important diagnostic features are the diminution of the urine in cases where it is normally in excess, as in chronic interstitial nephritis, denoting cardiac or renal complications; or the gradual increase in urine in people otherwise in health, denoting the onset of chronic interstitial nephritis; or the excessive increase, such as occurs in diabetes insipidus, or accompanied by wasting, as in diabetes mellitus.

Finally, mention should be made of a peculiar finding of diagnostic significance, namely, the Bence-Jones proteid. This has also been called myelopathic albumosuria; it is not, however, an albumose, but an indefinite proteid, with peculiar reactions. It is present in a rare type of cancer characterised by multiple myeloma.

CHAPTER XVII

DEPOSITS OF THE URINE

Microscopical examinations—CHEMICAL ELEMENTS—Phosphaturia; oxaluria; uric acid; urates; leucin and tyrosin; cystin—FORMED ELEMENTS: Pyuria; hæmaturia; hæmoglobinuria; epithelium — Spermatozoa — Bilharziosis—Calculus.

DEPOSITS are formed in the urine both in health and in disease, and depend in great part upon the reaction. Though evidence of the nature of the deposits can be obtained from the reaction itself, in all cases it is necessary to confirm this by microscopical examination. It is true that various deposits present such characteristic appearances that they can be identified with the naked eye. These include the brick-red deposit of urates; the white deposit of oxalates, which occurs around the edge of the glass or in the cracks; pus; mucus and blood. Often also the flocculent appearance due to casts can be detected in the same manner, but it is not wise to trust entirely to the naked eye in diagnosis. In urine which is passed clear and free from deposit there occurs as a result of bacterial contamination (the *Micrococcus ureæ*) a deposit of alkaline salts, —ammonia being produced from decomposition of the urea. Highly concentrated urines also deposit a dense layer of urates on cooling.

Deposits may be classified into—

(1) Chemical, the common varieties of which are uric acid, the urates, calcium oxalate, calcium carbonate, and phosphates, and, rarely, leucin, tyrosin, xanthin and cystin.

(2) "Formed" varieties, including blood, pus, mucus, epithelium, casts, spermatozoa, various bacteria and, occasionally, parasites. It will be necessary to discuss these in detail.

Phosphates which are derived from the food—mostly from the vegetable acids, are found in alkaline, or neutral, or even slightly acid urines, and are deposited on warming as a "cloud," which is distinguished from the "cloud" of albumin by dissolving in acetic acid. Occasionally calcium phosphate is deposited as acicular crystals, more particularly in dyspeptics; these crystals may cause mechanical irritation of the urinary passages, especially in children. After a diet rich in proteid material, which necessitates an abundant supply of hydrochloric acid to the stomach, the diminished acidity of the urine may result in the deposit of phosphates; hence the slight deposit often found after meals. In nervous and hypochondriacal individuals also, phosphates are deposited; the condition in which they occur in excess is known as phosphatic diabetes. In decomposing urine the ammonia combines with the phosphates, producing the typical large, coffin-lid crystals of triple phosphates (ammonium magnesium phosphates). These formations occur in all urines after standing, but their presence in the

urine immediately on passing is significant of chronic cystitis, in which condition they are associated with large quantities of mucus. Phosphaturia must not be mistaken for pyuria, to which it bears only a superficial resemblance.

Carbonates are derived from the food, particularly from the vegetable acids, and thus are frequently found in vegetarians, in whom the urine tends to be alkaline, so that a deposit of carbonates and phosphates is formed on standing.

Oxalates, in the form of typical octahedra or "dumb-bells," which crystallise on the side of the glass as a fine white line above the level of the urine, are often found in health, and especially after a diet rich in rhubarb or other vegetables. They are also found associated with dyspepsia and in neurotic conditions. But in small quantities they are of little, if any, significance, and are certainly no proof of the existence of a calculus.

Uric acid is deposited in all urines after standing for some hours, and the distinctive reddish, hard, and definitely crystalline brick-dust deposit is unmistakable, though occasionally colourless crystals are deposited. It is most frequently found in concentrated highly acid urines, and is only of importance when passed as such or at least deposited in excess shortly after the collection of the specimen. People of gouty diathesis readily pass uric acid, and even children of gouty parents are liable to do so. The presence of uric acid deposit does not signify any calculus, although the constant passage of such would favour the

formation of a calculus in the passages. Little can be learned from an estimation of the quantity of uric acid.

Urates are the salts of uric acid in combination with sodium, potassium, calcium and magnesium, and are only slightly soluble, so that in concentrated urines, such as occur in febrile states and after severe sweating, etc., they appear as a brownish-red, amorphous deposit. They are increased in dyspepsia and diseases of the stomach, and in hepatic disturbances. It is important to remember that they are able to reduce copper salts, but they cannot ferment or produce phenylosazone crystals. Sometimes definite crystals of ammonium urate, which owing to their spiky nature irritate the urinary tract, are associated with slightly alkaline urines. Spherical crystals of sodium urate are also occasionally found.

Leucin and *tyrosin* are products of proteid disintegration. Therefore, in diseases associated with destruction of the liver, these bodies are found in the urine as crystals (spherules of leucin and sheaves of tyrosin), and they are of the utmost diagnostic importance in acute yellow atrophy, serving even in the earlier stages to distinguish this condition from the milder disturbances which produce jaundice. They are described also as occurring in phosphorus poisoning, the characteristic lesion of which is degeneration of the liver. Stellar crystals of the phosphates, at first glance, may be mistaken for tyrosin, but it is not difficult to distinguish between these.

Cystin in the form of hexagonal flake-like crystals is found as a constant occurrence in the urine of those occasional cases of what has been called "chemical malformation" of the body. In a case seen by the author, the passage of these crystals was associated with the formation of numerous large cystin calculi. The disease appears to be of a hereditary and family nature.

Very rarely, and only twice within the author's experience, a deep blue deposit of true indigo blue is seen in the specimen. This has been discussed under the heading of "Indicanuria." (See p. 188.)

Pyuria

The presence of pus in the urine, which ought always to be diagnosed by the microscope, indicates inflammation of the parts bathed by the urine. Large quantities of pus can be found in balanitis and urethritis. Pus in an alkaline urine is mostly of vesical origin, and is associated with mucus and triple phosphate crystals and also with various bacteria. But in coli cystitis, as has already been pointed out, the urine is markedly acid. Pus from the pelvis or from the kidney itself is found in an acid urine. The specific organism causing the suppuration can readily be identified and cultivated for diagnosis. Occasionally pus is found in large quantities in an apparently sterile urine, and under these conditions tubercle of the kidney and pelvis, or calculus must be suspected. Special investigations

ought to reveal the presence of the tubercle bacillus, and final corroboration can be obtained by animal inoculation. Numerous polymorphonuclear leucocytes, hardly sufficient to be designated as pus, are found in the inflammations, both acute and subacute, of the kidney, but in such cases the other elements, casts, etc., are of greater significance.

Mucus, rendering the urine and the deposit slimy, is evidence of inflammation and is associated with cystitis, often entangling crystals and bacteria.

Blood[1]

Blood in the urine is either unchanged and bright red or else intimately mixed and altered, producing a brownish discoloration, which in the lesser degrees forms the characteristic smoky appearance of the urine in acute nephritis. Whether unchanged or intimately mixed, it is best diagnosed by the microscopical finding of the red blood corpuscles; these, however, may become disintegrated into brownish débris, from which can be obtained the characteristic hæmin crystals. But occasionally the blood pigments alone

[1] The tests for blood in urine in order of importance are—

1. Microscopical finding of red corpuscles.
2. Guaiacum and ozonic ether test.
3. Production of characteristic hæmin crystals from blood or blood detritus; of special value in the latter.
4. Spectroscope.

are found in the urine, as a result of destruction of corpuscles in the blood stream. It is necessary to determine the origin of the blood. Bright, red, fresh blood, comes from the urethra or from the bladder, as in papilloma, where large quantities of blood may be passed; or in bilharziosis, where the blood is passed at the end of micturition, the result of rupture of the venules that are distended with the bilharzia ova: the diagnosis of this condition is readily made by the finding of the ova themselves. Bright red blood is occasionally found in minute papilloma of the ureter, and still more rarely in what is known as renal epistaxis, in which no lesions can be found *post-mortem.* Altered blood occurs in acute nephritis, in which other characteristic deposits are found, and as an intermittently appearing product in tuberculosis of the kidneys, where it is associated with pyuria. Tuberculosis of the urinary tract is often associated with hæmaturia, which may be intermittent.

Hæmoglobinuria is a condition in which the blood pigments alone appear in the urine, which is brown from the presence of methæmoglobin. It is characteristic of paroxysmal hæmoglobinuria; or of black water fever or Raynaud's disease; or of various toxic hæmolytic processes, such as result from the administration of arseniuretted hydrogen, chlorate of potash, pyrogallic acid and carbolic acid. This must be distinguished from other conditions of pigmentation which resemble it.

Epthelial elements

Epithelium is found in the urine as cells, discrete or in masses,—either epithelial squames from the prepuce or urethra, or the slightly different transitional cells from the bladder or upper urinary tracts. The former are of little significance unless associated with pus cells; both are found in quantity during the healing process following any lesion, and especially after urethritis which has been treated by local applications. Rarely, it is possible to discover masses of cells which are significant of epithelioma of the bladder.

Spermatozoa are not infrequent in the urine of men, and occasionally in the urine of women; in the latter case they can remain alive in the vagina for several days. They are more frequent in constipated young adults, but are not uncommon in old men, and sometimes are so numerous as to result in a cloudiness of the specimen (*spermatorrhœa*).

Parasites.—In the urine of patients suffering from bilharziosis, characteristic ova are readily found, and the freely swimming parasite itself can easily be hatched out by adding distilled water.

Calculus.—Evidence of the existence of a calculus in the urinary tract, apart from the existence of pyuria already mentioned, is only forthcoming when definite calculi, no matter how small, are found. But this is exceptional. Occasionally by allowing large quantities of urine

to stand, or sometimes by filtering through fine gauze, minute uric acid calculi can be discerned. Larger calculi give evidence of their passage in the form of severe pain, but in the majority of cases in which urines are sent to determine evidence of calculi they can afford no assistance.

CHAPTER XVIII

THE BACTERIOLOGY OF THE URINE

Method of collecting sample—B. coli—Acute coli infections of bladder—B. typhosus—B. proteus—B. tuberculosis—B. pyocyaneus—Staphylococci—Streptococci in acute nephritis and cystitis—Pneumococcus—Yeasts—Treatment with vaccines.

NORMALLY the urine, as it is excreted from the kidneys and passed from the bladder, is sterile, and, if collected in an aseptic fashion, will remain so indefinitely. But in passing out from the urethra it collects bacteria from the meatus and from the vulva—parts which often swarm with a prolific bacterial flora. Under pathological conditions bacteria can be found in the urine. These may originate in the blood stream in cases of septicæmia, or more frequently bacillæmia as in typhoid fever; or in the kidneys as in local suppurative lesions such as pyelonephritis or tuberculosis; or in the bladder; or from the urethra as in acute or chronic gonorrhœa; or in the prostate. In addition to the pathological organisms themselves, when these have set up any condition of cystitis, saprophytic bacteria may obtain entry and thrive.

In all cases, therefore, in dealing with a bacterial infection, it must be determined at which part of

the tract the infection lies. If there is a suspicion that the urethra be the site, then the urine should be collected in three or four sterile vessels in succession, and whilst the first will contain a large quantity of pus and bacteria, the second will contain less, and the third or fourth will be quite free from organisms, these having been washed away in the first passing. If the bladder is infected or the parts above, then all the samples will contain bacteria, and a catheter specimen is, in men, advisable and, in women, essential. It is seldom, if ever, that in female urines epithelial cells and bacteria of vaginal origin are absent. A markedly alkaline urine containing triple phosphates is significant of cystitis, though cystitis due to the bacillus coli or to the bacillus proteus is associated with an acid urine. An acid urine containing organisms other than bacillus coli is highly suggestive of a nephritis. It then becomes necessary to determine which kidney is infected, and for this purpose separate urines ought to be drawn off by ureteral catheterisation, always into sterile vessels. In retention from nervous or organic causes an important means of infection is from without through careless catheterisation.

In order to isolate the specific organism different media with selective activity must be employed, and often the type of organism can be suspected from the appearance of the urine. A marked pyuria in which no bacteria can be found is highly suggestive of tuberculosis. A large variety of organisms have been described in the genito-

urinary tract, and the more important of these will now be taken *seriatim*.

Bacillus coli

The bacillus coli may occur in the urine at all ages, commonly in young children, especially females, and also in the aged, either in an acute or a chronic state. Clinically the acute cases are characterised by pyrexia, often rigors and pain-

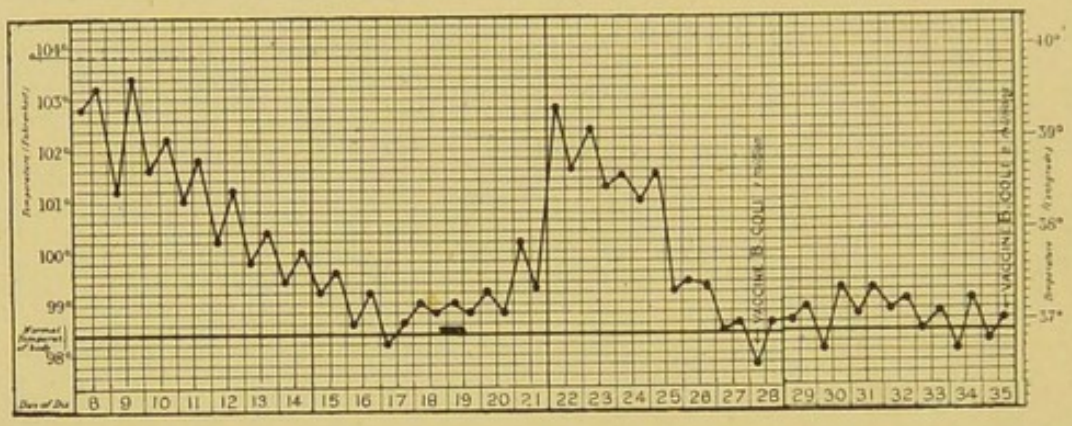


FIG. 25.—Case of coli bacilluria simulating typhoid fever. A girl aet. 9, with headache, pains in back, abdominal pain and some spots. Agglutination tests with typhoid and paratyphoid bacilli negative. B. coli isolated from urine and vaccine from this satisfactorily employed.

ful micturition and may resemble typhoid fever. Many cases of pyrexia in children, otherwise unexplainable, are only diagnosed by a bacteriological examination of the urine. Usually it seems to be a hæmatogenous infection, though it would appear that occasionally it can work its way up from without, from the perineum, which would account for cases of coli cystitis, in females especially, and also for the cases of coli infection superadded to a chronic gleet. Also it is highly probable that infection of the bladder

can result from the direct passage of bacteria from the bowel or an adherent inflamed appendix. It seems reasonable to suppose that the bacillus coli, together with other organisms normally existing in the body, is constantly entering the blood stream and under normal conditions is either destroyed or eliminated. But if there be a site of diminished resistance, then these organisms can flourish, as is not infrequently seen. This is probably the explanation of a variety of pyelonephritis, especially that which is so common in pregnant and puerperal women. In this condition there is a highly acid urine containing much pus and many bacilli. Pyuria, with a high acidity, is characteristic of B. coli infection of the kidney or bladder, and the irritation produces frequent micturition. The bacillus, however, is not often a typical colon bacillus when it is found in the urinary tract, inasmuch as it does not give all the characteristic cultural reactions, but when it is remembered that the colon bacillus outside of the intestinal tract rapidly alters its character, the finding of a large variety of atypical bacilli is readily understood. Recognition of this is an argument in favour of the use of autogenous vaccines in these infections. *Bacillus coli* in the urethra will be treated of later. Coli infections of the urinary tract readily respond to vaccine therapy, and after several injections of an autogenous vaccine, though often also of a stock vaccine, the symptoms subside: the frequency of micturition diminishes, the urine becomes less

acid, and the bacilli rapidly disappear. In children, who suffer generally from the acute variety, the cure appears permanent, and also in the acute variety in adults; but in the chronic coli infections, and especially in those of old people, though the bacteria disappear and the symptoms are relieved, the cure is only temporary, and after an indefinite interval the symptoms return. They can, however, be kept in check by occasional prophylactic doses of a vaccine (Fig. 46).

B. typhosus

The typhoid bacillus is occasionally found in the urine during the course of, but more frequently during the convalescence after, typhoid fever, and here it seems that the bacilli can pass through the kidney tissue without producing any damage. Occasionally bacilli are found in the urine in such large quantities as to render it turbid. This bacilluria is not necessarily accompanied by pyuria or other signs of nephritis: the bacilli can readily be cultivated upon special media (MacConkey's), and give the characteristic cultural and agglutinative reactions of Eberth's bacillus. They usually disappear of themselves, and may disappear with urinary antiseptics; very occasionally they are discharged in the urine periodically for a long time after recovery and in a potentially virulent stage. Hence the person harbouring them forms one variety of typhoid carrier.

Bacillus proteus

This is a common organism, causing putrefaction with a characteristic odour. It is said to be able to produce a cystitis when introduced into a healthy bladder, and it is frequently found in the highly smelling urines of chronic cystitis. In many respects it resembles the colon bacillus, but the putrefactive odour readily directs attention to the proteus bacillus. The absorption of its products of decomposition gives rise to a condition of intoxication (sapræmia). It is amenable to vaccine therapy, though not so satisfactory in that respect as is the B. coli infection. It is often superadded to some chronic lesion such as enlargement of the prostate; when it is only possible to keep the infection in check with vaccines.

Bacillus lactis aërogenes.—This is occasionally found and has to be distinguished from bacillus coli.

Bacillus alkaligines.—This is also sometimes present in the case of cystitis, and though actively motile like the colon bacillus, differs from it in producing an intense alkaline reaction of the urine.

Bacillus tuberculosis

This organism is found in the urine from cases of tuberculous cystitis or tuberculous lesions in one or both kidneys. It is associated with a definite pyuria, and, when seated in the kidney,

the urine is always acid. Unilateral lesions may produce only intermittent pyuria, but, as already remarked, pyuria apparently sterile is suggestive of tuberculosis. Occasionally there is severe and intermittent hæmorrhage, especially in tuberculous cystitis, though the ulceration may be small. The localisation of the lesion to the bladder, or to the respective kidney, falls within the province of cystoscopy. Typical bacilli can be found, though often with great difficulty, in the urine which has passed naturally or has been obtained from the individual ureters; this necessitates a high speed centrifuge and repeated washings of the sediment to remove the salts which obscure the staining reactions. It is often confounded with the smegma bacillus, which is harboured in the prepuce at times in great numbers; but the catheter specimen would readily prevent this mistake, as also would a thorough appreciation of the staining characteristics of these two acid-fast bacilli. Tuberculosis of the genito-urinary tract has been treated by tuberculin injections with great success by genito-renal surgeons, who, indeed, used it long before the modern era of vaccine therapy. There are two methods of diagnosing tuberculosis of the urinary tract which, although as yet still in the purely scientific stage, give evidence of being of practical utility. Russ has put forward a very ingenious electrolytic method of isolating the bacilli from large quantities of urine, depending on the fact that when a weak current is passed through the

fluid the bacteria will all collect at one pole. The complement-fixation method of diagnosis, analogous to the Wassermann reaction for syphilis, has also been applied with some measure of success; it has for its object the demonstration of the tuberculous antibodies in the urine itself.

Bacillus pyocyaneus

This organism has been found in the urine, and can be readily identified in cultures by the characteristic blue growth. Occasionally it leads to a greenish discoloration of the purulent discharge or of the edges of a suprapubic or perinæal wound. It produces a cystitis and an ascending infection of the genito-urinary tract. Vaccine therapy is efficacious in removing the bacilli from the urine (see p. 100), but there is uncertainty as to the permanency of the cure.

Staphylococcus pyogenes aureus. — This also occurs in a pus-forming lesion of the kidneys or bladder. It can be readily isolated from the urine. It is also amenable to vaccine therapy.

Streptococci are occasionally found, and search ought always to be made for them in cases of acute nephritis, where it is possible that the lesion is due to an infection with these organisms which may have obtained entry through the tonsils or perhaps through the intestines, and more especially in scarlatina nephritis. So far investigations on these lines have not been very fruitful. But in the present state of our ignorance this line of investigation should constantly be borne in mind. Cystitis

is occasionally due to a streptococcus which probably has its origin in the intestines, whence it spreads directly to the bladder. In a case recently seen by the author, this organism abounded in the urine, but could only be obtained in culture on nutrose agar, and then with some difficulty, but the administration of a vaccine so prepared was accompanied by improvement.

Pneumococcus has also occasionally given rise to cystitis and nephritis.

Yeasts.—Occasionally large quantities of yeasts are found in the urine, generally in diabetic patients, and most frequently in women, the yeast obtaining a direct entry along the urethra and flourishing in the sugar media. Indeed, it is possible for fermentation to take place to such a degree that the specific gravity of the urine is considerably diminished, and the gas formed may produce the condition known as pneumaturia.

Note.—In many cases of calculi in the kidney or bladder or other lesions in which contaminating organisms have set up a process of inflammation, it is often advisable to precede operation with a preparatory course of vaccines in order to remove the organisms in question.

CHAPTER XIX

INFECTIVE CONDITIONS OF THE URETHRA AND EXTERNAL GENITALS

Saprophytes normally present—Pus cells as evidence of infection — Method of collecting samples — "*Threads*" — Leucocytes as result of local treatment—*Gonococcus*—superadded secondary infections—Results of vaccine therapy—*Staphylococcus*—*B. coli*—Bacteriology of external genitals—Spirochæta pallida, technique of examination.

NUMEROUS organisms have been identified as causing urethritis. Most important among these are the gonococcus, the staphylococcus, diphtheroid bacilli, and the bacillus coli. All these may set up a primary urethritis, or a secondary infection superadded to an existing lesion—most frequently chronic gonococcal infection. They may produce either acute inflammation accompanied by a purulent discharge, or they may go on to chronic inflammation with little and only occasional discharge, but always, at some time or other, pus cells can be found, though often in small quantities. A bacterioscopic examination of the discharge reveals the nature of the infection, but it must be remembered that the orifice of the urethra, and still more so the prepuce, are the seat normally of organisms of a saprophytic nature, which are liable to be

mistaken for pathogenic organisms. More especially is this the case with a diplococcus which resembles the gonococcus morphologically, but differs from it in its staining properties. Although some observers have identified in the urethra a Gram-negative diplococcus resembling the gonococcus, the author has not met with this. The micrococcus catarrhalis has indeed been described in a few cases of urethritis, but this must be of very rare occurrence. In females the bacteria normally present in the vulva are much more varied and prolific, so that the difficulty of identifying the pathogenic organism is greater. But, if it be recognised that the pathogenic organisms produce inflammation which is associated with pus, then the presence of pus cells will be an important diagnostic aid. But here again it must be determined whether the pus comes from the prepuce or from the urethra itself. We have known a tertiary ulcer of the glans accompanied by a profuse purulent discharge swarming with the smegma bacillus, which was mistaken, owing to a superficial examination, for tuberculosis of the urinary tract.

Collection of material

In acute inflammations sufficient pus can be expressed from the urethra to allow of a direct examination, but in the chronic stage this can often only be obtained first thing in the morning before the urethra has been washed out; sometimes even this is not possible. A satis-

factory method of examination is to collect the first urine in the morning into three tubes, respectively containing one dram, two or three drams, and in the third tube, the remainder. The first tube will contain the urethral contents, the anterior urethra having been washed in transit, whilst in the second tube may be found some pus cells, and, what is more important, a number of threads from the urethral lacunæ or from the prostatic ducts; these are significant of chronic inflammation. If prostatitis exists, it may be necessary to massage the prostate previously, and again collect into three vessels.

"Threads"

These ought to be examined immediately, and can be removed from the urine with a fine pipette without centrifugalising, which indeed breaks them up. The significance of threads is a little indefinite. Now that the danger of a chronic gleet is recognised even to some extent amongst the laity, many "matrimonial candidates" are sent, or voluntarily present themselves, for examination, desirous of being declared free from infection. In these cases the difficulty of giving a decided opinion is considerable.

Threads consist of mucus entangling leucocytes and occasionally epithelial cells, and careful examination sometimes reveals, in certain of them, bacteria and occasionally gonococci. Experience points to the fact that many people have threads in the urine perpetually, and yet do

not seem to produce any infection in others. There are, it is true, threads that come from the prostate, consisting of mucus and prostatic cells, but it must be taken for granted that wherever polymorphonuclear leucocytes are found they are significant of inflammation. Thus an attempt should be made to discover the site of the inflammatory focus, and also the infective agent, either by direct bacterioscopic examination or by cultural methods.

But an important point is that after local treatment, which is often drastic, the process of repair forming part of a traumatic inflammation results in the appearance of leucocytes. Hence an examination of a case of gonorrhœa recently treated by local applications often results in the finding of large numbers of cells which might be mistaken for the inflammatory cells resulting from the primary infection. In these cases, however, there is frequently associated a large number of exfoliated, squamous epithelial cells, and specific bacteria are not found; furthermore, if the case be cured, these cells disappear shortly from the urethra. A recognition of the organisms associated, more especially, with chronic urethritis is important: many refractory cases of long-standing infection, in which local treatment is unable to reach the depths of the urethral lacunæ and other recesses where bacteria are harboured, are often amenable to treatment with vaccines of the bacteria concerned in maintaining the inflammation. For this purpose it is necessary

to carry out cultural investigations and obtain the organisms in pure culture. Thus various media possessing selective activity for the different organisms have to be employed, and as several, notably the gonococcus, will not survive very long after removal from the body, it is necessary to inseminate culture tubes direct from the patient and incubate immediately.

We may now touch in detail upon the commoner bacteria found in this connection.

The *gonococcus* can readily be found in the acute stages in and amongst the leucocytes, but as the inflammation subsides it becomes much more difficult to find it, and still more so if local treatment is being employed. But suspension of treatment for a day or so will cause a reappearance of pus and of gonococci. Cultures can be obtained in the untreated cases by inseminating the pus in quantity, or the deposit obtained from the urine by the centrifuge, on to specially prepared human blood-agar tubes. It must be said, however, that one often meets with failure, even when the discharge is profuse. In chronic gleet, gonococci can be found occasionally, though sparsely, in the threads. It seems that the gonococcus may set up a chronic urethritis or a chronic prostatitis, and in the course of time other organisms, such as the staphylococcus or the bacillus coli, or the diphtheroid bacillus, may obtain an entry and take part in the inflammation. Many of these chronic infections also are maintained by the secondarily infecting organism long after

the gonococcus has been eliminated. In these cases it is necessary to obtain cultures directly from the patient himself in the manner described above, and to treat with a mixed vaccine containing the organisms concerned.

In females the gonococcus can readily be found in the purulent discharges of the acute stage, but in the chronic stages it is exceedingly difficult. Direct investigation of the urethral material and sometimes of swabs from the cervix will occasionally reveal the organism. But it is seldom possible to cultivate the gonococcus from these long-standing cases. The presence of pus cells is of great importance in suggesting an infection, though they may, of course, be due to cervical erosions, etc., but their absence is of great value in investigating cases of leucorrhœa. Leucorrhœal discharge often is found to consist entirely of squamous epithelial cells with numerous saprophytic organisms, but no pus cells.

Staphylococci of themselves can set up a urethritis and maintain it. Recently the author has seen several cases in which pure cultures of staphylococci were obtained and which responded readily to bacteriotherapy.

Bacillus coli can also set up urethritis primarily, but more often it is superadded to an old gonococcal infection.

In addition, various diphtheroid organisms have been found, and in a few cases which have been subject to local treatment the bacillus subtilis has also been obtained.

Results of Bacterial Treatment

Though acute gonorrhœal infections have frequently appeared to improve rapidly with autogenous vaccines in doses increasing from one million up to twenty millions at short intervals, it is difficult to say how far this treatment is responsible for the cure. But in chronic gonococcal infections, whether due to the gonococcus alone, or to a mixture of bacteria, the administration of autogenous vaccines has frequently resulted in satisfactory cure. As regards staphylococcus and bacillus coli infections, the same good results are found with vaccines as in infections with these organisms in other parts of the body. But it appears to be more essential in these than in other cases to employ autogenous vaccines.

The Bacteriology of the External Genitals

The ordinary saprophytes have already been mentioned, but there are two organisms associated with ulcerative lesions in this neighbourhood which are important and perhaps diagnostic. The *Spirochæta pallida* can be obtained readily and by anybody after a very little practice from all syphilitic lesions *before treatment.* Local treatment rapidly causes disappearance of these organisms. Sometimes they are present in enormous numbers, at others only scantily, but always in the serous exudate obtained from the base of the ulcers or from their surroundings. It is not sufficient merely to examine the discharge

from a suspicious sore, which is usually swarming with contaminating germs, but the lesion must be cleaned up and the serum taken and examined directly.[1] The importance of identifying them is

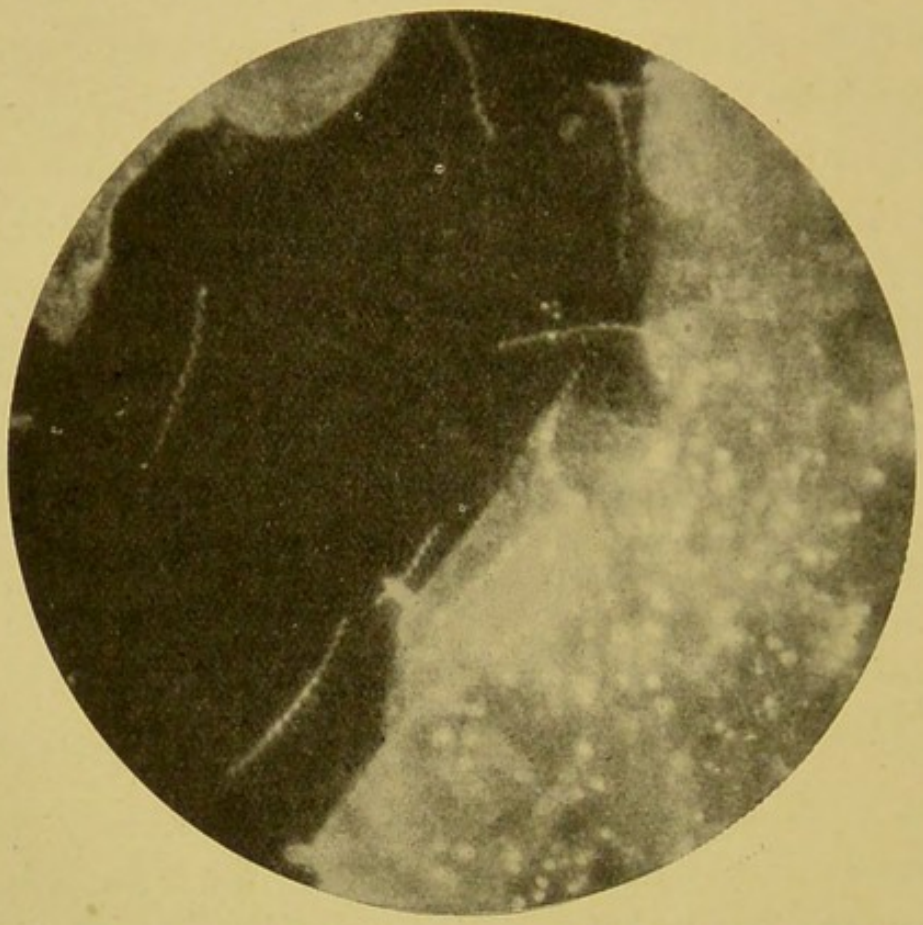


FIG. 26.—*Spirochæta pallida*, dark-ground illumination (from film by Pathé Frères).

greatest in those atypical and occasionally multiple syphilitic ulcers, which may not even be indurated;

[1] The serum is obtained by gently rubbing the base of the sore with a piece of lint, after applying methylated spirit; in a few minutes clear serum wells up and can be examined either directly by the "dark-ground illumination" method and seen alive; or after preparation by the Indian-ink method. For this latter the serum is mixed with double its volume of Indian-ink and a film made as for a blood-film: the organisms stand out on a black background.

and more important is it to make prolonged search before deciding against the infection, since it is recognised that the efficacy of modern syphilitic treatment depends upon its promptness. Other spirochætæ are found, more commonly the *S. refringens*, but these to the trained eye can readily be distinguished. Spirochætæ can also be found, often in numbers, in the serum obtained by scarifying chondromata or the indurated areas around the vulva. They can also be found in urethral chancres, from which a little serum has been made to exude by pressure.

Soft sores have been associated with a small diplobacillus, known as *Ducrey's bacillus*, but although this can often be found in them it has no absolutely specific importance.

CHAPTER XX

DISORDERS OF DIGESTION

Vomitus — Test Meal—Hydrochloric Acid — Variations in Disease; hyperchlorhydria; peptic ulcer; cancer—Digestive activity—Motility of stomach; atony, obstruction—Hæmatemesis—Pus, etc.—Bacteria.

At the present time the means at our disposal of diagnosing disturbances of digestion and diseases of the stomach are limited. But from various laboratory methods we are able to derive some information. Either in a test meal of known amount or in the ordinary meal that has been withdrawn or vomited, we can estimate the quantity of gastric juice secreted by the stomach and test its activity, as well as the rapidity of absorption and the motility; by other methods we can certainly diagnose coarse lesions, such as ulcers and cancers, and perhaps in some cases even the early stages of disease. The activity of the digestive ferments can be tested against proteids, milk, etc., *in vitro*, and indications for treatment thus obtained.

It must be remembered in investigating the gastric juice that the stomach has a marked capacity of functional adaptability, as was shown by Pawlow in his fascinating experiments. With different diets there is a variation in gastric juice production. For example, with a carnivorous

diet, the hydrochloric acid content is increased, but on changing to a vegetarian diet the hydrochloric acid after a time becomes diminished to meet the altered circumstances.

It may be taken, however, that in a normal adult, eating a normal mixed diet, a definite amount of gastric juice is secreted, containing hydrochloric acid and the ferments, pepsin and rennet. The amount of hydrochloric acid is usually about 0·2 per cent., and it is the variations from this quantity that are of the greatest assistance in diagnosis.

The hydrochloric acid does not remain long in the stomach in the free stage, but enters into combination with the proteid matter of the food, forming acid albumen. The earlier methods consisted of colour tests for the presence of free hydrochloric acid; although an excess of free hydrochloric acid can be taken to denote diseased states, such as hyperchlorhydria and gastric ulcer, such tests by no means give an accurate idea of the amount of hydrochloric acid that the stomach secretes. For this purpose an accurate estimation of the total combined chlorides—that is, the acid proteids—and the free hydrochloric acid is necessary; this can be carried out readily by the method introduced by Willcocks, which gives the so-called "physiologically active hydrochloric acid."

Test meal

The gastric juice for examination is easily

obtained by means of a test meal given early in the morning on an empty stomach. If, however, dilatation of the stomach is suspected, the stomach ought to be emptied first thing in the morning in case any contents have remained over night. The test meal should consist of a pint of weak tea, with a little milk and sugar, and thinly buttered toast. It should be drawn off from forty minutes to an hour afterwards. No water should be poured down the stomach tube to start the syphon action, but a suction bottle might be employed and the contents obtained thereby in the bottle. The amount obtained is generally about 3 to 4 ounces. It gives an acid reaction to litmus and to Congo red, indicating the presence of free inorganic acids (HCl). It contains pepsin, and so digests a disc of coagulated egg albumin in a few hours, and also rennet, which coagulates milk in a few minutes, whilst the solid material shows microscopically the starch granules from the food, but no micro-organisms; also various products of the partial digestion of the proteid quota of the test meal.

Variations in Acidity

The fluid filtrate has to be tested for the total amount of *physiologically active hydrochloric acid*, which should be present to the extent of 0·2 per cent. Hydrochloric acid is increased in acid dyspepsia (hyperchlorhydria) and true peptic ulcers whether of the stomach or duodenum. Between these it is often difficult to distinguish. An amount equal

to 0·3 per cent. is not uncommon in these conditions, often accompanied by a marked excess of free hydrochloric acid. And in one case of hyperchlorhydria in an asylum patient there was present 0·4 per cent. of physiologically active hydrochloric acid. The amount is diminished in

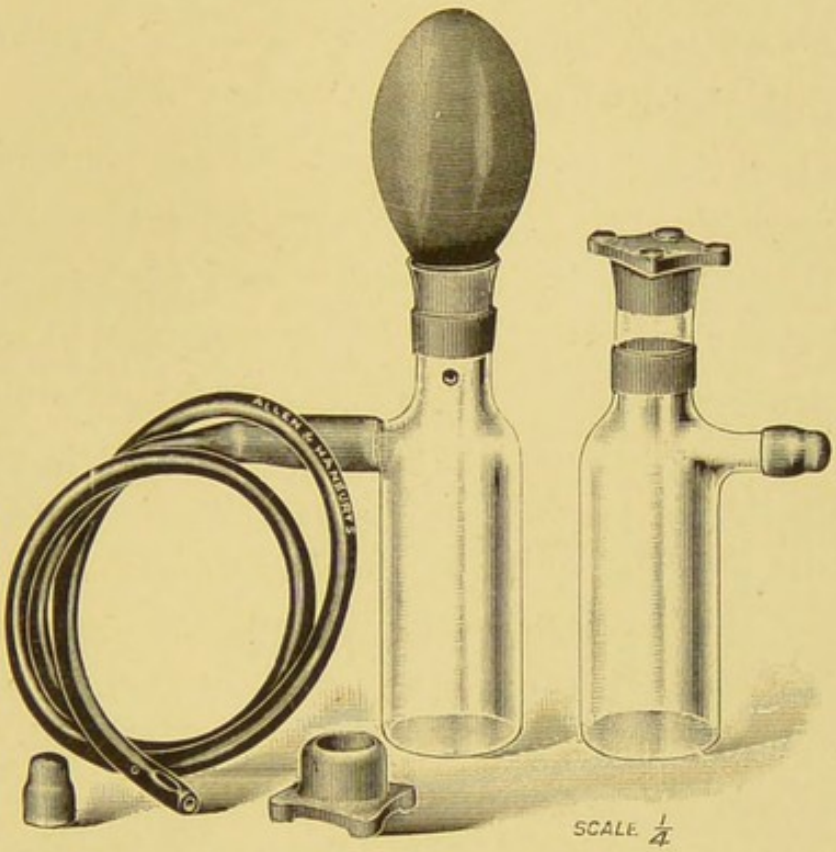


FIG. 27.—Senoran's Stomach Aspirator. (Allen and Hanbury.)

atonic dyspepsia, in anorexia nervosa, and, often to almost complete absence, in cancer of the stomach. The age of the patient will be of assistance in differentiating between these conditions.

In cancer of the stomach the hydrochloric acid content varies with the site of the growth. In growths at the cardiac end the diminution is most marked, reaching to as little as 0·04 per cent., with no free hydrochloric acid, but in growths at

the pyloric end the diminution is not so considerable; occasionally the figure may be 0·1 per cent., but again there is no free hydrochloric acid. In the early days of these investigations it was suggested that the diminution of hydrochloric acid was due to an excessive use of chlorides by the neoplasm, and hence that malignant growths in any part of the body would be accompanied by a diminution of hydrochloric acid in the gastric juice. But this was soon proved to be incorrect in the case of man, and investigations on cancerous mice, carried out by Copeman and Hake, demonstrated that, if anything, the hydrochloric acid was increased. It may be that the explanation of the diminution in acid-production in cancer of the stomach is to be found in the destruction of the acid-secreting cells of the stomach. These are probably the peptic cells which are confined to the glands at the cardiac end of the stomach, and hence neoplasms in this part would result in a greater interference with the acid secretion than at the pyloric end. This agrees with the facts observed. But it must be remembered that the secretion of gastric juice is in a high degree dependent upon the nervous element, as shown by its marked diminution and occasional absence in the nervous states already mentioned.

In connection with peptic ulcer it must be remembered that the acidity of the contents of the stomach is retained in the duodenum as far down as the entrance of the common duct, and so peptic ulcers are found in the duodenum up to

this point. Hence the hyperacidity of the test meal is significant of ulcer, either of the duodenum or the stomach.

In the vomitus of cases of gastric ulcer there is usually a marked excess of free hydrochloric acid, even when the vomiting occurs two hours or more after a meal: the evacuation often of itself gives relief from the burning pain due to the acid.

Digestive activity of Gastric Juice

This depends upon the adequate presence of ferments and hydrochloric acid. Valuable information can be gained by testing the activity of the filtrate against discs of egg albumin, milk and starch respectively in test tubes kept at body temperature.

Pepsin is seldom much altered in quantity, though occasionally diminished, but its activity is influenced by variations in the hydrochloric acid. An excess of hydrochloric acid will impede digestion, even of the albumin disc in the test tube. But the addition of a few grams of bicarbonate of soda will remedy this and result in complete digestion and solution of the albumin, thus pointing to the line of treatment to be followed in cases of hyperchlorhydria. If hydrochloric acid be deficient it will be necessary to add a minute amount to obtain complete digestion of the albumin; again indicating the line of treatment.

The examination of a test meal as a routine procedure should also comprise an investigation into the starch digestion of the saliva, which is

supposed to continue in the stomach until a certain amount of hydrochloric acid has been secreted. This is denoted by the presence of reducing sugars.

Motility of Stomach

Under normal conditions the stomach should empty itself in from three to four hours. When, however, from special conditions, such as atony or dilatation, food is retained in the stomach for a considerable time, fermentation occurs and lactic acid and butyric acid are produced; at the same time the bactericidal factor due to the hydrochloric acid-content having been removed, there is a growth of micro-organisms. Yeasts, sarcinæ, and occasionally long bacilli, can be identified in the vomitus which in these cases is present in considerable amounts. At one time the long bacillus found in the vomitus under these circumstances was taken to denote cancer, but this so-called Oppler-boas bacillus is now looked upon as merely an association of fermentation.

The presence of *lactic acid*, then, which is easily revealed, is indicative of fermentation and retention of the product in the stomach in such conditions as atony and dilatation from any cause whatever. Hence it is found in cancerous obstructions.

The motility of the stomach can be coarsely investigated by administering salol, and then repeatedly at intervals examining the urine with perchloride of iron to determine the time when the

salol derivative (salicyluric acid) is excreted by the kidney; this gives a characteristic violet colour. The salol is only decomposed when it reaches the duodenum and comes in contact with the alkaline juices. This under normal conditions should occur in from twenty minutes to an hour. Perhaps this test is of more value when the time of disappearance of the derivative from the urine is taken: this, normally, should be twenty-four hours, and if delayed long beyond this the motility may be taken to be impaired. Another means of determining the motility of the stomach is to empty it the morning after a moderate evening meal, at which time little or no contents ought to remain in the organ.

An excess of *mucus* in the gastric contents, either obtained by test meals or the ordinary vomit, denotes gastritis. It is unnecessary to adopt any tests for mucus, which can be diagnosed at a glance. Its presence is sometimes so marked that it interferes with the chemical examination. Though a constant feature in the gastritis of chronic alcoholics and in cirrhosis of the liver, it is found in any variety of chronic gastritis. It should be remembered that only excess of mucus is indicative of an abnormal state.

Hæmatemesis

Blood in the stomach contents may be derived from lesions in any part of the alimentary tract, from the mouth to the pylorus, and may even have

come from the lungs and have been swallowed. Blood freshly shed will be obtained in its red condition, but in the stomach it is rapidly converted into acid-hæmatin, which gives to the stomach contents, especially in some cases of carcinoma associated with atony, a characteristic coffee brown appearance.

The presence of blood denotes either oozing from the congested vessels, as in cirrhosis of the liver; or small hæmorrhages from ulcers or large cancerous masses, in which case the blood is usually retained for some time; or else severe hæmorrhages from a perforated vessel in a true peptic ulcer, when the vomitus is bright red. It is not necessary here to detail the various causes of gastric hæmorrhage, or the differential diagnosis of other conditions in the neighbourhood of the pharynx, or mouth, or lungs, which might simulate it, nor even to give the methods of testing for blood. But it may be said that fresh blood can readily be determined under the microscope, and in our experience the best test for altered blood in the stomach contents or even in the fæces is the production of the characteristic hæmin crystals from the detritus.

Pus, which is diagnosed by the microscope, is rarely found in the stomach contents, and only in conditions of phlegmonous gastritis—a condition, seldom occurring, of diffuse suppuration, spreading throughout the coats of the viscus, and always fatal. Pus cells are sometimes found in cancer of the stomach, and have been reported as coming

from a subphrenic abscess which has burst into the stomach.

Bacteria

We have already touched upon the bacteria present under abnormal conditions of fermentation, and we have only to supplement this by pointing out that in chronic gastritis where such fermentation has taken place there is no limit to the prolific flora that can be found. This is often aided and increased by a secondary infection from a foul mouth. It must be remembered that all these bacteria, such as bacilli, staphylococci, streptococci, and the like, are all of the nature of saprophytes, though they may set up a condition of toxæmia. This has quite recently been treated by means of vaccines prepared from some of the organisms in question. The author has reported a case of diffuse phlegmonous gastritis due to a streptococcus infection.

Fæcal vomiting with its important significance does not necessitate any description here. Occasionally in the vomitus alimentary parasites are found, such as round worms, tape worms, and whip worms.

Little assistance, if any, can be obtained in diagnosing tumours of the stomach by searching for tumour fragments in the vomitus.

In most vomits epithelial cells in the form of large nucleated squamæ are found in quantities; they are derived from the saliva.

The investigation of the stomach contents for

various poisons is, of course, of medico-legal importance. This necessitates special toxicological knowledge, and usually attention is directed to a type of poison by the local lesions produced in the mouth and its neighbourhood.

Other means of diagnosis of the gastric contents which are being recommended do not appear to be of sufficient practical utility to be encouraged. The swallowing of a small silver bucket with food contents attached to a thread which is tied to the teeth, the whole being withdrawn after some hours, or the passage of test papers into the stomach, or of gelatine capsules, certainly do not commend themselves as suitable means of diagnosis.

CHAPTER XXI

THE FÆCES

Variations with diet—Quantity—Formation; pipe-stem stools, Colour; acholic stools; effect of drugs; green stools in infants; Acid fermentation—Mucous colitis—Pus and inflammation — Blood; occult hæmorrhage — Gallstones and biliary sand—Intestinal sand—Parasites—Bacteriology; food poisoning—Gærtner's bacillus—B. coli—B. typhosus—B. paratyphosus, etc.—B. tuberculosis.

THE investigation of the fæces is generally neglected, although it must be recognised that much can be learned from them. The behaviour of the alimentary canal as far as the pylorus can be followed by means of test meals, as already described; but beyond that point information can only be obtained from examination of the fæces. The digestive processes, the activity of the pancreas and the liver, the musculature, evidence of obstruction, either in the intestine or in the bile or pancreatic ducts, alterations in the mucosa, and the influence of certain drugs, can all be deciphered, or at least some light can be thrown upon them by such an examination. It is true that the average hospital patient, and many other people also, can give no information as to the nature of their stools; in fact, it is perhaps only amongst neurasthenics that daily observation is made.

The *quantity* passed daily varies with the individual and with the diet. Diet containing vegetables and quantities of indigestible foods results in bulky stools.

The consistency varies with the peristalsis and with the amount of water. The liquid contents of the ileum, in passing through the large bowel, lose water and become inspissated, under normal conditions, as "formed" stools. If peristalsis is hastened, as in some cases of enteritis or colitis, and at times in neurotic subjects, then the contents are hastened through the colon, and liquid or lienteric stools result. If, on the contrary, the transit through the large bowel is delayed from any of the causes that produce constipation, such as want of secretion, too little fluid, or too little bulk, then hard inspissated scybala result.

The *size* and *shape* which the stool assumes correspond to the lumen of the large bowel; although in partial obstruction, such as is seen in new growths, the motion is narrowed and sometimes typically pipe-stem in appearance, equally small stools can be found in various states of neurasthenia, consequent upon a spasmodic stricture of the bowel. These small stools, however, are often found in chronic obstruction, whether from new growths or from a fæcal mass which has become channelled; if alternating with attacks of diarrhœa these stools are of greater significance.

The *colour*, though normally dark, and due to stercobilin—a pigment identical with hydro-

bilirubin—also varies with the diet. A vegetable diet causes a pale colour, a milk diet a light yellow colour, and flesh diet a dark colour, owing to the combination of iron in the hæmoglobin of the meat with sulphur. Depending as it does upon the presence of bile pigments or their products, the colour forms an index to the bile excretion. When there is complete occlusion of the common bile duct, the stools are white and typically acholic. On this appearance has been based a very valuable classification of the varieties of jaundice, dividing them into jaundice with acholic stools, and jaundice with normal bile-containing stools. The former class include all the cases of obstruction from the duodenum to the hilum of the liver, and, according as the stools have a temporary or permanent acholic character, the transitory conditions, such as catarrhal jaundice, can be separated from those which are permanent, such as gallstones or neoplasms.

An absence of pancreatic secretion will result in imperfect digestion of fats, and the stools will be pale yellow and typically greasy. But it is hardly possible to distinguish by ordinary means of observation between the fatty stools thus produced and the pale stools of a milk diet; chemical investigation will detect the difference. Marked colour changes are significant of other lesions. A black colour denotes blood escaping into the bowel from a point high up, generally seen in duodenal ulcer, the black colour

being the result of the decomposition of the hæmoglobin and the combination of the iron thereof with sulphur. If this is in excess the stools are black and tarry, and very significant, especially when associated with a history of fainting or fainting feelings at stool. But black stools are also found as a result of certain drugs, most commonly iron and bismuth, and here the astringent nature of the drug generally produces a black inspissated motion. Blood effused low down in the bowel would, of course, show as bright red, but instead of being intimately mixed would streak the motion, as seen sometimes in cancer of the rectum, or would follow it, as in hæmorrhoids. In children melæna is not uncommonly the result of nose bleeding and swallowing of blood and in infants it is occasionally seen from blood sucked from the maternal nipple. A yellow stool results from the taking of rhubarb, senna, santonin, etc.; it is the normal appearance found in children. A greenish stool can result from an excess of bile, the colour varying from light to dark green. But the green stool becomes of importance in young infants. The green colour here is probably due, though definite proof is lacking, to chromogenic bacilli, and several such have been described. But, whatever the etiology, the fact remains that these green stools form a most important danger signal.

The *odour* is the result of bacterial decomposition and putrefaction, and is not a necessary part of the digestive process. It depends on the bacterial

flora of the intestine and on abnormally prolonged retention. It is significant that the healthy stools of a breast-fed infant are not objectionable, whilst the stools of a milk-fed infant have a markedly sour odour, and the greenish stools described are highly offensive. The lactic acid fermentation of the sugar, which is often given in excess in the artificial foods of infants, produces much discomfort; the acid stools often lead to irritation of the buttocks and extensive excoriations, all of which disappear readily on proper feeding. The end-products of proteid decomposition are indol and skatol, which are the cause of the putrefactive odour.

The naked-eye examination is often repaid by the finding of indigestible food materials, such as fruit-stones, or undigested food, as in diarrhœic stools, or blood and fat, as well as many intestinal parasites, gallstones, enteroliths, an excess of mucus, and even pus. A microscopic examination will confirm the presence of mucus, of various resisting vegetable products, such as peel, skins, tendons, etc., and will definitely decide the presence of pus; identify the smaller parasites, and particularly their ova; detect the intestinal epithelium, as seen in colitis and sometimes in gangrene; and reveal the nature of intestinal sand, which is so often mistaken for biliary calculi. The bacteria will be treated of separately.

It is now necessary to discuss the significance of some of these findings, and to give a résumé of the conditions found in various diseases.

Mucus: mucous colitis

Mucus is normally present in only small amounts; in excess it is significant of inflammation—a generalisation which is applicable to all mucous membranes. Sometimes long, white gelatinous casts of the bowel, measuring many inches in length, and occasionally forming large flakes, are passed irrespectively of the true stools or at the end of them. This is the characteristic finding in *mucous colitis*—a condition by no means uncommon, but one which in the author's experience seems to puzzle many practitioners. The microscope reveals the absence of pus cells, or cells of the intestinal mucosa, and nothing save structureless, gelatinous membrane. The accompanying clinical history is always one of chronic constipation with periodical attacks of enteralgia, allayed by the passage of large quantities of these typical mucous casts.

Pus

Pus may be present in sufficient amount to be identified by the naked eye, as in cases where an abscess bursts into the rectum, such as a parametric abscess; or it may be present in small amounts only identified by the microscope. But the presence of polymorphonuclear leucocytes (pus cells) is always significant of inflammation, and is found in proctitis, or colitis, together with exfoliated cells from the mucosa. These appearances are found in ulcerative colitis—another disease which is less rare than hitherto supposed.

The presence of intestinal epithelium is of great importance in identifying pathological lesions.

Blood ; occult hæmorrhage

Blood is found in the stools in various guises, as already described. Bright red blood is indicative of lesions low down and from typhoid ulcers, whilst the dark tarry stools (melæna) are suggestive of hæmorrhages high up, such as duodenal and, less frequently, gastric ulcers. Occasionally the blood-sucking parasites, such as ankylostoma duodenale are found in the stools. Blood may be present in small quantities that can only be revealed by chemical tests, forming the condition known as *occult hæmorrhage*. Occult hæmorrhage is of great diagnostic significance in duodenal ulcers and cancer of the stomach. The determination of blood in these cases is often difficult. The hæmoglobin is disintegrated and so the corpuscles cannot be identified, and the simple guaiacum and ozonic test is here fallacious, but it is possible to determine the presence of blood by rather complicated modifications of the guaiacum test, or by the production of the characteristic hæmin crystals, which when found form most satisfactory evidence of the presence of blood.

Gallstones ; Enteroliths

The evidence of colic being due to gallstones is often sought for in the fæces. Fair-sized gallstones can be passed through the bile-ducts and often identified by washing and straining through a coarse sieve. Large gallstones measuring as

much as an inch have occasionally been passed through a direct fistulous communication between the gall-bladder and various parts of the intestine. These have to be distinguished from enteroliths, consisting of foreign bodies, fruit-stones, etc., which after a long sojourn in the intestine may become coated with phosphates; or even of fæcal concretions which have been similarly inspissated and coated. These latter are frequently present in the appendix. In one case several hundred enteroliths were evacuated through a colotomy wound in a boy aged fourteen, who suffered from a stricture of the rectum consequent upon an operation at birth for an imperforate anus. These consisted of plum-stones which he had been in the habit of eating all his life, the stones being surrounded by smooth phosphatic deposits.

Intestinal Sand

In searching for biliary calculi a condition, which is not uncommon, must be borne in mind, namely, the passage of intestinal sand. A sandy material is passed often in large quantities with the stool or apart from it, and this, on washing and straining, resembles large yellow grains of sand. Microscopically the nature of this is at once revealed. It is rarely, if ever, due to true biliary calculi, and it is found to consist mostly—and in the larger number of cases examined by the author, entirely—of vegetable sclerenchyma; the microscope reveals the characteristic cellulose vegetable cells. True sand was described as

occurring in the stools of the soldiers at the Modder River. The most minute gallstones, often as small as pins' heads, will on chemical investigation readily reveal their structure (cholesterin and lime).

Parasites

The parasites found in the alimentary tract are sufficiently discussed and repeatedly illustrated in most text-books. A careful examination of the stools, often assisted by stirring them up in a vessel of water and filtering through a coarse sieve, will reveal the larger and commoner tapeworms, such as tænia medio-canellata or tænia saginata, or the large round worm, or even the small threadworm; or perhaps the small ankylostoma duodenale. The stools should be examined in all cases of severe anæmia, especially if the patient come from districts in which these parasites are found. In the case of ordinary tapeworms the difficulty is not to diagnose the large elongated masses of body segment which are passed, often in large quantities, after medicinal treatment, but to find when the head of the worm has been discharged. This necessitates very careful examination of the segments which diminish in size until ultimately the minute head with characteristic suckers is picked out and its species identified under the low power of the microscope. Its discovery is facilitated by the fact that it has attached to it often several minute segments of increasing size.

Microscopic examination will reveal the characteristic eggs of the tapeworms already mentioned, also the eggs of bilharzia hæmatobia, which is a common cause of chronic proctitis in eastern climates, the various amœbæ, and the numerous bacteria which will be described later. In cases of amœbic dysentery, which are occasionally seen in this country, it is necessary to make a rapid examination, as the organisms die in a few hours after passage. The bloodstained mucus from these cases, placed on a slide, and preferably on a warm stage, reveals the characteristic amœboid protozoa. Occasionally other protozoa are found having very little significance, such as the trichomonas vaginalis, the lamblia intestinalis, and the paramœcium coli, all of which have at times been associated with diarrhœa.

Bacteriology

At birth the alimentary tract is sterile, but breast-fed infants soon develop the bacterium lactis aërogenes, and infants fed on cow's milk develop a more or less prolific flora, depending on the carelessness with which food is prepared. The normal alimentary tract forms a good breeding-ground for a large number of bacteria which obtain entry with the food, though for the most part these are destroyed by the antiseptic property of the gastric juice. Digestion is facilitated by the presence of many of these organisms, but when the process is abnormally prolonged, as in cases of constipation, further decomposition

products are formed, including putrefactive bodies such as indol, skatol, etc., and these, when absorbed into the system, produce the manifestations of toxæmia, which have been designated *coprœmia.*

In addition to this condition of toxæmia resulting from the more common intestinal bacteria, occasionally bacteria are introduced with food which are capable of producing toxins of greater severity. These include Gærtner's bacillus, which is found in many epidemics of food poisoning. But in investigating the etiology of food poisoning it must be remembered that toxins or characteristic ptomaines may have been produced in the food before cooking, which, although it may destroy the bacteria themselves, may not affect the ptomaines. Also solution of the tin, etc., in which foods are preserved may lead to poisoning. In these cases, therefore, it would be useless to search for specific bacteria in the stools. The rapidity of onset of the symptoms, however, would distinguish these cases from the true bacterial infections, which require a definite period of incubation before the toxic symptoms are produced. The mere bacterioscopic examination of the fæces throws little light upon the nature of the organisms therein. As most of the pathogenic bacteria morphologically resemble B. coli, elaborate cultural and experimental investigations are necessary for their identification.

An investigation of a case of food poisoning will necessitate the following procedure—

(1) Bacterioscopic finding of an organism in the fæces.

(2) The finding of a similar organism in the remains of the suspected food.

(3) The cultivation of the organisms on media with selective activity to further identify them.

(4) Agglutinative experiments with the serum of the patient against the different bacteria obtained. In infections with Gaertner's bacillus definite agglutinins are found in the patient's blood, which have a specific action against these bacilli.

(5) Animal feeding experiments with the organism in question.

Constantly present in the alimentary canal are the bacillus coli and a streptococcus group. The type of streptococcus found has been called by some workers the *S. fæcalis*, and this appears to have certain characteristic reactions. It is undoubtedly a streptococcus of little or no virulence, but under certain conditions apparently it can give rise to pathological lesions. It is probably the cause of the majority of cases of chronic infective endocarditis, and, like *B. coli*, it can set up infections in the kidney, peritoneal sac, etc. These organisms, on escaping from the alimentary tract into the peritoneum, acquire an exalted virulence; it has also been shown that in cases of obstruction, either simple or severe, *B. coli* can have its virulence considerably exalted; the same phenomenon is found in association with typhoid fever.

Coli infections are treated of elsewhere. Other organisms frequently found are the bacillus pyocyaneus, staphylococci, the bacillus alkaligines, the proteus group, and the bacillus lactis aërogenes; also numerous yeasts, and occasionally, in conditions of dilatation of the stomach, sarcinæ. Although the bacillus coli, the streptococcus, the pyocyaneus, and others are all capable of acquiring pathogenic properties, there are other organisms which are only found under definite pathological states and which are always pathogenic. These are Gaertner's bacillus (associated with food poisoning), the bacillus of dysentery (Flexner and Shiga), the bacillus of typhoid and paratyphoid fever, etc., all of which can be grouped with the colon bacillus. There are also the more definitely specific organisms of cholera and tuberculosis.

The *bacillus typhosus* is morphologically indistinguishable from the bacillus coli. Numerous attempts have been made to discover a means of distinguishing between these two organisms, but so far with little results of value to the clinical pathologist. If the bacillus typhosus could be identified in the fæces, then the diagnosis could be made in the very early stages, whereas now it is necessary to delay several days until sufficient reactionary products are formed in the blood to give a definite agglutination test.

The *bacillus paratyphosus*, of which two distinct varieties are described, is now recognised as the cause of a disease closely allied to typhoid fever with milder symptoms and shorter course,

known as paratyphoid fever. The bacillus cannot, however, be separated from the stools, but can be obtained in pure culture from the blood of the patients, and in such cases gives typical cultural reactions. There are also several varieties of para-colon bacilli described; here it ought to be mentioned that, although the typical bacillus coli can be found in the stools, elsewhere species are found with varying characteristics forming a large group of atypical bacillus coli. The evidence points to a close relationship between all the organisms mentioned as belonging to the coli group (*see also* p. 68).

The *bacillus tuberculosis* occasionally can be found in the stools of tuberculous enteritis, and frequently in children. It is best sought for in pieces of mucus or pus, especially if bloodstained. It is not a method of diagnosis often adopted, although it has many possibilities. The bacilli are often found in the fæces of children suffering from pulmonary tuberculosis: this is a valuable diagnostic feature, as no sputum can be obtained from children, who swallow it; hence the appearance of the bacilli in the fæces.

A brief summary of the more or less characteristic stools of the various diseases will not be out of place here.

Typhoid fever is often accompanied by copious greyish-yellow "pea-soup" stools, although it has to be remembered that a large number of cases of typhoid are often accompanied by constipation.

Enteritis stools are large and fluid, though not

frequent, and contain quantities of undigested food.

In colitis the stools are frequent and small and contain much mucus and occasionally blood; often also pus and shreds of the intestinal mucosa. These stools are frequently foul-smelling.

In true amœbic dysentery the stools are frequently gelatinous and sanguineous, often consisting solely of blood and mucus, and among them the typical amœba coli can be found.

Cholera gives copious "rice-water" stools containing the characteristic spirilla.

In intussusception blood and mucus alone are passed.

CHAPTER XXII

BACTERIOLOGY OF THE MOUTH AND NEIGHBOURING PASSAGES

Saprophytes—Reaction of mouth and relation to growth of organisms—Associated toxic symptoms: arthritis, etc.—Streptococci, B. coli ; Oïdium albicans—*Diphtheria*: acute and chronic; carriers; membranous rhinitis; persistence of bacilli in mouth; diagnosis—*Pneumococcus; Micrococcus catarrhalis; B. influenzæ*—Ulcers of buccal cavity—Syphilis; tuberculosis; actinomycosis—Pyorrhœa alveolaris—Vincent's angina—Inflammation of cranial sinuses as cause of arthritis.

An examination of the mouth and upper air passages is often desirable to determine the presence of different pathogenic organisms, producing lesions which clinically give rise to suspicion. These may include the organisms of syphilis, tuberculosis, glanders, actinomycosis, diphtheria and influenza; less harmful fungi, such as thrush; and the bacterial changes concerned in such conditions as pyorrhœa alveolaris and the chronic suppurations of the nasal sinus which appear to be associated with chronic multiple arthritis.

The ordinary bacterial flora of these parts is prolific and varied, depending in great part upon the condition of health of the individual. In

healthy individuals it is possible that only a few varieties of micro-organisms may be found, and in these cases the alkalinity of the mouth is retained. But with slight digestive disturbances, etc., and in many town dwellers, there appear streptococci, staphylococci, spirilla in quantities, leptothrix, various bacilli and fermentative organisms such as yeasts, and others which can originate or sustain caries. And when the caries has sufficiently prepared the soil, various pyogenic organisms can take up their position and result in the condition of pyorrhœa alveolaris. In these conditions the reaction of the mouth becomes acid—a fact which must be borne in mind in treatment and in attempting to cultivate many of these organisms. The simple treatment of toothache by bicarbonate of soda was based on the recognition of this marked acidity, even before the bacteriological era. Even at the present day it seems most probable that simple alkaline mouth washes will eliminate many of the saprophytic organisms or inhibit their growth.

Many of these bacteria have an important bearing on the production of multiple arthritis and other toxic lesions, and their recognition is important. Also the constant ingestion of discharges, laden with bacteria, from chronic inflammations of the throat and pharynx is associated with the production and maintenance of a form of dyspepsia.

Of the organisms commonly found in the mouth the *streptococci* are perhaps the most constant.

The *streptococcus salivarius* as it has been called, appears to be able to attain to a state of pathogenic virulence. Possibly at times it can break down the defences of the tonsil and obtain an entry into the blood stream, and this may account for some varieties of nephritis or perhaps infective endocarditis; or its virulence may even become so exalted that it may complicate a diphtheritic infection and enhance the danger.

The *bacillus coli* has occasionally been found in the mouth, together with other putrefactive organisms.

Under certain conditions parasitic fungi proliferate enormously, and of these *Oïdium albicans* forms a characteristic membrane, lining the tongue and lips, and sometimes the œsophagus as far down as the stomach; this is known as thrush. Fungi also are found in quantities in that peculiar condition known as *black tongue*, where black proliferating masses form in the centre of the organ. Although up to the present no specific fungus has been grown from these masses, it is possible that the condition may be caused by them.

In the rare condition of noma or cancrum oris, characterised by a rapid and extensive necrosis of the cheeks, numerous fungi and putrefactive organisms are found, but none that can be identified as specific.

Another common and almost constant organism found in the mouth is a diplococcus, identical in many respects with the *pneumococcus*, but

usually avirulent. It seems possible, however, that under certain conditions of diminished resistance this can attain to sufficient virulence to set up pathogenic lesions. It is found in the mouth, the pharynx, the posterior nares, and in the middle ear, whither it probably travels by the Eustachian tubes.

Staphylococci and the *micrococcus tetragenus* are also frequently found in the mouth, but these lead for the most part to milder disturbances.

It is now necessary to discuss a little more definitely the distinct diseases produced by the better recognised pathogenic organisms.

Diphtheria

The early recognition of diphtheria is of the utmost importance, and depends upon the finding of the specific bacillus. But as often such recognition is necessarily delayed for the greater part of a day, it follows that, in severe cases at all events, treatment must be based upon the clinical diagnosis. Such points as the character of the membrane, the low pyrexia, the slight severity of the local symptoms, and the general toxæmia, with the accompanying lack of discomfort, all contrast markedly with the pain and pyrexia and extreme discomfort in follicular tonsillitis.

Occasionally—a matter often depending on the experience of the observer—the typical diphtheria bacilli can be found by *direct examination of the swab* from the tonsils or of the membrane, if such be present. The possibility of a diphtheritic

laryngitis must be borne in mind when the throat appears unaffected to the naked eye.

Direct examination may reveal many or exceedingly few bacilli mixed with other bacteria; therefore the usual procedure is to make cultures on media with selective activity, which often results in a growth of characterisitic bacilli within eight hours. For this purpose swabs must be taken from the affected parts, and these should contain as much of the tonsilar secretion or the membrane as possible. They are often sent to the bacteriologist in a dried-up condition and, owing to the struggling of the child, the infected material is absent. Although it is possible to grow bacilli even by moistening the dried swab, it is preferable to get the material as fresh as it can be obtained. It should be noted that in taking swabs of a diphtheritic throat it is essential that no antiseptics should have been previously used, otherwise no cultures will be obtained.

These remarks apply to the acute variety of diphtheria infection. The diagnosis between the true diphtheria bacillus of Klebs Löffler and the pseudo-diphtheria bacillus of Hoffmann is one for the bacteriologist. But it must be mentioned that Hoffmann's bacillus is frequently present in sore throats and that its actual significance is as yet unsettled.

A point of practical importance has reference to the *persistence of the diphtheria bacilli in the mouth* after treatment. After a suitable injection of the antitoxin it is possible for the diphtheria

bacilli to disappear from the throat absolutely, and within a short time. In one case recently seen by the author no bacilli could be found a few days after such treatment. On the other hand, it often happens that bacilli persist even during convalescence or after complete recovery. They can also be found in the mouths of healthy people, especially of doctors and nurses in fever hospitals, without producing any lesion, but they are potentially virulent, and such people constitute a well-recognised class of "diphtheria carriers." They would be identified in the routine bacteriological investigations at institutions wherein diphtheria had become endemic.

The bacilli can also persist in the nose and produce chronic rhinitis and nasal discharge; especially in the schools, children with chronic discharges, often with a history of having recently returned from a fever hospital, frequently reveal diphtheria bacilli on examination.

Membranous rhinitis, as commonly seen in the nose and throat among hospital patients, is often of diphtheritic origin. In these cases the bacilli are frequently found almost in pure culture, in swabs taken directly from the site of the lesion. The bacilli here present numerous involution forms which makes their recognition easy.

Pneumococcus, etc.

The *pneumococcus*, *micrococcus catarrhalis*, and the *influenza bacillus* are all found as causes of catarrh of the throat and nose and upper air

passages. They often appear to have a mild epidemic nature. In the past winter the author found the pneumococcus in almost pure culture in the swabs from a large number of cases of nasal and laryngeal catarrh. Bacteriological recognition of the cause of these infections lends some aid to prognosis and perhaps to treatment. Clinically there appears to be definite distinctions in the effects produced by each; the micrococcus catarrhalis is a common organism producing the watery catarrhs accompanied by profuse nasal discharges, whilst the pneumococcus results in little discharge of a plastic fibrinous exudate. The latter is accompanied at the same time by a severe malaise and extreme weakness resulting from the more severe toxæmia.

Ulcers of the Buccal Cavity

The more complete diagnosis of granulomatous lesions occurring in the mouth is discussed in Chapter XXVII, but here it may be said that the recognition of syphilitic lesions, such as ulcers of the mouth or tonsils during the secondary stage, can often be made by direct examination of the lesions and the finding of the spirochæta pallida. This must be distinguished from the spirochæta refringens and other spirochætæ and spirilla which are common in the mouth (Figs. 28; 26).

Tuberculous ulcers of the tongue often reveal characteristic tubercle bacilli. *Actinomycotic lesions* are identified by the characteristic ray fungus in the discharges, if such exist.

But long-standing and extensive ulcers due to any of these causes, or to glanders, or to malignant disease itself, become so contaminated by the saprophytic germs of the mouth that direct bacterioscopic examination is often of little value.

Pyorrhœa Alveolaris

The association of pyorrhœa alveolaris with certain types of arthritis has directed much attention to the condition. Though it is doubtful that bacteria form the sole etiological factor, there is no doubt that they are a potent cause in maintaining the suppuration. Hence treatment directed against these organisms is often satisfactory both from the point of view of the local trouble and the toxic lesions elsewhere. A superficial examination of the discharges from the tooth socket reveals numerous organisms, and cultures are mostly contaminated. But the author has found that the use of acid media—to imitate the abnormal state of the mouth—results in pure cultures of a streptococcus : a vaccine of this has been administered with great success. The spirilla do not grow in ordinary media and it is undetermined whether they have any pathological action. It is advisable to make cultures from the pus deep down between the fang and the gum, expressing the pus after a preliminary sterilising of the neighbourhood. But the most satisfactory method is to make cultures from the fang and the socket of a tooth that it has been found necessary to extract.

Vincent's Angina

In this peculiar and severe type of suppurative tonsillitis various organisms have been described; a typical film reveals the presence of spirilla and fusiform bacilli which are constant, the whole

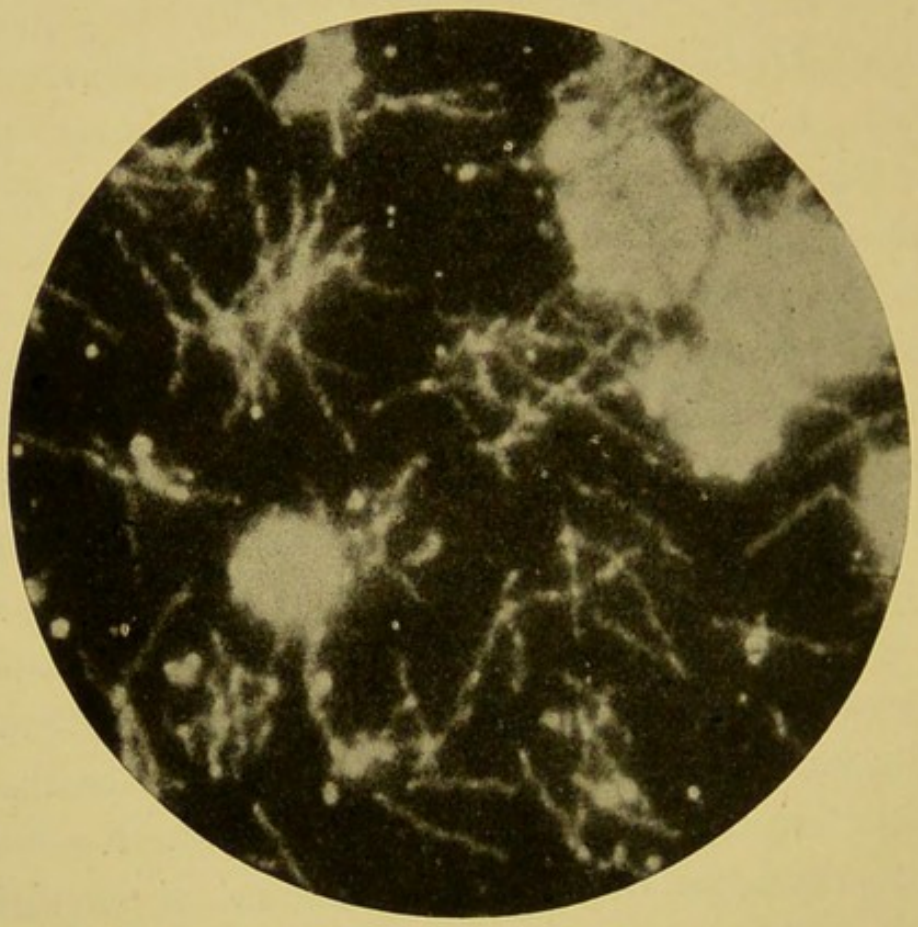


Fig. 28.—Material from mouth in Vincent's angina, seen by dark-ground illumination showing Spirochætæ similar to S. refringens (from film by Pathé Frères).

being so distinctive as to allow an experienced observer to distinguish between this condition and diphtheria.

In follicular tonsillitis the exudate, from its purely purulent character, is readily recognised as being different from diphtheritic fibrinous membrane.

Sinuses of Skull and Middle Ear

Owing to the difficulties of access to the sinuses of the nose and skull, bacteriological investigations are somewhat indefinite, but many cases of chronic sinusitis are maintained by bacterial infection, generally due to the staphylococcus. From these foci of disease the toxins can be absorbed into the system, and such seems to be the cause of some cases of multiple arthritis. This is corroborated to some extent by the good results of bacteriotherapy in these conditions.

In a recent case of multiple arthritis in a man, associated with enlarged tonsils, a pure culture of streptococcus was readily obtained from the nasopharynx, and a vaccine from the same was administered with rapid and satisfactory results. The joint-lesions completely subsided and the patient was able to return to his manual labour.

The presence of the pneumococcal organism in bacterial infections of the ear has already been mentioned; in the majority, if not all, of the middle ears of young children examined in the *post-mortem* room, even when death has occurred from any cause, pus is discovered, and in it a pneumococcic-like organism. This is identical in appearance with the pneumococcus that sets up middle-ear disease, occasional meningeal and cerebral suppuration, and even chronic otitis; but in these latter cases, and even in the acute stages after drainage, frequently

staphylococci, etc., are found as contaminations. It may happen, however, that in the acute stage a pure culture of the pneumococcus is readily obtained; these cases also respond satisfactorily to bacteriotherapy.

CHAPTER XXIII

SPUTUM

Structure—General considerations—Lung detritus—Curschman's spirals—fibrinous casts—*Bronchitis*—Fœtid sputa—Copious watery expectoration—*Bronchiectasis;* palliative vaccine therapy—*Pneumonia;* rusty sputum—*Phthisis*—*Blood in sputum*—Signs of disease adjacent to lung; liver abscess, cancer, etc.

THE sputum must be regarded as the secretion of the air passages and adjoining cavities. Normally, in health, no appreciable amount of sputum is produced, though occasionally in town dwellers on rising in the morning some accumulation of mucus, generally tinged by carbon particles which have collected overnight in the upper air passages and have been driven back by the cilia, is expectorated.

In investigating the conditions of the air passages it must be remembered that there is an admixture of the sputum with a greater or lesser quantity of saliva, and it is difficult to obtain sputum free from this. This is an important precaution to take in bacteriological investigation. It is true that in most acute infections of the air passages the specific micro-organism predominates everywhere, so that any portion of the sputum will reveal the causal agent. But

in more chronic infections it is necessary to tell the patient to wash out his mouth with boiled water several times in the morning, and then pass into a sterilised vessel the actual sputum that he coughs up. In children and in others who are delirious or too feeble there is no expectoration of the sputum, which is generally swallowed, but even in children some information can be obtained from an examination of the vomitus, which will contain this material; or it has even been suggested that the throat should be swabbed out with a piece of lint and the material examined.

The essential constituents of the sputum are: mucus from the mucous glands of the bronchial tubes; serous fluid exuded from the bronchial blood-vessels; and formed elements consisting of epithelial cells from the mucous membrane, leucocytes from migration from the blood-vessels, and sometimes endothelial cells from the pulmonary alveoli themselves. These elements in different proportions, mixed with air bubbles and saliva, constitute the different kinds of sputum, and according to the proportion of cell elements therein we get mucoid, serous, muco-purulent or purulent sputum. Here, as elsewhere, the extent of inflammation is denoted by the number of leucocytes. In addition the sputum may contain detritus—the result of lung destruction—or concretions, or small foreign bodies.

The quantity varies considerably. It is slight in early and in dry bronchitis, and in early phthisis.

It is excessive in bronchitis and extensive tuberculosis, especially with large cavities, and bronchiectasis, and gangrene of the lung. Enormous quantities of albuminous, frothy sputum result from thoracentesis, and occasionally pure pus pours from the mouth in cases where the empyema has perforated into the lungs, or in cases of abscess in neighbouring parts.

The frothy character of the sputum is due to admixture with air, and is most marked in inflammations of the small bronchi.

The *colour* of the sputum often gives a little information. Usually it is colourless, though often in town dwellers tinged black with the soot particles. In the various pneumoconioses there are characteristic tints from the foreign bodies inhaled. Coal miners, for example, expectorate black sputum, loaded with coal dust; masons, red sputum, from the oxide of iron, etc.

Blood appears in the sputum, either as red blood, or else as altered hæmoglobin products, giving to it a brownish, and sometimes even a greenish discoloration, according as to whether it be of recent or remote origin. The blood may be intimately mixed with the sputum, or merely streak it, or may pour forth apart from it, according to what part of the respiratory tract, or upper air passages, or the pharynx, or even the mouth or stomach, the blood may have arisen from. A greenish sputum—often grass green—is sometimes expectorated in cases of jaundice, and sometimes also in pneumonia from colour changes in the blood.

The *odour* becomes significant in cases of gangrene, but a putrid sputum is also present in cases of fœtid bronchitis, in bronchiectasis and in cavities in the lung, where stasis of exudate is accompanied by decomposition, and sometimes in empyemata discharging through the lung. Some drugs, such as paraldehyde, chloroform, ether, etc., are excreted by the lungs, and give to the sputum a characteristic odour.

Evidence of *destruction of lung tissue* can be obtained by the finding occasionally of lung detritus, but more frequently and more satisfactorily by the presence of elastic fibres—undigested remains of the lung alveoli. These can be seen, either by direct examination on a darkened background, or else by suitable treatment of the sputum with caustic potash; sometimes they are found to retain the appearance and arrangement of the alveoli. They occur in abscess and gangrene of the lung, but they are of much greater significance in tuberculosis, where they can occasionally be found in the early stages.

Other formed elements which are significant of definite pathological conditions are *Curschman's spirals* and *fibrinous casts*, both of which can be seen by the naked eye, though the former are very small. The former, with their characteristic spiral arrangement, are formed in the bronchioles. They are evidence of bronchiolitis, and are most frequently found in true asthma, in association with Charcot's crystals.

Fibrinous casts, of the bronchi, which often

reach large sizes, may be either true diphtheritic membrane from the trachea and bronchi in those rarer cases in which the disease extends so far down; or branching casts of the smaller bronchi, formed occasionally in croupous pneumonia; or very large branching casts, showing the outlines of many bronchi, and which form the characteristic feature of true idiopathic fibrinous bronchitis. In this latter condition the expectoration of these large, tree-like masses terminates an attack of paroxysmal dyspnœa, and brings the disease for the time being to a conclusion. All these casts are best sought for by floating the sputum in glass vessels full of water.

Calcareous concretions, sometimes branched, are occasionally found in the sputum from dilated bronchi; from their hardness and structureless appearance under the microscope, they are readily distinguished from the so-called *Dittrich's plugs*. These latter are soft, yellowish-white, putrid, sausage-shaped casts of bronchi, about the size of a mustard seed, consisting for the most part of masses of bacteria and fatty debris. They are found in sputums from gangrene and fœtid bronchitis. The expectoration of these masses may be accompanied by very violent coughing and dyspnœa.

The examination of the sputum alone is often insufficient to point to a diagnosis without taking into account other features of a disease. It is true that characteristic sputa are often asso-

ciated with definite lesions, such as, for example, in inflammations of the alveoli where alveolar contents, including endothelium and plugs of fibrin entangling corpuscles or leucocytes, are found; or in inflammation of the tubes with accompanying mucus and epithelial cells. But lesions of one part of the lung are often associated with lesions of other parts, so that alveolar discharge may be mixed with bronchial, etc. Hence we are compelled to describe the sputa occurring in different diseases.

Bronchitis

In *acute bronchitis* the secretion is at first scanty and viscid, consisting almost entirely of mucus. Soon, as the inflammatory process progresses, it increases in quantity and becomes more fluid, being mixed with serous exudate from blood-vessels. It contains few cells and resembles saliva. It is transparent, colourless or pale grey, and looks like white of egg; is viscid, frothy and may contain streaks of bright red blood and has no odour. It consists chiefly of mucus cells with a few small round cells. Later, during resolution, it becomes rich in cells which may have undergone fatty degeneration. It is then yellow and opaque and less viscid, and the yellow parts may float in the liquid. The character of the sputum thus indicates the stage of the disease and its appropriate treatment.

We have seen that fœtid sputum can occur in many conditions, so that the term fœtid bronchitis

should be confined to cases where the *bronchial* secretion itself is fœtid; it cannot be diagnosed from the odour alone. The sputum in *fœtid bronchitis* separates into three layers on standing. The upper is opaque, frothy and greenish, consisting of mucus and epithelial and pus cells. The middle looks like saliva; while the lowest is yellowish and contains soft grey fœtid lumps, varying in size from a millet seed to a pea. The sediment consists of epithelium, pus and a few red blood corpuscles, fat, Charcot's crystals, tyrosin, leucin and hæmatoidin. There are also various putrefactive and other organisms.

Copious watery sputa

A *copious thin* expectoration occurs in several conditions: In acute œdema of the lungs there is a profuse, thin, watery expectoration with occasionally slight traces of pinkish blood. It separates into three layers; the upper, frothy and white; the middle, opalescent; and the lower, viscid. It is rich in mucin and poor in albumin. It occurs in acute inflammations of the lung (sometimes at the onset of a pneumonia), acute fevers, acute nephritis, ether anæsthesia and after paracentesis. In the latter the onset may occur from a few minutes up to two hours after the operation, the quantity of fluid varying from a few ounces up to as much as three pints.

There is a condition (*bronchorrhœa serosa*) in which the sputum is profuse, thin, frothy, and contains a few shreds of mucus. It occurs in a

rare form of bronchitis and occasionally in acute miliary tuberculosis, asthma, empyema, morbus cordis and emphysema. There may be several pints in the day and unlike that of ordinary bronchitis its character remains the same throughout. Sometimes in aortic aneurysm, for weeks before the end, there may be a similar profuse watery saliva-like expectoration, but unaccompanied by dyspnœa. There is also a very rare form of *recurrent pulmonary œdema* occurring in the later stages of arteriosclerosis with high blood pressure, in which there are periodic attacks of dyspnœa, with abundant frothy, slightly blood-tinged expectoration and containing so much albumin as to become solidified on heating. As much as twelve ounces may be expectorated in an hour. During the attack there is extreme dyspnœa and distress, and the already high blood pressure may be still further increased. The onset of these attacks is generally ominous, the heart rapidly failing. A copious thin, frothy expectoration is sometimes found in tuberculosis of the larynx (*see* p. 291).

Bronchiectasis

The sputum in bronchiectasis is mucopurulent in character and varies much in quantity. It may be scanty, but is generally profuse, up to twenty or thirty ounces daily. It is brought up at long intervals and pours from the mouth in a stream. The patient can often be made to expectorate by inverting him.

The expectoration often has an offensive, sickly odour. In early cases there may be none. It may take years to develop and may then for a long time be faintly putrid. Subsequently, owing to putrefactive changes, it may become horribly fœtid. The odour is not quite like that of gangrene and has been compared to rotten cabbage. Bacteriotherapy may be of value in preventing its onset. It may be more marked in the breath (and especially during the expectoration) than in the sputum itself, and sometimes may occur in the breath alone. The sputum is diffluent, and after standing settles into three layers: an upper, thin, brownish, frothy, mucoid layer; a middle, clear, greenish layer; and a thick, lower, purulent layer containing pus cells, connective tissue, granular detritus and organisms.

Hæmoptysis occurs in 30 or 40 per cent. of cases at some time or other. It may be slight or profuse, and repeated and may even be fatal.

The quantities of expectoration in this condition will assist the observer to realise the anatomical picture of a large portion of the lung, excavated by supposed dilated bronchi in the midst of more or less consolidated lung tissue. To pretend that any curative treatment of such a deformity is possible is to blind ourselves to the true situation. But attempts can be made to deal with the excessive secretion, which is increased by repeated attacks of inflammation, and further to prevent the onset of putrefaction, the germs of which find so favourable a soil in the stagnant contents of cavities.

Avoidance of climatic conditions which favour bronchitis, antiseptic treatment, and to some extent also vaccine therapy directed against the bacteria, are all indicated, and all can be said to have a palliative effect. The sputum offers an index to the condition, and satisfactory treatment should aim at keeping the quantity at its minimum and avoiding putrefaction. Too often the treatment of bronchiectasis is delayed till it reaches an advanced stage.

Pneumonia

The characteristic sputum in lobar pneumonia generally appears from the second to fourth day, and sometimes is present on the first day. The sputum in an ordinary case may continue rusty well into convalescence. It offers a good picture of the anatomical changes in the affected lungs. The inflammation principally affects the alveoli; these fill with exudate from the engorged blood-vessels and coagulation produces fibrinous moulds of them. In the early stages these are expectorated as scanty, viscid sputum, sticking to the lips and mouth and also to the sputum cup. It averages one to two ounces daily. At this stage it is composed of mucus, fibrin threads and red corpuscles, numerous pneumococci, and occasionally casts of the small bronchioles. Owing to changes in the blood its colour is characteristically rusty.

Resolution is associated with an immigration

of phagocytic leucocytes into the alveoli, so the sputum changes in character and becomes of the catarrhal type and almost purulent. True purulent sputum denotes actual suppuration and abscess formation.

Rusty sputum is almost pathognomonic, but similar appearances may be met with in acute tuberculosis of the lung and in passive congestion. In the former the rusty sputum persists and the tubercle bacilli can be identified, though often these are not sought for until the duration of the illness beyond the period when the crisis might be expected arouses suspicion. The rusty colour is due to presence of red blood corpuscles and blood colouring matter; it may undergo further changes, and become brown, yellow or green; and may even suggest the presence of bile. Occasionally the blood is more abundant, and causes the sputum to be dark red (*prune-juice expectoration*). Rarely is it abundant enough to make the sputum bright red and still more rarely is there profuse hæmoptysis; this is suggestive of tubercle. In one case of unresolved pneumonia in a boy, which lasted some months, there were frequent attacks of hæmoptysis (several ounces at a time), and finally a fatal hæmoptysis caused suffocation. Frequent examinations of the sputum failed to show tubercle bacilli, yet the autopsy revealed a cavity in the apex, and definite histological tuberculosis. Similarly, in an adult with unresolved pneumonia going on to gangrene and empyema there was frequent hæmoptysis yet no

tubercle bacilli, though the post-mortem showed tubercles and cavitation of apex.

In unresolved pneumonia it is often possible to isolate the pneumococcus, which can then be used as a vaccine with satisfactory results.

Phthisis

The sputum in *phthisis* varies according to the stage of the disease and upon the amount of associated bronchitis. In the early stage there may be none or perhaps a little viscid mucus. The characteristic sputum is yellowish-green, scanty, viscid and nummular, and has a faint sickly odour. It does not appear till breaking-down of tissue occurs and it increases as the disease advances. It becomes nummular, when cavities form, and with large cavities may be very profuse and purulent, even gushing up in large quantities as in bronchiectasis. Nummular sputum is not pathognomonic of phthisis, but may occur in discharging empyema and cavities other than tuberculous. Rarely does it occur in bronchitis.

It is remarkable that in *acute* phthisis the expectoration may be very slight in spite of the fact that a large part of the lung may be in a state of caseating pneumonia. This absence of sputum may aid in diagnosing the condition from pneumococcic pneumonia.

The *amount* of expectoration varies from a few pellets to one or two ounces daily or sometimes four or five ounces. There will be still more if there is

much bronchitis associated with it, then the phthisical sputum can be distinguished from the bronchitic part. If there are large secreting cavities three will be much purulent expectoration.

The pellets are composed of mucus in which are entangled cells, caseous material, crystals, granular detritus and bacteria, together with fragments of lung tissue. The cells are chiefly small round cells, leucocytes and pus cells, and a few large epithelial cells, and a few blood cells. The caseous substances may be in lumps big enough to be seen by the naked eye. *Elastic* fibres are occasionally present.

Tubercle bacilli are generally present and are best found in the yellow caseous lumps. The number of bacilli varies greatly : in old tuberculous cavities the bacilli may be absent, as also in very acute cases, where there may even be no sputum at all; but generally speaking the more active the disease the more the bacilli. *Absence of bacilli should not upset the diagnosis.* Repeated careful examinations may be necessary before they are found. In some cases of tuberculosis in which the lungs are only slightly affected and the larynx much, there may occur copious expectoration of a thin, frothy nature even up to as much as twenty to thirty ounces in the day. In such a highly diluted sputum it may be difficult to find tubercle bacilli by ordinary methods, and as in these cases physical signs of pulmonary disease may be indefinite it is highly important to bear this in mind. It is, however, often possible to

find the bacilli by concentration methods of examination.

Other organisms, derived from the lung itself or from the air passages and mouth, may be present and indicate bacterio-therapeutic measures.

Blood in Sputum

Blood appears in the expectoration in different guise according to its seat of origin and the interval that elapses before it is passed out of the mouth. It may be derived from any part of the respiratory tract or the alimentary tract as far down as the stomach, or occasionally from large blood-vessels bursting into these tracts, or even from the blood-vessels of the skull after injury.

It is important to diagnose the seat of origin, but large hæmorrhages arising from any of these sources result in bright red alkaline blood pouring from the mouth so that it is impossible to distinguish by inspection alone the site of the lesion. The distinction must rest on clinical associations, in those cases which survive long enough.

Smaller hæmorrhages, in which the blood accumulates for some time, allow of the usual changes in the hæmoglobin, which results in a rusty colour of the pulmonary, and a black colour of the gastric blood from the further action of the acid gastric juice. The presence of lung material, air or food may help in a diagnosis in these less severe cases.

In neurotic women a condition of *pseudo-hæmoptysis* is likely to mislead, the blood being

derived from sucking of the gums; the expectoration, which may be thin and watery, has a brick-red or pink appearance, which is uniformly distributed.

Hæmoptysis denotes bleeding from the air passages, and occurs in any condition of congestion or rupture of the pulmonary vessels, or ulceration or destruction of lung tissue. In mitral disease the congestion of the pulmonary capillaries results in hæmorrhages into the alveoli, so that casts of these are formed by the coagula and coughed up as dark or purple pellets.

It is important to remember that there may be streaks of bright blood in the sputum from chronic pharyngitis after violent coughing. Streaks of bright blood on the sputum may also occur in chronic bronchitis after violent coughing due to rupture of varicose vessels in the large air tubes.

The cause of hæmoptysis may be extrinsic to the lung. In thoracic aneurysm there may be a fatal hæmorrhage from rupture of the sac, so sudden that very little is expectorated, or there may be time for many mouthfuls to be discharged. Or there may be coughing of small quantities of blood for some time, not from the aneurysm itself, but from congestion due to pressure on the air passages. This condition is known as *weeping aneurysm.*

Similarly, a slight hæmoptysis, though occasionally profuse, may occur in intrathoracic growths.

Hæmoptysis in pneumonia, bronchiectasis and bronchitis, gangrene and abscess of the lung, has

been described above. The hæmoptysis in infarct of the lung is usually sudden and is preceded by pain and dyspnœa. In plastic bronchitis it may precede the expulsion of the cast. Pure blood mixed with air bubbles may be expectorated in injury of the chest.

Pure blood in quantity, generally bright red in colour, brought up in small quantities at frequent intervals and mixed with air bubbles, is the ordinary form of profuse hæmoptysis, and is especially seen in *phthisis*. Here hæmoptysis may be an early or a late symptom—sometimes even the first. If early it may be either in small quantity, due to congestion, or copious and due to ulceration into small peribronchitic blood-vessels. This latter frequently occurs as the *first* symptom in strong, healthy-looking men, generally in the third decade. If the hæmoptysis occurs late in the disease it is generally copious from rupture of an aneurysm of a branch of the pulmonary artery.

The amount of bleeding in phthisis varies greatly, and perhaps in half the cases none occurs. It may vary from a few streaks up to a pint or more in the day. The cessation is gradual, the sputum generally continuing to be tinged with blood for several days. If the hæmoptysis is slight the blood is intimately mixed with the sputum or occurs in little dark pellets. In the commonest type the blood is bright red and frothy, alkaline and mixed with sputum and does not clot. It is brought up easily in small mouthfuls with cough. If the bleeding is profuse the

patient coughs almost incessantly, bringing up with each cough a little blood; this may last for days. Especially bad is the prognosis if there be pyrexia, death often occurring from exhaustion in a week or two. Less commonly death occurs suddenly from hæmoptysis, which causes suffocation, so suddenly that very little may be expectorated.

Signs of Disease adjacent to Lungs

The sputum sometimes also serves as a channel of escape for materials from lesions extraneous to, but in contiguity to, the lungs. The hæmorrhage from an aneurysm rupturing into the air tubes has already been mentioned. But of greater significance is the appearance in the sputum of characteristic evidence of more chronic conditions. *A liver abscess* may burst through the diaphragm and discharge detritus by the mouth. In this, typical amœbæ can be found in the live state. An empyema may empty itself through the lung, producing large quantities of purulent sputum. New growths can invade the bronchial tubes, though cancer cells are probably never found. But in *cancer of the œsophagus* this not infrequently occurs and results in a septic pneumonia with a profuse fœtid sputum, the symptoms of which have on many occasions been known to overshadow those of the primary lesion, and especially in those cases of cancer of the œsophagus without dysphagia.

CHAPTER XXIV

BACTERIOLOGY OF THE SPUTUM

Classification—*Pneumococci* in (1) pulmonary diseases, (2) upper air passages—*Micrococcus catarrhalis*—Tuberculosis; significance of findings—Streptotrichosis—Saprophytes in (1) air passages, (2) cavities, etc.—Bacteriotherapy—causal agent—in secondary infections, in bronchitis and bronchiectasis—Asthma—Phthisis.

THE bacteria present in the sputum may be tabulated as follows—

(1) Common saprophytes occurring normally in the mouth, and also occasionally non-virulent species of pathogenic germs themselves, such as the pneumococcus and diphtheria bacillus.

(2) Pathogenic germs associated with some diseased process, in the lung itself, or in surrounding parts such as an empyema, or in abscess of the liver or subphrenic abscess, which may have ruptured into the lung.

(3) Saprophytes that are found as secondary infections in dilated bronchial cavities, etc., this group including a large variety of moulds and yeasts.

The first group has already been treated of in Chapter XXII, and the true pathogenic organisms of the second group may now be considered individually.

The *pneumococcus* is readily found in typical rusty or grey sputum from a lobar pneumonia, and in children when the sputum can be obtained; also in some cases of lobular or broncho-pneumonia. In the acute stages of pneumonia it is the preponderating organism in the sputum, from which it can readily be cultivated and be shown to possess a high grade of virulence. Not infrequently it can also be found in the discharges, often scanty, plastic and tenacious, associated with acute tracheïtis and pharyngitis. In a series of such inflammations of the upper air passage recently observed by the author, pneumococci were found in great abundance in the films from the sputum. In chronic unresolved lobar pneumonia, pneumococci often abound in the sputum, but appear to possess diminished virulence. In these cases it is an easy matter to obtain pure cultures and to prepare an autogenous vaccine which is of curative value. The finding of the pneumococcus in the sputum is of importance in those cases of central pneumonia where clinical signs are masked.

We have already discussed the significance of the pneumococcic organism of little or no virulence, which frequently occurs in the mouth and air passages.

The *influenza bacillus*, which can produce diseases of the upper air tract or central pneumonia, mostly of the lobular type, is somewhat difficult to detect and to cultivate, but by careful methods it can be identified in great numbers

in the greenish-yellow clumps found in the sputum.

Friedlander's bacillus is found associated with the pneumococcus, and also as a causal agent in bronchitis or in catarrh of the upper air passages.

The *micrococcus catarrhalis* is a rather large organism, arranged as a reniform diplococcus, which is found as a primary cause of catarrh of the upper air passages, or the nose, or the bronchi; or as a secondary infection in cases of chronic bronchitis, or asthma, or bronchiectasis, in which conditions it often produces the acute exacerbations. In all cases this is associated with profuse mucous or muco-purulent discharge, from which the organism can be easily obtained in prolific and characteristic cultures on most media.

Streptococci are sometimes found alone in cases of septic pneumonia, as was seen recently in a case of acute septicæmia where they abounded in the sputum, and were obtained in a few hours in pure culture. They can also be found in association with other organisms; they exhibit all grades of virulence.

In purulent inflammations of the bronchi and lungs, *staphylococci* are not infrequent, and often there is also found the *micrococcus tetragenus*.

Amongst the rarer organisms found in the sputum must be mentioned typhoid and anthrax bacilli; *B. pestis* in cases of pneumonic plague; and the bacillus mallei has been described as occurring in the sputum of glanderous patients, but this is a little uncertain.

The *bacillus tuberculosis* is proof positive of a tuberculous infection, but it must be added that its presence bears no relation to the stage of the disease. The focus of infection may be shut off entirely from a bronchus, or a small focus may be in close communication with a bronchus, producing vast numbers of bacilli in the sputum; or in some acute process, such as acute miliary tuberculosis and caseous pneumonia, no bacilli may be present in the sputum at all; indeed, there may be no sputum. But in all cases repeated examination of the sputum should be made, and it can only be said that the positive finding is of diagnostic value, whereas the negative finding is not absolute. Sometimes, where the lesions are deep-seated, tubercle bacilli appear before clinical signs; in other cases the bacilli only appear when there is distinct evidence of softening in the affected parts. They are best sought for in the purulent nodules found in the sputum, and, what is better still, in a blood-stained portion, if such exists.[1] Large numbers of bacilli have been known to be passed in the sputum for several years, although it may be taken that this is an exceptional instance, and

[1] To examine for tubercle bacilli by concentration methods—

(i) Shake with ten volumes of 1 in 20 carbolic acid; allow to sediment; stain deposit in usual way.

(ii) *Antiformin Method.*—Add to sputum one-fifth volume of antiformin (bleaching powder with fifteen per cent. caustic soda); allow to stand for several hours until disintegrated; then stain deposit. Suitable for sputum, pus, fæces, etc.

that the continued passage of large numbers indicates an extensive and spreading lesion.

It is by no means necessary, and certainly it is extremely inadvisable, to delay treatment in the case of tuberculosis until the tubercle bacilli are found: there can be no doubt that the diagnosis by an experienced clinician can often be definitely made before bacteriological corroboration is forthcoming. These are precisely the cases which should be treated so promptly as to prevent bacteriological corroboration ever being possible.

The *streptotricheæ* form a large group of branching bacilli of which there are many pathogenic varieties. Some of these can produce lesions in the lungs, which caseate and break down, and to the naked eye resemble tuberculosis, though in their distribution they often differ from it inasmuch as they are more frequently basal or pleural in situation. Some of the streptothrix organisms are acid-fast and might be confused with the true Koch's bacillus. But the acid-fastness of these bacteria is by no means as great as that of the bacillus tuberculosis, and they appear to be decolorised after a short stay in acid, whereas the true tubercle bacillus will resist for at least twenty-four hours. A characteristic feature of these streptothrix organisms is their pleomorphism, and though branching forms are not found in the same sputum, bacillary forms and coccal forms are frequent. Some can be further identified by their pathogenic action on animals, which is rapid and often fatal, markedly contrast-

ing in this respect with the slow action of the bacillus tuberculosis. The disease, which may be either acute and fatal or more chronic and curable, is accompanied by hectic temperature and by signs of consolidation and caseation in the lungs, but not confined to the apices; although

Fig. 29.—Beaded mycelium in pus from a fatal case of Pulmonary Streptotrichosis.

superficially resembling tuberculosis, it ought to be possible by attention to the points mentioned to distinguish these two conditions.

In the sputum obtained from large cavities or from dilated bronchi a large variety of saprophytic moulds and yeasts is found, including the aspergillus, the oïdium albicans, varieties of leptothrix, and occasionally sarcinæ.

Among the unusual conditions met with is the finding of *amœbæ coli* in the greenish sputum which results from a perforation of an abscess of the liver through the lung. More rarely still is to be noted the presence of *hydatid hooklets* in a portion of the cyst wall expectorated in cases of hydatid of the lungs.

Bacterial Treatment.—In many cases of infective diseases of the air passages bacteriotherapy is of value, but the difficulty, especially in chronic infections, is to obtain the causal organism in pure culture. The preponderating organism is not always the desired one, especially as the associated saprophytes frequently are more prolific. This difficulty is marked in cases of chronic bronchitis, and more so in bronchiectasis. In this latter condition it is evident that the underlying anatomical lesions are such as to put out of question any real and permanent cure; no vaccine will close up a dilated bronchus or bronchiectatic cavity. But these lesions form a ready focus for implantation of secondary infections with resulting bronchitis and acute exacerbations, and it is these attacks of bronchitis that can be treated satisfactorily by vaccines, and perhaps be held at bay. The micrococcus catarrhalis is a common cause of these attacks; less frequently the pneumococcus. If the sputum be obtained during one of the attacks in the cases mentioned, or in cases of what is known as chronic asthma, often pure culture of these organisms can be obtained and a vaccine made. Many sufferers from repeated

attacks of bronchitis, during the winter months, can be kept free from such by suitable treatment with autogenous vaccines. This, however, cannot apply to the cases of true idiopathic asthma, where the causal agent is not bacterial.

In ordinary abscess cavities and in bronchiectasis, it is almost impossible to isolate from the prolific flora any specific bacteria. In chronic tuberculosis, where secondary infections are frequent, especially among town dwellers, and where possibly the pyrexia and toxæmia are in great part due to such, it often happens that good results follow suitable injections with vaccines of the infecting organisms; more especially when these are the micrococcus catarrhalis or the pneumococcus or sometimes the streptococcus.

Tuberculin treatment will be discussed in Chapter XXVIII. In connection with the mixed infections in tuberculosis, it is an interesting observation that although in tuberculous patients living in towns numerous contaminating bacteria are found, yet in patients living in sanatoriums these saprophytic organisms are rarer; often the tubercle bacilli are found alone.

CHAPTER XXV

PLEURAL EFFUSION

Pleural sac ; method of obtaining fluid; inflammatory and dropsical effusions—Cytology—Effusions in disease—Hæmorrhagic effusion — Chylothorax — Pneumothorax—Empyema—Fœtid empyema—*Bacteriology*—B. tuberculosis—Pneumococcus—Streptococcus—Streptothrix.

NORMALLY, the serous membranes of the thorax form merely a potential cavity, cohesion between the smooth surfaces of the visceral and parietal layer resulting in a union which is difficult to separate. When inflammation of the membrane sets in, whether it be acute or chronic and associated with great thickening, the layers separate and inflammatory products or exudates collect in the sac. These accumulations may be either simple œdematous, containing only a few endothelial cells derived from the serous membrane itself; or inflammatory, containing varying amounts of serum, fibrin or pus cells, and the specific bacteria that incite the infection.

Fluid for examination is obtained by puncture of the chest wall, but it must be remembered that occasionally the exudate is so thick that it may fail to enter the exploring needle. For bacteriological investigation the fluid must be obtained in an aseptic manner in sterile

tubes and examined bacterioscopically with the aid of a centrifuge, and also culturally. To obviate the tendency of some exudates to undergo coagulation after removal from the body, it is useful to collect them directly into a solution of sodium citrate. Not infrequently after a serous effusion has been opened, the secondary infection changes its character and becomes purulent, so that it is advisable to determine the nature of the primary infection from the fluid obtained at the first puncture.

Inflammations of the pleura may give rise to effusion of coagulable lymph, either alone (dry pleurisy), or mixed with serum or pus (pleurisy with effusion). Diagnosis between these two forms is often impossible, and the nature of the effusion is never certain, without the aid of an exploring needle. Dropsy of the pleura must be distinguished from inflammatory effusion: both are serous fluids, but the inflammatory contains also fibrin and red and white blood corpuscles. Dropsy of the pleura is usually part of a general dropsy, though it may occur first, and is due to cardiac, renal and marasmic diseases. Inflammatory effusions are associated with a leucocytosis, which varies with the severity of the condition (see Chapter III).

Serous effusion is usually a clear and transparent fluid, sometimes pale yellow, alkaline in reaction, with a specific gravity of 1012 to 1024. It may be slightly turbid from admixture of white cells or pus cells, and may contain a few

fibrinous, gelatinous threads, grey or yellow, from plastic exudation ; oil globules and cholesterin may occur; the chief proteids are serum globulin, fibrinogen and serum albumin, and in inflammatory exudate these may reach over 4 per cent.

Cytology.—The non-inflammatory effusions con-

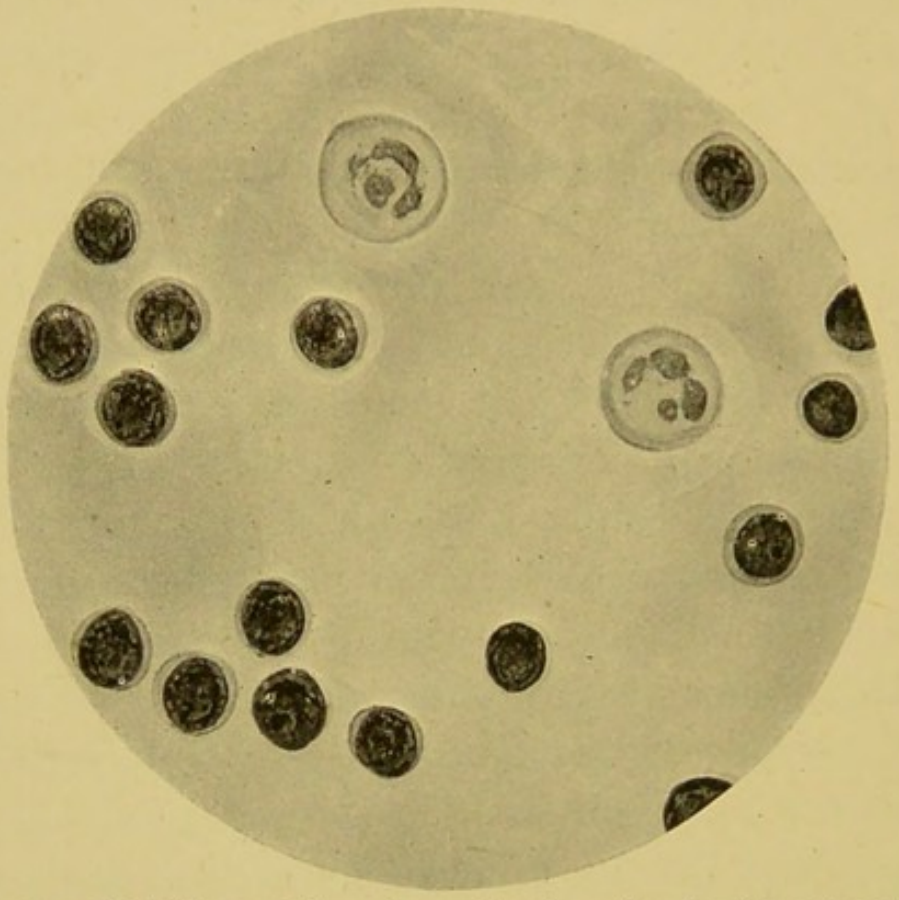


Fig. 30.—Fluid from tuberculous pleurisy, showing lymphocytosis. Two polymorphonuclear cells are seen (× 1000).

tain very few cells, except a few endothelial. The cells in inflammatory pleurisy are more numerous. In the tuberculous effusions the cells are chiefly small lymphocytes, even up to 100 per cent., together with a few large lymphocytes (*see* Fig. 30). There may be a few polymorphonuclear cells at the beginning, and they may even remain in excess during the first two or three

days. In septic effusions the cells are chiefly of the polymorphonuclear variety. The effusion due to malignant disease of the pleura or lung may show cells of the new growth. It is occasionally purulent.

Broncho-pneumonia is rarely accompanied by pleurisy, unless the condition is of the tuberculous type, in which it is common.

Effusion may be secondary to gumma, new growth or abscess of chest wall, or to caries of rib and spine, the latter more often causing empyema. Occasionally there is extension to the pleura from an inflamed pericardium. Or it may follow inflammation of peritoneum, hepatic abscess, subphrenic abscess and appendicitis. It is not necessarily purulent, though the primary condition in the abdomen may have that character.

The pleurisy associated with aneurysm of the aorta or new growth in the mediastinum is often dropsical in character rather than inflammatory, and is due to venous obstruction from pressure.

In acute Bright's disease and amyloid disease it is generally dropsical, though a true pleurisy may be associated with nephritis and even with gout and rheumatic fever, but this rarely happens.

A large hydatid cyst might be mistaken for a pleural effusion, whether above or below the diaphragm (in the latter case the diaphragm being pushed upwards). The fluid is unlike that of pleurisy, as it is *free from albumin* and more watery, and the echinococcus hooks may be found in it.

Hæmorrhagic Effusion

This must be distinguished from hæmothorax, *i. e.* hæmorrhage into the pleural cavity following injury to lung or chest wall, rupture of aneurysm, or erosion of blood-vessel by new growth or abscess. In hæmorrhagic effusion the fluid is blood-stained and varies in colour from pale pink to black. It may be due to exudation from blood-vessels in intense inflammation. Serous effusions are not commonly hæmorrhagic, and purulent effusions still more rarely. The chief causes are tuberculosis of the pleura, especially the acute form, but also the chronic, and cancer. Very rarely does it occur in simple effusion. Hæmorrhagic and turbid effusions are very suggestive of tuberculosis. They are usually sterile. Hæmorrhagic effusion may also occur in general hæmorrhagic conditions and in the virulent forms of the specific fevers.

Chylothorax

In this condition the effusion is milky in appearance, a pale yellow in colour, and may contain much fatty matter. Its specific gravity is 1015–1020. It contains fat globules in suspension and sometimes cholesterin crystals, and may coagulate on standing. The composition depends upon the origin. If it is due to actual leakage from the thoracic duct (a rare event), its composition will be that of chyle containing about 7 per cent. of organic matter. The fatty particles may rise to the surface like cream.

But it may be simply a serous effusion, with fat from degeneration of cells. The fat here will be much less in quantity and in the form of an emulsion. Some of the cases are associated with cancer. From the appearance alone no deduction as to the nature of the pleurisy should be drawn.

Effusion in Pneumothorax

Effusion sooner or later occurs in 90 per cent. of the cases, and may be serous or purulent. In the serous effusion tubercle bacilli can often be demonstrated, and this fact contrasts markedly with the difficulty of finding the tubercle bacillus in ordinary pleurisy. The effusion may remain serous for a long time, but sooner or later it generally becomes purulent. Then other organisms such as staphylococci and putrefactive bacteria may also be found. The effusion may, indeed, be purulent from the first and may accumulate rapidly, reaching as much as eighty ounces in a week.

Empyema

The effusion varies in character in different cases. It is generally homogeneous and creamy in appearance, sometimes greenish, terra-cotta, pink or brown. It may be thin and turbid and on standing separate into a sediment of pus with a supernatant turbid fluid. It has a faintly sour or sickly smell and may be fœtid. Sometimes

it is glutinous, at others it may contain much gas.

Fœtid empyema may be of primary origin or it may be secondary to adjacent putrefactive inflammation, such as gangrene of the lung, though empyema occurring near fœtid bronchiectasis or cavities is not necessarily fœtid itself. It may also follow necrosis of bones of the thorax or perforating disease of the digestive tract. The primary fœtid empyema is generally localised, and the discharge soon becomes sweet after resection of ribs and drainage.

Sometimes the empyema is loculated, and fluids of different character may occur in the separate compartments. Thus in the case of a boy who was thought to have empyema exploration of the chest withdrew clear fluid only. On aspirating the fluid no improvement occurred. The chest was explored again; this time fœtid pus being withdrawn. The suspicion that the case might have been infected in the aspiration was found to be erroneous, for on operation loculi containing clear serous fluid were found, side by side, with pus-containing pockets.

Purulent effusions, if left to themselves, may become partly absorbed and inspissated, and may be incapable of being drawn through a syringe. The absorption may be continued further, leaving a firm mass in which lime salts are deposited. The pleura may be so hard and calcified as to require a chisel and hammer to remove it. Long-standing effusions often contain cholesterin.

Bacteriology

Organisms are difficult to isolate from pleural effusion. With the pyogenic organisms, centrifuging and sedimentation may be sufficient, but the tubercle bacillus can seldom be found by such methods, and it is necessary, if corroboration be needed, to resort to animal inoculation. Even this may be unsuccessful, although the after-history of many of these cases proves that they may be tuberculous in nature.

In old empyemata the organisms are often dead, and in films stain badly or not at all.

B. tuberculosis is by far the commonest cause of pleurisy with effusion, and often also of dry pleurisy. The condition may be primary, or part of a general miliary tuberculosis, but it is more often secondary to tubercle of the lung. Serous pleurisy is more often tuberculous than dry pleurisy, but possibly the great majority are tuberculous.

The commonest organisms associated with empyema are the *pneumococcus* and the *streptococcus*. These occur in about 75 per cent. of the cases. The streptococcus is most common in adults and the pneumococcus in children. The effusion in the streptococcic infection is thin, being sometimes sero-purulent rather than purulent. In the pneumococcic empyema the pus is greenish and viscid, and contains much fibrin. Rarely they may give rise to serous effusions.

Other organisms are the tubercle bacillus, the

staphylococcus, Friedlander's bacillus, the typhoid bacillus, bacillus coli and actinomyces. In fœtid empyema putrefactive organisms may be present. In pyopneumothorax from extension of gastric ulcer or appendicitis, the bacillus coli and the bacillus aërogenes capsulatus may occur.

Actinomyces and other varieties of *strepto-*

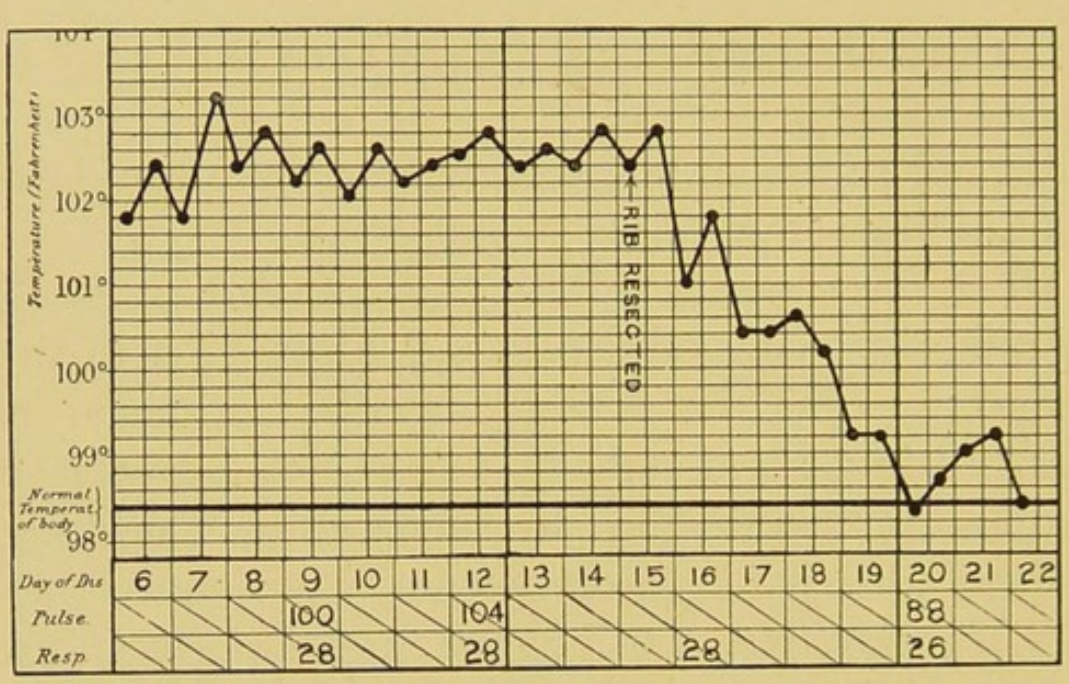


FIG. 31.—Case of Empyema due to a streptothrix, complete recovery after drainage.

thrix may attack the pleura. The effusion in these cases is purulent, and may contain minute yellowish granules visible to the naked eye, which under the microscope are seen to consist of a mycelium and spores. Other organisms may or may not be present. In one case of streptothrix infection the pus contained many masses as large as peas and hazel nuts. These consisted of a dense network of filaments of the streptothrix. After

rib resection and drainage the case did very well (Fig. 30).

Specific inoculation is chiefly of service in empyema sinuses which will not heal, especially the pneumococcal cases.

CHAPTER XXVI

INFECTIVE CONDITIONS OF THE SKIN

Saprophytes — Infective conditions — Secondary lesions — Staphylococci — Streptococci—Ulcers—Chronic abscesses —Tuberculosis, glanders, actinomycosis—Acne—Ringworm; examination of hairs—Tetanus—Anthrax—Pediculi and animal parasites—Leprosy.

THE etiology of skin diseases is a subject belonging peculiarly to the dermatologist, but there is much that can be learned from the simpler examinations concerning those diseases which are due to or are complicated by parasites, either bacterial or animal.

Normally the skin harbours various harmless saprophytic bacteria, which, it is true, change in their variety and quantity according to the hygienic condition of the individual. These have to be remembered in any bacteriological investigation into the cause of certain lesions, more especially as they are exceedingly prolific and easily overgrow any pathogenic germs. The *staphylococcus epidermidis albus* is always found in the skin. Occasionally, in people of dirty habits, the *bacillus coli* can also be found, more particularly around the perineum and down the legs; often, too, the *bacillus pyocyaneus*, and at times the *proteus bacillus*.

Definite pathogenic germs have to be sought for, as, for example, the staphylococcus pyogenes in boils, carbuncles, sycosis and acne; occasionally the micrococcus tetragenus in abscesses; the streptococcus in erysipelas and lymphangitis; the bacillus pyocyaneus in "blue pus"; the anthrax bacillus in malignant pustules; the bacillus tuberculosis in abscesses and chronic ulcers; Ducrey's bacillus in soft sores; the bacillus lepræ in the nodules; the bacillus mallei in glanders; the diphtheria bacillus in ulcers; and the streptothrix in the discharging nodules of actinomycosis. Spirochæta have also to be looked for in syphilitic lesions; various ringworm parasites in lesions of the scalp, body or beard; the achorion Schönleinii in the crusts of favus; animal parasites, such as scabies, pediculi; and, finally, indefinite bodies exuded from the lesions of molluscum contagiosum, and the more recently described sporothrix causing the condition of Sporotrichosis.

Whatever may be the primary cause of a lesion of the skin, there is frequently—and *always* in open lesions—contamination with staphylococci and other saprophytes. But with certain precautions the specific organism itself can often be obtained in pustular eruptions, such as acne, boils and carbuncles. The staphylococcus pyogenes aureus is easily found and obtained in pure culture in the pus from an open lesion. In the vesicular and bullous eruptions which are sometimes associated with the streptococcus, it is more difficult to obtain the organism. But at times it

can be found and grown from the serous discharge in the floor of a previously unopened vesicle. For cultivation purposes the material ought to be taken at once into a fine tube containing nutrient broth. A streptococcus has been obtained from some cases of pemphigus, and also in impetigo, but some of these become secondarily infected with staphylococcus and hence change to a pustular eruption. In many vesicular eruptions, however, bacteriological investigations are negative. In patches of erysipelas the streptococci can only be obtained by incising, after thorough sterilisation, the spreading edge of the patch. But in lymphangitis and the eczematous condition resulting from streptococcic infection, the organism can be obtained readily in pure culture from the discharges themselves.

Ulcers

Ulcers of the skin, though often presenting many characteristics as regards appearance, base, surroundings and situation, which allow of a clinical diagnosis, are often so indefinite as to necessitate pathological investigation. Chronic ulcers will certainly be contaminated with numerous organisms, but some bacteria with characteristic staining properties can often be found, such as the bacillus tuberculosis, and the spirochæta pallida (see Chap. XXVII); while in non-bacterial ulcers, into which the question of malignancy enters, histological investigation of an ulcer's edge will readily reveal its true nature, as in the case of

rodent ulcer or true epithelioma. In suspected hard chancres of the finger, the breast, and the lips, etc., the spirochæta pallida can always be found, provided no previous treatment has been applied, and in atypical chancres, especially where multiple, a similar finding will reveal the cause.

In soft sores the strepto-bacillus of Ducrey has been described, but this is probably not specific. In examining ulcers for spirochæta pallida the precautions given on p. 240 must be borne in mind. Chronic ulcers of the skin are sometimes due to the true diphtheria bacillus, which can be identified by the usual methods, and the disease rapidly cured by antitoxin treatment. The complete diagnosis of granulomatous conditions of the skin is discussed in Chap. XXVII.

Abscesses

Chronic abscess of the skin and subcutaneous tissue may be due to tuberculous or glanderous infection. It is seldom that the bacillus tuberculosis can be found in these lesions, and only occasionally that the bacillus mallei can be discovered by direct examination; so that in dealing with apparently sterile collections of pus it is necessary to bear these two infections in mind. The elucidation of the condition depends upon inoculation experiments, both in the patient and in animals.

Actinomycosis produces abscesses, most frequently about the face and neck, with a characteristic inflamed nodular appearance, and in the discharges typical ray fungus can be found by

direct examination, and in some cases cultivated. It must be remembered that actinomycosis is only one variety of a large group of streptothrix organisms, some of which are pathogenic.

According to some bacterial therapists, acne is due to a specific bacillus which can be cultivated by employing media containing oleic acid to imitate the sebaceous material of the skin. But it is possible that these bacilli are just as much skin contaminations as are the staphylococci that render the acne eruptions pustular. In the true papillar stage of acne the author has failed to cultivate any other organisms than the staphylococcus epidermidis albus, which is an ordinary skin contamination: it does not seem at all probable that true acne is a result of local bacterial infection.

Ringworms

It is often necessary to diagnose the various ringworms that infest the skin, and these are best sought for in scrapings from the affected parts. The fungus is readily found in glabrous ringworm; pityriasis versicolor will reveal the true nature of the brownish discoloration spreading over the chest and back of many people, as well as the finer brownish patches on the warm and moist parts of the body, such as the flexors and the groin. It is a little more difficult, however, to find the ringworm fungus in infected hairs. With a hand lens the characteristic broken stumps lying loosely in their follicles can be found. The

roots of these are covered with a whitish coating of fungus, which is typical of the small-spored variety of ringworm. These hairs are found on and at the periphery of the bald patches, and before the cure can be determined it is necessary to be assured that not a single infected hair is remaining. In the large-spored variety of ringworm, in which the lesions are more scattered, the broken stumps give a typical appearance known as "black dot," and it is these black, broken-off stumps that have to be extracted and examined for the fungus.

A not uncommon lesion on the exposed parts of workers amongst horses is due to horse ringworm. This is found in the form of a spreading, irregular reddish area, often pustular from secondary infection; in scrapings of the lesion the typical fungus can be found and obtained in characteristic cultures in special media.

Another disease of the hairy parts that has fallen into the province of the pathologist in virtue of the great successes obtained by bacteriotherapy is sycosis. In order to carry out the bacteriological investigation of the affected hairs, they must be withdrawn from their follicles, and cultures made from the roots. These produce readily pure growths of staphylococcus pyogenes aureus.

Affections of the *nails* include ringworm, which can be revealed by microscopical investigations of scraping of the diseased parts. The microscopical finding of the characteristic fungus also

will enable the typical yellow crusts of favus to be readily diagnosed.

Tetanus

It is often desired to determine the presence of tetanus in a wound, but it is seldom that such an investigation is rewarded with success. On several occasions only has the writer succeeded in finding in culture and in histological preparations from the supposed site of infection characteristic spores and bacilli. Although perhaps inoculation experiments might be more productive, it must be remembered that not infrequently tetanus symptoms develop after the wound is completely healed.

Anthrax

In investigating a malignant pustule for the anthrax bacillus, it is necessary to examine the lymph from the deeper portions where the bacilli are found. The frequent occurrence of the hay bacillus—*bacillus subtilis*—on the skin, especially in stable workers, must be borne in mind, and on one occasion the author has known this to be mistaken for anthrax, whereas the true primary lesion was horse ringworm.

Animal parasites in the skin are more frequent in the tropics than in this country. But it is often necessary to search for the acarus in scabies. For this purpose an untouched burrow must be carefully explored with a hand lens, and the small parasite removed from its depths with a needle.

This investigation is rendered more difficult by the contamination that is so frequent as a result of inflammation subsequent upon the scratching by the patient. It must be remembered that amongst certain workers whose hands are steeped in chemicals continuously, the lesions are not found in these parts.

Pediculi are often the underlying cause of skin lesions, such as impetigo—a bacterial infection being superadded in the excoriated areas. Likewise glandular swellings can result from secondary infections and reach a large size, especially in the cervical region.

Though not proved to be of parasitic nature, it is perhaps suitable to mention here the condition of molluscum contagiosum. In this condition the characteristic molluscum bodies can be expressed from the lesions and identified under the microscope, or can be seen in histological sections of the excised lesions themselves. These, indeed, are often so simple as to obscure their true nature.

Leprosy.—In the nodular lesions of leprosy, the numerous typical bacilli can be expressed and stained.

CHAPTER XXVII

MODERN MEANS OF DIAGNOSING CERTAIN INFECTIVE DISEASES WHICH BELONG ESSENTIALLY TO THE PROVINCE OF THE CLINICAL PATHOLOGIST

Glanders—Syphilis—Tuberculosis—Actinomycosis—Leprosy—Methods : *Bacterioscopic ;* cultural ; experimental—*Specific "reactions" ;* inoculation, cuti-reaction, ophthalmo-reaction—*Serological ;* agglutinins, complement-fixation by antibodies, precipitins—Summary.

It will be useful to take separately certain diseases which have been classed under the title of granulomata—that is to say, syphilis, leprosy, tuberculosis, glanders and actinomycosis—in order to detail the routine procedure by which a final diagnosis is obtained. All these infections produce surface lesions, and perhaps the means of diagnosis with which we are concerned are best exemplified in glanders. Although glanders is a disease which most thought, and many still think, belongs solely to the realm of the veterinary surgeon, nevertheless there is a marked incidence of glanders among people who attend to horses, and this incidence extends, not only to the stable-keeper and the coachman, but to their wives and children, and to those who come into contact with them.

It is known now that glanders is due to a specific organism—the bacillus mallei—which produces either surface lesions, such as skin abscesses or

ulcers, or lesions of the internal organs, primarily or secondarily, such as nodules in the lungs. It may also produce, as a terminal condition only, general septicæmia. The veterinary school divides cases into farcy and acute glanders. Farcy is characterised by surface abscesses, nodules along the course of the lymphatics, and ulceration of the lesions. Acute glanders results in an acute nasal discharge from acute rhinitis, and glanderous pneumonia which is rapidly fatal.

Bacterioscopic Diagnosis

The first line of diagnosis is the *bacterioscopic*. Bacterioscopy results in the direct finding of the typical bacilli in the discharges from abscesses or ulcers or the sputum or other discharges. In speaking generally of all ulcers of the skin, it may be pointed out here that the old classification, which long divided ulcers into categories according to their general appearances, shape, size, edge, base and surroundings, is now not of much value. Ulcers are diagnosed to-day more by the bacteriologist or pathologist than by coarse appearances. Bacteria, and occasionally specific bacteria, can be found in them, but it is extremely difficult to isolate from a surface lesion the specific organism in question, in view of the numerous contaminating organisms. In the open lesions of glanders it is almost impossible to find the bacillus mallei.

In tuberculous ulcers, the difficulty is lessened by the fact that the tubercle bacillus is an acid-

fast organism—a peculiar staining property which allows it to be distinguished in many cases from the contaminating germs. Hence in ulcers of the tongue it can occasionally be identified.

In syphilis the bacterioscopic method is, in the first stages, the only means available to corroborate a clinical diagnosis of a hard chancre; or to distinguish those lesions which are multiple and which resemble soft sores, but are so indefinite that the clinician cannot give an opinion. It is possible for the bacterioscopic examination definitely to decide, in view of the finding of the spirochæta pallida, that an ulcer is in reality of syphilitic nature.

As regards leprosy lesions, the leprosy bacillus is an acid-fast organism, which can be readily found in surface lesions.

In lesions due to actinomycosis, or its allies, the ray fungus or branching streptothrix can readily be determined and occasionally a variety is found that is acid-fast. Such appearances are found in the skin lesions, pleuritic effusions, appendicular abscesses, etc. (Fig. 29).

Thus the bacterioscopic examination is valuable in any condition due to one of the distinctive organisms with a peculiar selective method of staining or a characteristic appearance.

Cultural Diagnosis

The *cultural means of diagnosis* results in the obtaining of a pure growth of the bacterium with typical and often diagnostic character-

istics. Cultural methods are useless in the open ulcers of glanders, because the contaminating organisms grow too quickly. For the same reason cultivation of material from open sores due to any of these organisms is of little use. But the fluid, taken out aseptically, from closed abscesses or from the farcy buds, will give pure cultures of the organism. The glanders bacillus can be cultivated on potato, giving the chocolate gelatinous growth which is somewhat typical. The organism in syphilis cannot be grown in this manner, and in tuberculosis it is almost impossible. The organism in some varieties of streptothrichosis can be grown readily on its special media, though the streptothrix actinomyces cannot be grown. The cultural method, however, is principally of use in glanders. Often in dealing with horse workers, who are the seat of multiple subcutaneous tuberculous abscesses, glanders must be first of all excluded.

Experimental Diagnosis

The third method is that of *animal inoculation*. This is perhaps the most valuable of the bacteriological methods of investigating disease that we possess. The material is taken either from the abscess, from the discharging ulcer, or from the lungs or affected viscus, and inoculated into an animal, either subcutaneously or intra-peritoneally. In the case of glanders an adult male guinea-pig is used and there results in eight or ten days a peritonitis, with a large swelling of the testicles

and a typical periorchitis. From the lesions the bacillus mallei can be obtained and cultivated.

In the case of tuberculosis a guinea-pig will develop, in the course of from four to six weeks after inoculation, a typical tuberculosis, which differs a little according as to whether a human or a bovine strain is being dealt with.

In the case of actinomycosis, or, rather, in the larger group to which it belongs, namely, the streptothrix group, by inoculating some of the pus into the guinea-pig characteristic results will be obtained with some varieties only. The animal either dies or emaciates, and at autopsy presents typical lesions, from which it is possible to obtain a pure culture of the branching streptothrix which is characteristic of this group.

With regard to the open lesions, such as ulcers or abscesses, which are necessarily contaminated, here, if inoculation is made into the peritoneal cavity, the animal may die within twenty-four hours from general peritonitis. But if a piece of tissue from the edge of one of these ulcers be taken, emulsified and inoculated *subcutaneously* into the guinea-pig, the animal will probably survive the contaminating bacteria and develop characteristic lesions which will be of diagnostic value.

We have seen a chronic ulcer of the soft palate and fauces diagnosed as both syphilitic and tuberculous, but only shown to be really glanderous after injection of a small portion of its edge into the subcutaneous tissue of a guinea-pig.

These, then, constitute the first group of methods, which may be called bacteriological, and which result in the finding of the bacteria and the furnishing of positive proof of the infection. But they are obviously only useful in cases with external lesions, and are of little or no use in cases of internal, or generalised, or occult infections.

Diagnosis by "Reactions"—Mallein—Tuberculin

The second group of methods of diagnosis to be considered is concerned with inoculation methods. In the first place, referring again to glanders as typical, it is found that by inoculating animals with the bacterial products, definite and distinct reactions can be obtained in the animals which are infected. Such a product is mallein, which is the filtrate from pure liquid cultures of the bacillus mallei. A definite amount is inoculated into the subcutaneous tissues. If the animal be not glanderous no result follows; if it be glanderous, even though it be apparently perfectly healthy, with some hidden focus of disease, a marked reaction is obtained, the manifestations of which can be divided into local and general. The local reaction, coming on in the course of the next sixteen hours, results in a large inflammatory œdematous swelling at the site of the inoculation; the general reaction is accompanied by a rise of temperature, and the animal may fall ill and be quite unfitted for work. By this means it has

been possible to isolate large numbers of cases of occult glanders in apparently healthy horses, when the test has been used systematically in large studs. Mallein in doses even as large as fifteen minims, injected into the human glanderous suspect, will give the same general reaction,

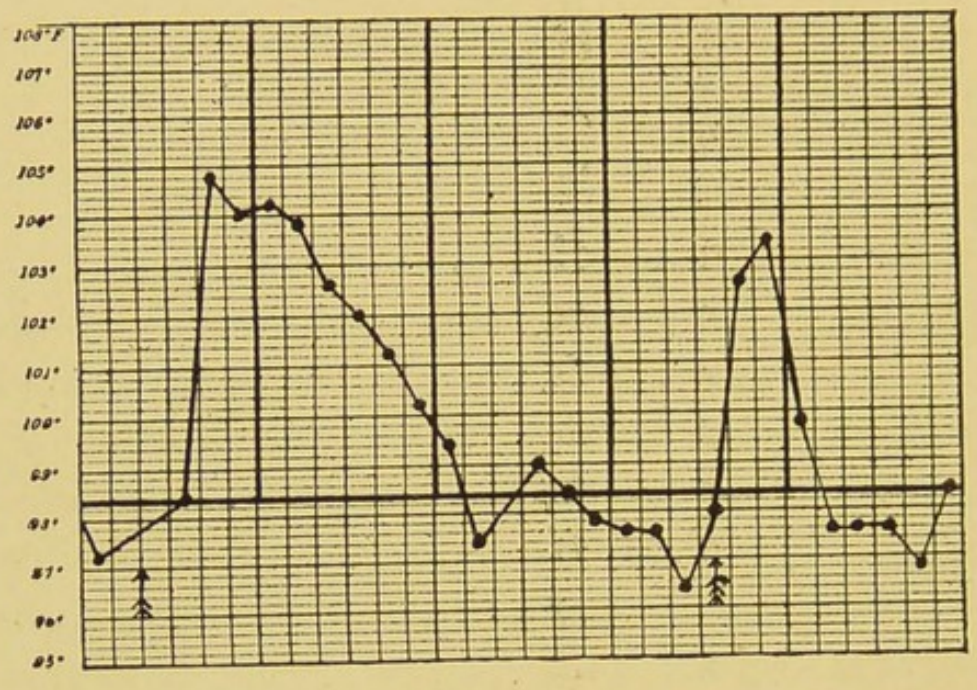


FIG. 32.—Mallein reaction. Minims xvi injected on two occasions, at times shown by arrows, in a case of a man with chronic ulceration of palate. Previous to inoculation the temperature had been normal for forty-eight hours. A week after the second injection tuberculin was injected and no reaction ensued. (From *Observations on Human Glanders*, by Bernstein and Carling.)

and some local reaction, with a marked rise in temperature in the course of the next twenty-four hours (Fig. 32).

Tuberculin, which has been used in the case of cattle for many years as a means of diagnosis, will give in the tuberculous patient exactly the same reaction as mallein in the glanderous patient. Old tuberculin is injected subcutaneously, and if the patient is tuberculous there is a local

reaction with general malaise and a rise in temperature (Fig. 35). The specific value of this test is such that, repeatedly, tuberculosis cases, which have been diagnosed as suspected glanders, have given no reaction to mallein, but a marked reaction to tuberculin. The reaction is positive in all cases. It is true that a few which have ceased to be tuberculous may give the tuberculin reaction, but if a means of diagnosis will pick out all the positive cases, it is not of great moment if it occasionally reacts with a few of the negative and cured cases as well.

Tuberculin at the first injection even in a tuberculous patient may not give any reaction. It may have to be repeated a second or a third time, either in the same dose or in increased doses, and ultimately a marked rise of temperature is obtained, falling again in twenty-four hours. These reactions cannot be carried out where there is already pyrexia. In the case of phthisis with a marked temperature one can learn little from a tuberculin reaction. In the case of acute glanders also just as little can be learned where there is a marked pyrexia. The subject will be discussed in greater detail in the chapter dealing with Tuberculin (Chap. XXVIII).

The "reaction" methods include the *cuti-reaction*, which consists of rubbing a little tuberculin or mallein into the skin. In the course of twenty-four hours, if the disease in question exists, a marked hyperæmic area makes its appearance around the site of the disease. This is called

the *von Pirquet reaction.* In most cases of tuberculosis a marked red areola is produced, but the reaction is very delicate, and cases in which there has been a focus of tuberculosis, no matter how long previously or how well healed, seem to respond to the von Pirquet test. A modification is the *ophthalmic reaction*, in which drops of tuberculin or mallein are put into the eye. In infective cases there results with the specific substance an acute conjunctivitis and hyperæmia. This again is far too active, and, what is more important, it is dangerous. In a number of cases acute ophthalmia has been set up in this manner, and occasionally sympathetic ophthalmia, with serious results (*see also* p. 339).

These constitute the second group of methods of diagnosis, and depend upon the fact that a marked reaction is obtained in those cases which are infected with the specific organism.

Serological Diagnosis

Agglutination; Complement Deviation; Precipitins.

The third group of reactions, which is the latest and perhaps the most fascinating, is the group of methods which depend upon the *finding of antibodies in the blood stream*, formed in response to infection. The antibodies thus sought for are various and have been described in Chapter VII.

The first method is the *agglutination method.* Just as the test is made for typhoid fever by using the bacillus typhosus in the agglutination method,

so the test is made for the glanders infection by testing the bacillus mallei against the blood serum of the patient, either human or equine. The serum of healthy people, however, has a natural agglutination reaction, and this requires to be borne in mind. The highest dilution of human serum that will be agglutinated by the bacillus mallei may be taken as one hundredfold. Normal horse blood will agglutinate in one thousandfold. Above these figures, viz., one hundredfold in humans, and one thousandfold in horses—agglutination may be regarded as positive evidence of glanderous infection. In Prussia the agglutination reaction obtained in horses with blood, diluted more than 1,500 times, is considered diagnostic of glanders. In the comparatively few cases in which the glanderous infection has been discovered in man, the blood of the patients has been proved to agglutinate bacillus mallei in over a hundredfold dilution.

Agglutinins have no practical value in the diagnosis of tuberculosis.

Included in this group of reactions directed to detecting the presence of antibodies, is that very important method known as *diagnosis by complement deviation.* This depends upon the fact that the antibody in question will fix complement in the presence of specific antigen. The blood of the patient is taken, mixed with glanders bacilli together with complement from another animal, followed later with hæmolysin and specific blood corpuscles, and the resulting hæmolysis or inhibition

of hæmolysis denotes respectively the absence or presence of infection. This procedure is fully described elsewhere. We have seen that the complement-deviation method is extremely valuable in syphilis, and it is also of great value in glanders. It has been tried in tuberculosis, but so far has not come into practical use.

Finally, there is the method of diagnosis by means of the *precipitins*. It consists of mixing with the serum of the suspect an emulsion of dead bacteria, which will be precipitated in the presence of the specific precipitin. This also has been adopted with success in glanders.

Summary

In the first place, attention is turned to the simplest means which are at hand, namely, the bacteriological means of diagnosis. Search is made for the bacteria direct. An attempt is made to cultivate them or to isolate them by animal inoculation. Secondly, the inoculation methods are carried out with a specific virus with a view to producing a specific reaction. This necessitates the introduction of the virus—either tuberculin or mallein—into the system, and although it has been shown that it is extremely valuable both in tuberculosis and in glanders, still, if it could be replaced by a method that did not necessitate the introduction of more toxins into an already intoxicated system it would be an advantage. At the present day we have little information about anaphalaxis, though enough

to appreciate the importance of not injecting toxins into patients unnecessarily. Anaphalaxis is a condition in which, instead of having an increased resistance to an infective agent (which previously was thought to be always produced), there actually occurs in some cases after inoculation a diminished resistance, with the result that a minute dose of this same body reinoculated is apt to produce serious symptoms and sometimes death. These drawbacks do not apply to the third group of diagnostic methods. The agglutination method necessitates the withdrawal of blood without harm to the patient. The complement-fixation method necessitates the withdrawal of some small quantity of blood, and the precipitation reaction likewise. The complement-fixation method of diagnosis is based on more scientific premises, and is the most scientific means of diagnosis at present available, and at the same time the most accurate.

With regard to the isolation of bacilli from the blood serum in these infections, it may be said that in glanders, which produces only local lesions, no bacteria can be found in the blood stream until the very last stage, and then the patient is moribund. It would seem that tuberculosis was also a localised infection with no invasion of the blood stream until the terminal stage, and several investigators have brought forward cases and specimens which suggest this. Recently, however, Miss Rabinowitch has brought forward a new method of demonstrating tubercle bacilli in the

blood stream in patients who have subacute tuberculosis. But this is much belittled by the fact that in most samples of water acid-fast bacilli can be found and these have often been mistaken for tubercle bacilli in the blood.

Little has been said about actinomycosis, but it may be pointed out that this is now known to belong to the streptothrix group of infections, and actinomycosis with its typical lesions, in the skin, chest, abdomen, etc., is now no longer regarded as a single infection. There are many varieties in this streptothrix group; and some that occur in man, giving rise to abscesses in the lung, kidney and other viscera, were originally thought to be tuberculosis; some of these are now termed "pseudo-tuberculosis."

Leprosy has recently come into line with these other infections, and the bacilli have been obtained in pure cultures and inoculated into animals with the production of typical leprous lesions.

CHAPTER XXVIII

TUBERCULIN

General considerations—Tuberculin and mallein—Different from other toxins—Varieties of tuberculin—In diagnosis; methods: cutaneous; quantitative (von Pirquet's method); conjunctival—*Subcutaneous* "reactions"; focal reactions in cryptic phthisis; contra-indications in treatment of pulmonary tuberculosis—Methods—Schemes of dosage—Mode of diluting—Classification of Cases—Suitability of such for tuberculin treatment—Conclusions—Localised tuberculosis elsewhere.

THE use of the products of tubercle bacilli in diagnosis has already been mentioned, and it is now necessary to devote some space to the details of this, and also of the treatment of tuberculosis by the same products. But before doing so a little must be said concerning the substance tuberculin and its analogous product mallein.

These are formed in the media in which the respective bacilli grow. They differ essentially from the toxins already mentioned, namely, the exo-toxins of diphtheria, etc., and the endo-toxins of typhoid, plague, etc., in that they are specific in their action, and only exert harmful results in tissues already affected with tuberculosis or glanders respectively. Injected into healthy men or animals no ill-effects follow, but in subjects already infected great activity results both locally at the site of inoculation and generally; whilst

around the lesions themselves such activity sometimes results as to lead to softening, and general dissemination of infective germs, with occasional generalisation of infection. This activity constitutes a *focal reaction.*

The results vary with the dose. Large doses are dangerous, from the liability to produce dissemination of infection. Small doses are stimulative and often beneficial, and can be used in diagnosis if given in sufficient amount to produce a febrile but not severe reaction.

Tuberculin is extremely resistant to high temperatures, sunlight, etc., and so again different from the other toxins. Its great import is as a diagnostic agent, for whilst producing improvement in a tuberculous patient, probably by producing immunity to the toxic substances, it does not necessarily stay the progress of the disease.

Hence other methods allied to bacteriotherapy are advocated; and under the term tuberculin are included many products consisting of varying mixtures of tubercle bacilli and their products. These are used with the object of raising the patient's resistance to the toxins of tubercle bacilli, and at the same time increasing his resistance to the bacilli themselves. It would appear that there is little to choose between all these products, and the general description will apply to all, though variations in dosage must be recognised.

Some of the many varietes of tuberculin may be mentioned—

(1) The Old Tuberculin (T.) is prepared from a four- or five-weeks-old culture of tubercle bacilli by evaporating to one-tenth of its bulk at a temperature not exceeding 70° C. and filtering. It contains exo-toxins with some endo-toxins obtained during the evaporation. It is used for diagnosis as well as for treatment.

(2) Bovine Tuberculin (P.T.) is prepared in a similar way, only bovine tubercle bacilli are used instead of human. This applies to the other tuberculins mentioned below.

(3) Koch's New Tuberculin (Tuberculin T.R.) is made by centrifugalising triturated bacilli with sterilised water to dissolve out all soluble products. The supernatant liquid containing the soluble products is decanted. The insoluble matter is alternately treated with sterilised water and centrifugalised until fine emulsions are obtained; these together are T.R. One c.c. contains the insoluble residue of 10 mg. of tubercle bacilli. In actual bulk this amounts to about 2 mg. It is used for treatment only, as are all the following forms.

(4) Tuberculin B.E. (Bacillary Emulsion) is prepared by emulsifying half a gram of triturated bacilli with 50 c.c. of glycerine and 50 c.c. of sterilised water, so that 1 c.c. contains 5 mg. of bacillary substance.

(5) *T.O.A.* (*Tuberculin original alt.*).—Four- or five-weeks-old cultures of human bacilli are filtered through bacteria filters, so that the filtrate (T.O.A.) is absolutely free from germs.

Denys' Tuberculin B.F. is similar to this. This form of tuberculin may be evaporated to one-tenth of its bulk at low temperature, and is known as Vacuum Tuberculin.

(6) Tuberculin A.F. (Koch's Albumose-free Tuberculin) is prepared from tubercle bacilli which have been grown on a special medium of inorganic salts and citrates free from albumoses and peptones, the only nitrogenous constituent being asparagin. It is used similarly to the old tuberculin, and is about the same strength. It has an advantage over old tuberculin in that anaphylactic symptoms due to proteins are excluded.

(7) T.Bk. (Tuberculin Béraneck) is composed of a mixture of equal parts of an extract of the bacillary bodies in 1 per cent. phosphoric acid and a filtered culture of bacilli in an albumose-free medium, and which has not been altered by heating.

Tuberculin in Diagnosis

Cutaneous Test (von Pirquet).—A little old tuberculin is scarified into the skin as in an ordinary vaccination. A control scarification is also done without the tuberculin. In a positive reaction there is a distinct inflammation with or without the formation of vesicles. It is not of great value, as the reaction may be positive in the case of foci in the lung or bronchial glands, which have become so inactive as no longer to deserve the name of disease. In adults, then, a

positive reaction points only to a tuberculous infection having occurred at some time, no matter how remote. A negative reaction is more valuable, and most likely points to the absence of tubercle.

In children also this test is of some value. In older children a positive reaction may indicate inactive foci, while a negative reaction is of great significance. The reaction is of no value as regards prognosis. In very advanced cases there may be no reaction.

Quantitative von Pirquet Test.—This is a refinement of the cutaneous test. It is asserted that tuberculin-sensitiveness is an index to the activity of the disease. Ellerman and Erlandsen have worked out a method of expressing the results of the cutaneous test numerically. For the test are used solutions of old tuberculin in four strengths, viz. one, four, sixteen and sixty-four per cent. Four scarifications are made along the forearm with a small platinum spade by a rapid twisting movement, gently enough not to draw blood, and a drop of the solutions applied, the weakest most distally and the strongest most proximally.

In a positive result different-sized papules are produced by the different concentrations. They are measured in twenty-four and forty-eight hours. The papule-size, and especially the papule-difference, are stated to have certain values in diagnosis and even prognosis, and from tables the *degree* of sensitiveness is found.

Conjunctival Test (Calmette).—This is now rarely done on account of the danger of ophthalmia.

A single drop of a one per cent. solution of tuberculin is instilled into one conjunctival sac as near as possible to the inner canthus. The eye should not be rubbed. The reaction generally begins in from twelve to twenty-four hours, occasionally earlier, and may remain several days. The eye should always be examined within twenty-four hours. A mild reaction consists of reddening of the caruncle and palpebral conjunctiva. If more intense there is marked reddening, with involvement of the ocular conjunctiva and increased secretion, while in some cases there may be intense inflammation of the whole conjunctiva, with fibrinous and purulent secretion, and even small ecchymoses. A single instillation is insufficient for diagnosis; tuberculosis can only be excluded if there is no reaction after three or four tests on the same eye.

Subcutaneous Test.—It must be remembered that a tuberculin reaction does not distinguish healed from unhealed tuberculosis. But this is the most valuable test, inasmuch as *focal reactions* may occur. The old tuberculin is always used for this purpose. Before the injection a four-hourly temperature chart must be kept for at least forty-eight hours, and the injection should not be given if the temperature during that time has been above normal, or at most 99° F. in the mouth. All cases should not be injected indiscriminately. In a case with typical physical signs, even if no tubercle bacilli are found in the sputum, this test should not be used. The more expert the physician

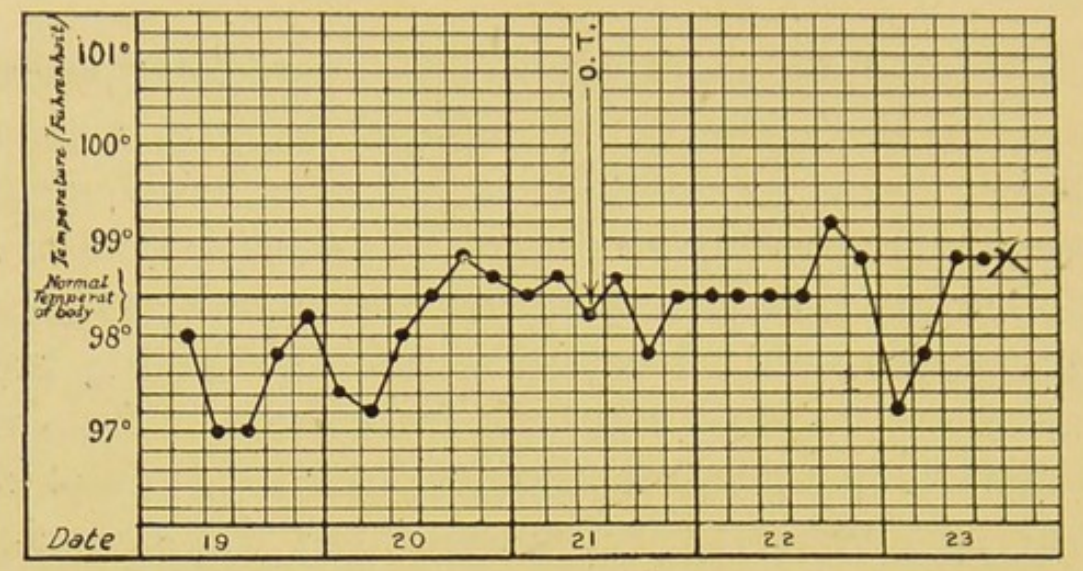
the less will he use it, for, as we will see later, there is a real danger in it. It is usual to start with a dose of $\frac{1}{10}$ mg. (= 0·0001 c.c.) O.T. The four-hourly temperature chart is continued for another two days. If there is even a rise of half a degree F. (above the highest of the forty-eight hours preceding the injection) the dose must not be increased, but in a few days the same dose repeated. It should only be increased if no reaction has followed the last dose. In doubtful cases it is taken as a negative result when a slight rise of temperature disappears or is less marked on repetition of the same dose. If there is any doubt as to diagnosis and the temperature only rises slightly, say 1° F., the same dose should be repeated when the temperature has again reached normal. A cumulative reaction is very characteristic of tubercle.

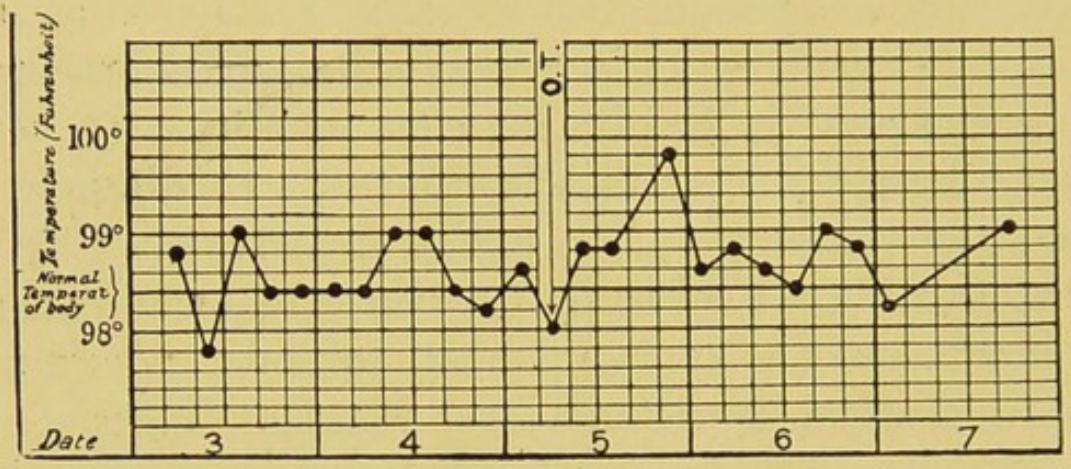
The dose may be increased as follows: $\frac{1}{10}$, $\frac{1}{2}$, 1, 2, 5, 10 mg. every four days; for children half or quarter of these doses might be used.

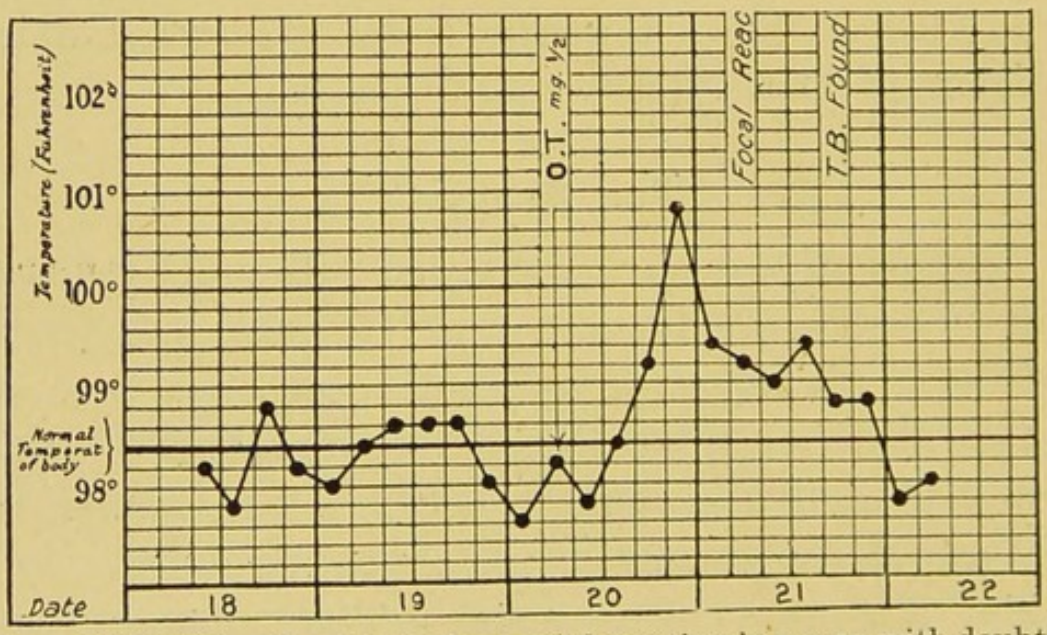
The Reaction

The Reaction may be divided into: (1) general and febrile, (2) local, and (3) specific (*focal reaction*). A reaction is positive when a rise of temperature of 1° occurs. A temperature of 100° would be called a slight reaction; 102° moderate, and above that, severe.

The *Reaction Curve varies.*—The most typical is a rapid rise with a slower fall, the normal being reached after twenty-four hours. The rise begins in six to eight hours; sometimes it is earlier,







FIGS. 33–34–35.—Showing a short mild reaction in a man with doubtful physical signs at right apex and no bacilli found in sputum. O.T. mg. $\frac{1}{10}$ given on Jan. 21, and mg. $\frac{1}{2}$ on Feb. 5, with slight reaction. A repetition of mg. $\frac{1}{2}$ on Feb. 20 resulted in a more marked reaction, with production of crepitations at the suspected apex and tubercle bacilli in the sputum.

and sometimes delayed for thirty hours; the acme is usually reached in nine to twelve hours. The smaller the dose used, the later the reaction begins, and the later it reaches its height. It is also slighter the smaller the dose. The charts show other types of reaction.

Other General Symptoms.—A severe reaction begins with a rigor, shivering and a feeling of

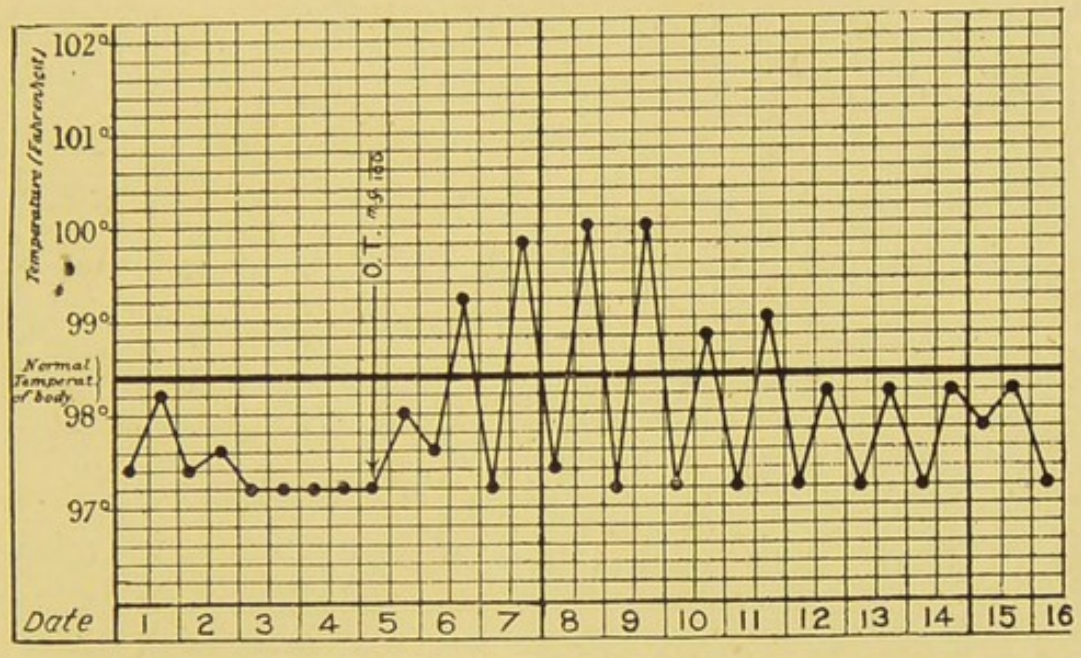


FIG. 36.—Prolonged reaction to O.T. mg. $\frac{1}{100}$ in a boy æt. 11, with tuberculous cervical glands.

warmth or chilliness. There is malaise, with giddiness, nausea and vomiting. The patient may have a feeling of lightness, as though he were floating in the air. Later there is headache, pains in the limbs, and stabbing or dragging pains, palpitation, loss of appetite, sleeplessness and lassitude. With a fall of temperature there is general weakness, and after the reaction has passed off the patient often has a remarkable feeling of well-being, which makes him quickly

forget the discomfort he has suffered. There may also be *objective symptoms*, as swelling and pain at the site of injection. Pulse and respiration are increased in rate. There is an irritable cough and increase of sputum, and often tubercle bacilli are found in the sputum when they could not be found before. Albuminuria occurs, and sometimes swelling of the spleen and lymph glands. Rarely is there loss of consciousness.

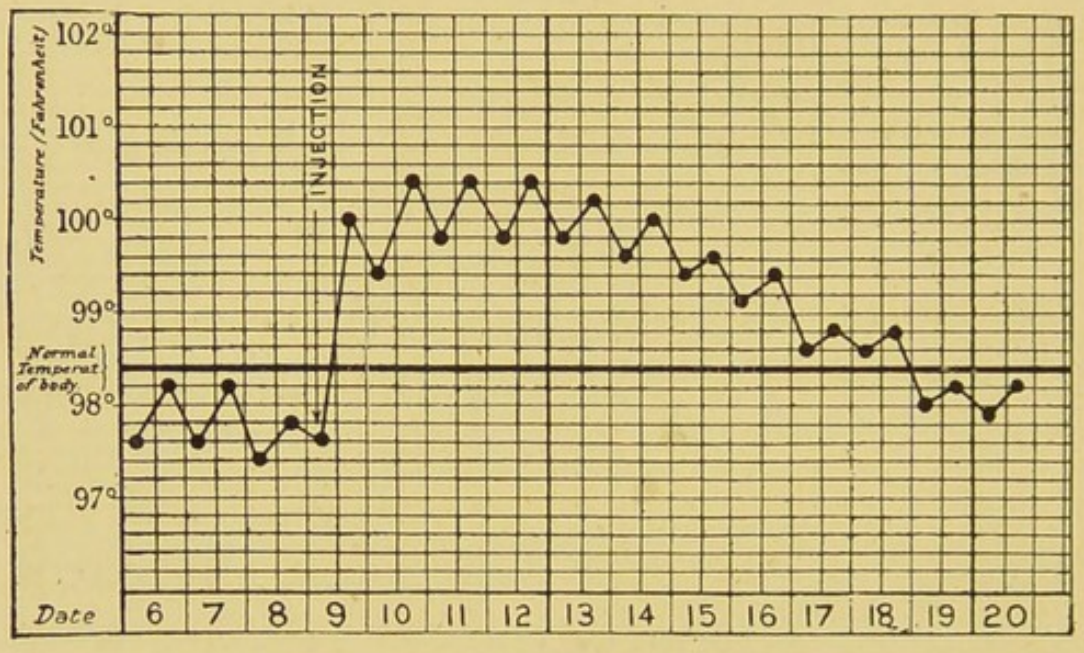


FIG. 37.—A prolonged mild reaction.

Localising Symptoms, such as tension in the chest or tenderness over the sternum, may occur.

A *focal reaction* often results in an accentuation of physical signs around a lesion or the appearance of crepitations, etc., in a suspected area, which previously gave no definite signs; also it accounts for the occasional appearance of bacilli in the sputum.

In treating a reaction, antipyretic drugs must not be given for the headache until the highest

temperature is passed, as this will obscure the reaction.

Contra-indications.—It is not safe to use the test if the temperature is above 98·4° in the axilla or 99° in the mouth during forty-eight hours. It should not be used in cases where the clinical history and signs are positive; nor where there has been recent hæmoptysis; nor in patients who are evidently seriously ill with cardiac or renal disease or diabetes, or are recovering from a serious illness, as pneumonia or typhoid. It is also contra-indicated in active pleurisy, intestinal tuberculosis, and when miliary tubercle is suspected.

The test should be used to establish early diagnosis and to confirm doubtful physical signs, not definite physical signs. In such cases a *focal reaction* is extremely important, and hence the subcutaneous method is superior to the others. A rise of temperature and the production of crepitations at a suspected part is practically diagnostic, nor is there much danger if the patient is kept in bed till all signs of reaction have quite settled down. Nevertheless it must be remembered there is some danger, and the application of the test should be carefully considered.

Sometimes it is important in a differential diagnosis from cancer, syphilis, actinomycosis and bronchiectasis, but in the majority of cases the skilled physician will make his diagnosis without the risk of using tuberculin. The dangers will be more fully discussed later.

The determination of the tuberculo-opsonic index might in doubtful cases be tried before the use of tuberculin for diagnosis. An abnormal swing of the opsonic index before and after exercise is very significant. We have already discussed the technical difficulties regarding this, and certainly as regards treatment we will see that it is not necessary nor practicable, as we have other and simpler guides for the use of tuberculin.

Tuberculin in Treatment of Pulmonary Tuberculosis

At the present time this treatment is very much in vogue, perhaps too much. We will see that tuberculin should not be used in every case, and that skill is required in its use.

It is important to remember that tuberculin has no direct healing properties. Its action is not like that of a serum in diphtheria; nor is it toxic to healthy animals. Its results compare with those of natural tuberculosis. We know that a tuberculous patient up and about may have fever and headache and generally feel out of sorts, accompanied by definite extension of disease; he is being poisoned by toxins derived from his own tuberculous foci. When he is put to rest all his symptoms may improve and his temperature slowly return to normal in steady "staircase" type.

It is important to understand that a patient is febrile if his temperature is above normal *at any*

time in the twenty-four hours, but unfortunately many patients are allowed out of bed whose evening temperature only is distinctly raised, their chance of recovery thereby being much lessened if not absolutely lost. When by rest in bed the temperature does not return to normal, "absolute rest" is ordered, and the patient is treated much as a typhoid case. He is not allowed to sit up or feed himself, but is given a liberal diet. As the temperature becomes normal he can be allowed up more and more every day, but always only if his temperature remains normal all day. Later he is allowed gradually increasing walking exercise, and still later graduated labour. This is the idea on which modern treatment of tubercle is based. It is comparable with the immobilisation treatment of a tuberculous joint.

Unfortunately, patients with fever are allowed to be up and about only too frequently, each day getting tired and inoculated with their own toxins and steadily getting worse. It is the carefully graduated rest and exercise of the sanatorium that is required, so that the system can get more and more accustomed to larger doses of the toxins produced, till finally the patient can do a full day's work without any symptoms of fever. (It may be well to point out here that occasionally we meet with patients who are apparently steadily improving—if we judge by their increasing ability to work without getting fever—while at the same time their physical signs are extending.)

Tuberculin contains the toxic substances of the tubercle bacilli, and these excite the production of antibodies in the way that the bacilli in the body do. After an injection in the tuberculous subject it becomes a toxic substance which irritates the tuberculous lesions, and these often become the seat of marked activity.

The toxic bodies arising from diseased foci, whether excited by tuberculin or not, cause febrile and focal reactions. Reactions can be produced without inoculations from absorption of toxic products; this is called *auto-inoculation.*

The irritative actions cause breaking down of the tissues, and the more unfavourable the case the greater is this destruction of tissue. It is the aim in using tuberculin that this destruction be of the slightest and the reactions as slight as possible. Obviously it is not wise to produce violent reactions, as this means the breaking down of much tissue, with the danger of the infection becoming generalised.

A "reactionless" method, or one with very slight reactions, is the best and perhaps the only safe method. The aim of treatment is to stimulate the natural healing forces in the same manner as in the spontaneous arrest of tuberculosis. In the natural cure of tuberculosis there need not be any fever or inflammatory signs. Early tuberculosis heals better without these; and it is important to remember that it does not necessarily follow that because tuberculin gives no definite signs and symptoms there is no slight reaction

at the affected foci. There is almost certainly some hyperæmia and exudation and other signs of inflammation. It is frequent to find healed tubercle that has never caused febrile symptoms.

In the early days of tuberculin treatment violent reactions were produced, and many cases made worse. If this treatment by marked reactions comes much in vogue again, and especially in dispensary work, where each case may not be under sufficient supervision, tuberculin will again be brought into disrepute. The forced treatment by big doses may very occasionally bring about a rapid improvement, but the risk is too great, and the great majority of the cases will suffer harm.

Cases of healed tubercle are sensitive to doses of tuberculin. The immunisation may be looked upon as temporary, and the natural healing process is stimulated. It is not necessary that every case should have a large dose of tuberculin, but every individual has his own optimum dose; this is the amount which at a given time can be borne without ill-effects. In a successful case the optimum dose will be raised gradually. Each case must, therefore, be carefully observed and treated on its merits. As patients, and even the same patient at different times, differ greatly in their sensitiveness, it is not wise to have a mathematically absolute scheme of dosage. Below, such schemes are given, but they must not be rigidly adhered to in every case if there are contra-indications.

From what has been said it is obvious that tuberculin should only be used in those patients

who are under most careful observation. The pulse, temperature, respiration and weight charts should all be carefully watched and the sputum measured daily, and frequent examinations of the chest made to detect fresh foci of disease. The method of slow increase of dosage with avoidance of marked reactions is perhaps the best, and certainly the only safe one to be used by those

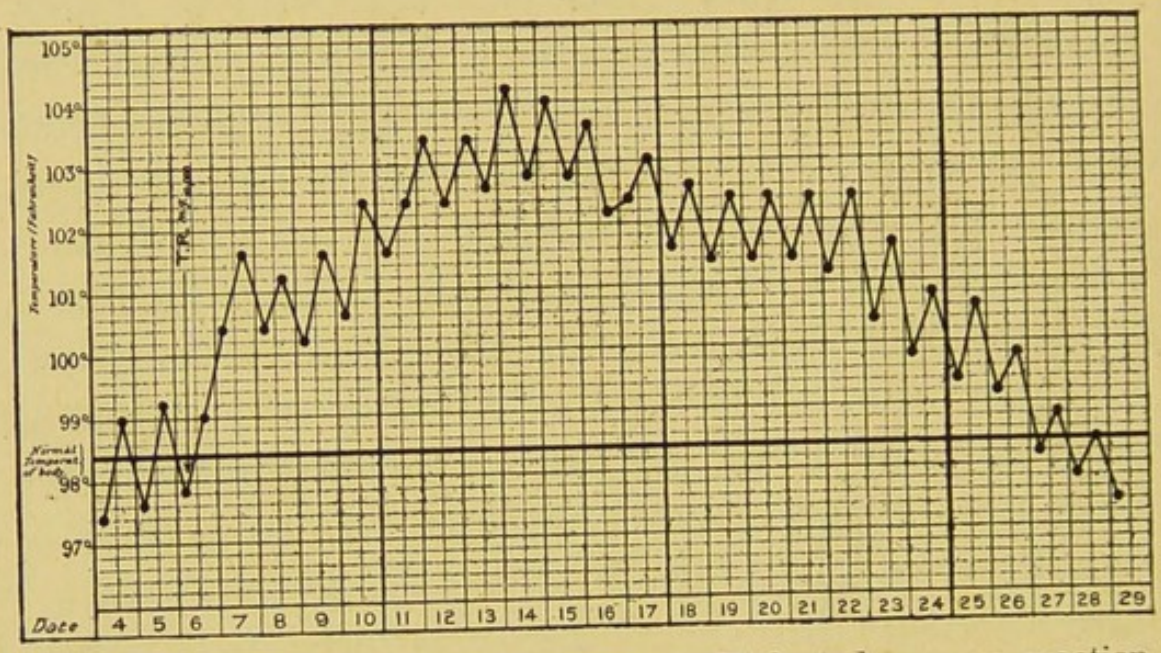


FIG. 38.—Case of hypersensitiveness. Violent dangerous reaction produced by T.R. $\frac{1}{10000}$ mg. in a girl with slight apical disease and no pyrexia. Acute pleurisy with effusion and great toxæmia followed, and pulse became very rapid. Steady improvement on *absolute rest*.

who have not had great experience. Similarly, no one but the expert should use tuberculin in febrile cases, even although the fever may be due to the tubercle and not to secondary infection.

Suitability of Cases for Tuberculin Treatment.—If Turban's classification, based on the anatomical changes in the lungs of first (infiltration), second (consolidation) and third (excavation) stage be accepted, then cases in any of these stages may

be suitable. Or, again, a case in the third stage (cavitation) may be suitable while a case in the first stage is not. For this classification tells us little of the condition of the patient, *e. g.* stage three might include a very chronic case with cavity and fibrosis without any signs of activity, the patient being apparently quite well and fit for

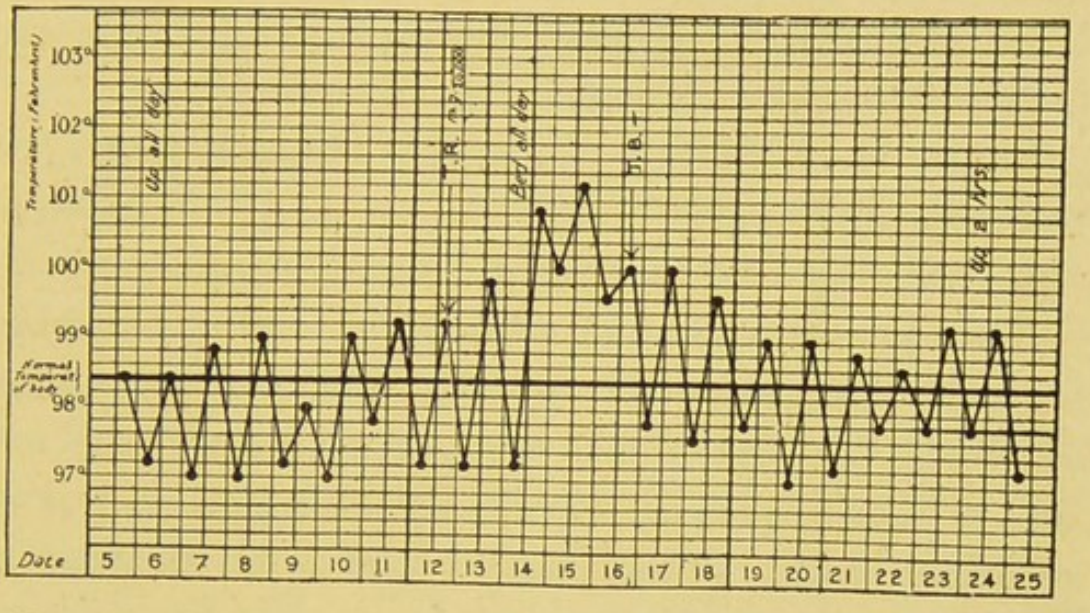


FIG. 39.—Hypersensitiveness in a man whose only physical signs were slightly impaired breath sounds at left apex. Repeated examinations for tubercle bacilli were negative. Marked reaction to T.R. $\frac{1}{20000}$ mg., with tubercle bacilli in the sputum.

many years' work; or else a very acute and hopeless case with rapid breaking-down of tissue and formation of cavities. A much more workable classification has been suggested (Inman). In this cases are divided into—

Class I. *Working Afebrile*, that is, cases able to do their work without a rise of temperature; the auto-inoculations are not too great, and the patient is in the stage to which we want to reduce all.

Class II. *Ambulant Afebrile.*—The patient can do a *certain amount of walking exercise* without pyrexia, and consequently the auto-inoculations are not too great with that amount of exercise, but with any additional work the temperature will rise.

Class III. *Ambulant Febrile, Resting Afebrile.*—Here the patient has no temperature while at rest in bed, but fever is produced if he is up and about. In other words excessive auto-inoculations are induced by the exercise.

Class IV. *Resting Febrile.*—The patient has pyrexia although confined to bed. Excessive auto-inoculations are produced spontaneously.

This classification is clinical as well as pathological, and gives a practical basis on which to work. It does not take into account the extent of the lesion in the lung, but that is not of so much importance, for a case with disease in four lobes, even with cavitation, may be so well resisted and slow and afebrile that the prognosis may be infinitely better than a febrile case with infiltration of only one apex where the resistance is low, and the case rapidly going downhill. With this classification we are better able to discuss the indications for tuberculin treatment.

Class IV,—cases which are febrile, although confined to bed, should not be given tuberculin except by an expert, and even then it may be only rarely if ever indicated. Only too frequently is this the type of case referred to the bacteriotherapist for treatment as a last hopeless resort.

Class III, where the patient has no temperature

while in bed but cannot walk about without developing one, possibly is best not treated with tuberculin. It is better to continue the *rest treatment* till the patient is sufficiently improved to stand gradually increasing exercise, and at the same time is getting accustomed to increasing auto-inoculations, until he comes into Class II, where he can walk about without a rise of temperature. Here tuberculin can often be given with advantage, and more safely. Nevertheless it can be used safely in Class III because the patient, having a normal temperature while in bed, can be watched as regards reactions, and gradually increasing exercise can be given simultaneously with tuberculin.

Patients in Class I are frequently benefited by the treatment, and with them the risk of using tuberculin is much less.

It must always be remembered that a dangerous remedy is being used. Loss of weight or increase of pulse-rate, or increase of sputum and cough, or rise of temperature may indicate over dosage, in which case the intervals should be increased or the doses made smaller. Sometimes there is a cumulative action—a hyper-susceptibility. Thus if a dose cause a rise of temperature, some days should elapse, and at the next injection the same dose be repeated ; this often produces no reaction, but sometimes it gives a greater reaction. It is then wise to wait a week or even two weeks and give a smaller dose.

When any doubt exists as to dosage, it is always

better to err on the safe side in the smallness of the dose. Attempts should never be made to force the treatment simply because certain schemes of dosage have been devised. It must be remembered that the patient who is having tuberculin treatment with violent reactions feels better in spite of loss of weight, increased sputum and physical signs. We must not be misled by the patient's subjective sensations, for indeed we find that improvement follows for a time on any treatment. Too great caution cannot be used in the use of this remedy.

It is perhaps true that some workers have seen improvement even in bad cases where recovery seemed impossible, and have seen many of the symptoms disappear, as dry cough, vomiting, headache and palpitation, dyspnœa, fever, night sweats and pleuritic pain. Still the writer thinks it is rather in spite of the injections and not on account of them; or if it is due to the tuberculin, it so rarely happens that it is not worth trying if we consider the great risks of producing fresh foci, pleurisy and hæmoptysis. Many of the bad symptoms also can be treated by the ordinary methods with good results, especially with *absolute rest* in fresh air.

Tuberculin should never on any account be used in cases with recent hæmoptysis, or active pleurisy, or where there is any other serious disease, as nephritis, diabetes, etc.

It sometimes happens that the pyrexia may be due to secondary or mixed infection. Vaccine

treatment is useful in these cases, but this is described elsewhere. Early cases of tubercle treated from the start in the open air and away from infection rarely get these secondary infections.

Modes of Administration and Technique.—Tuberculin is sometimes given by mouth, but here the amount absorbed is uncertain; it is then best given on an empty stomach, and T.R. used. It may be a useful method for those patients who fear the prick of a needle. The *subcutaneous method* is by far the best, as the action is sure and the dosage accurate. The site chosen is generally the upper arm or the interscapular region, after the skin has been sterilised by painting with iodine solution. The needle and syringe are sterilised either by boiling in water or by Wright's method of drawing hot olive oil (temperature 140° C.) through the needle into the syringe; with this latter method care must be taken that only the needle and no part of the syringe itself touches the oil, lest the syringe be broken. The dose to be injected should be made up to a uniform bulk—5, or better, 10 minims; or, better still, fractions of a cubic centimetre used.

It is well in practice to confine oneself to one or two varieties of tuberculin. We have said that there are only slight differences in the actions of all apart from their different strengths.

The different dilutions can easily be made. A series of sterilised rubber-stoppered vaccine

bottles are required. In withdrawing a dose from the bottle, place a drop of lysol on the rubber stopper; plunge the sterile needle through this drop, and draw the solution into the syringe. The diluting fluid is—

Pure Lysol 2·5
Sodii Chloridi 8·5
Aq. destil. ad 1000

or—

Acid Carbol. 5
Sodii Chloridi 8
Aq. destil. ad 1000.

With six such bottles containing different strengths of tuberculin it is possible easily and accurately to measure out any dose at once. Thus—

		T. P.T. P.T.O. T.O.A. A.F.		T.R.	
1st bottle.	1 c.c. contains	100	mg.	1	mg.
2nd ,,	1 c.c. ,,	10	,,	$\frac{1}{10}$	,,
3rd ,,	1 c.c. ,,	1	,,	$\frac{1}{100}$	,,
4th ,,	1 c.c. ,,	$\frac{1}{10}$	,,	$\frac{1}{1000}$	,,
5th ,,	1 c.c. ,,	$\frac{1}{100}$	,,	$\frac{1}{10000}$	,,
6th ,,	1 c.c. ,,	$\frac{1}{1000}$	,,	$\frac{1}{100000}$	,,

1 c.c. of original fluid is equivalent to 1000 mg. T., P.T., T.O.A., P.T.O. and A.F.; to 10 mg. T.R. and P.T.R.; and to 5 mg. B.E. and P.B.E.

A long, thin record syringe of 1 c.c. capacity divided into tenths or smaller divisions is used. It is better to have the divisions marked on the rod, which should also have a screw top. With a well-graduated syringe it is possible to get enough

dilutions for all practical purposes from the different bottles.

Schemes of Dosage.[1]

Koch's O.T. Initial dose—

mg. $\frac{1}{1000}$ (= 0·000001 c.c.).

Sequence of doses—

$\frac{1}{1000}$	$\frac{2}{1000}$	$\frac{4}{1000}$	$\frac{8}{1000}$ mg	
[0·000001	0·000002	0·000004	0·000008 c.c.]	
$\frac{1}{100}$	$\frac{2}{100}$	$\frac{4}{100}$	$\frac{8}{100}$ mg.	
[0·00001	0·00002	0·00004	0·00008 c.c.]	
$\frac{1}{10}$	$\frac{2}{10}$	$\frac{3}{10}$	$\frac{5}{10}$	$\frac{7}{10}$ mg.
[0·0001	0·0002	0·0003	0·0005	0·0007 c.c.]

1·0	1·5	2·0	3·0	5·0	7·0	10·0	15·0	20·0 mg.
[0·001	0·0015	0·002	0·003	0·005	0·007	0·01	0·015	0·02 c.c.]

If with any dose a reaction occurs the dose should not be increased, but the same dose repeated at a longer interval or a smaller dose given. With the larger doses, such as 10 to 20 mg., there may be a reaction, so it is better to increase from 10 to 15 and then to 20. The intervals between the doses should be about four days. But if the doses have reached about 100 mg., an interval of about a week should elapse. Even up to 1000 mg. (1 c.c.) may be given in some cases, but there is no need to work up to this large dose in every case. It must be remembered that even a high degree of

[1] Throughout this chapter the fractions are combined with the French weights for convenience, as such is more frequently used by English workers.

tuberculin immunity does not of necessity arrest the disease; indeed tuberculosis can be arrested without general tuberculin immunity.

T.R.

$\frac{1}{100000}$	$\frac{2}{100000}$	$\frac{4}{100000}$	$\frac{8}{100000}$	$\frac{16}{100000}$ mg.
[0·000001	0·000002	0·000004	0·000008	0·000016 c.c.]

	$\frac{2}{10000}$	$\frac{4}{10000}$	$\frac{6}{10000}$ mg.
	[0·00002	0·00004	0·00006 c.c.]

$\frac{1}{1000}$	$\frac{2}{1000}$	$\frac{3}{1000}$	$\frac{5}{1000}$	$\frac{7}{1000}$	$\frac{10}{1000}$	$\frac{15}{1000}$ mg.
[0·0001	0·0002	0·0003	0·0005	0·0007	0·001	0·0015 c.c.]

$\frac{2}{100}$	$\frac{3}{100}$	$\frac{5}{100}$	$\frac{7}{100}$	$\frac{10}{100}$	$\frac{15}{100}$ mg.
[0·002	0·003	0·005	0·007	0·01	0·015 c.c.]

$\frac{2}{10}$	$\frac{3}{10}$	$\frac{5}{10}$	$\frac{7}{10}$	$\frac{10}{10}$	$\frac{12}{10}$	$\frac{15}{10}$	2 mg.
[0·02	0·03	0·05	0·07	0·1	0·12	0·15	0·2 c.c.]

These doses are also given every three or four days at first, but when the bigger doses are reached, intervals of a week should elapse thus—

$2\frac{1}{2}$	3	4	5	6	7	8	9	10 mg.
[0·25	0·3	0·4	0·5	0·6	0·7	0·8	0·9	1 c.c.]

B.E. is given similar doses, but it is made up in twice the strength of T.R. 10 m.g. should be the maximum dose for B.E. and 20 mg. for T.R.

It must be pointed out again that these schemes are not to be strictly adhered to. Some cases are peculiarly sensitive (Fig. 39), and the doses must be very gradually raised, while with other cases the doses can be more quickly raised. The main point to note is that if a dose produces too much reaction, always wait till this has passed off; then either repeat the same at a longer interval, or give a smaller dose.

The danger of trying to force the treatment has been explained. Some cases are so highly sensitive that it is wise to abandon the treatment by tuberculin, or at any rate to postpone it. In some of these cases a dose as small as $\frac{1}{20000}$ mg. T.R. may produce high pyrexia lasting a week or two, with intense toxæmia and even pleurisy with effusion and extension of the disease (*see* Fig. 38).

Very many cases will not reach the high doses mentioned, and indeed the writer believes it wise to keep to small doses. Sometimes in a case that has become stationary one single small dose seems to start a remarkable improvement, which continues.

Absolute rest is indicated in these cases, and indeed rest, more or less absolute, is indicated during every reaction from tuberculin, no matter how slight it be, and then a gradual return to exercise. Occasionally exercise is taken too soon, even after the reaction appears to have gone; there is then a return of the reaction; if so, the treatment should be rest in bed till the temperature is normal and steady.

Localised Tuberculosis elsewhere than in the Lungs

Infection of the glands, bones, joints, skin and viscera can all be treated and often benefited by tuberculin. The same scheme of dosage can be employed, though it is possible to begin with large doses, *e. g.* $\frac{1}{20000}$ mg. T.R., as an initial dose.

Occasionally focal reactions are only produced when much bigger doses than this are reached.

Tuberculin, however, can be but a part of the treatment, and other aspects are of great importance. The primary focus of infection must be sought and treated, as, for example, in glandular disease following lesions of the mucous membranes, the teeth or the skin.

Caseous material will not be influenced by tuberculin, and chronic fibrosis may impede healing; consequently surgical measures are often indicated. In the first place, softening glands must be excised where possible; renal tuberculosis, perhaps, is always best treated by nephrectomy. Tuberculin has produced good results in tuberculous cystitis, sinuses, skin and occasionally in ocular lesions. Arthritis is often cured; but rest is an important factor in the treatment, as auto-inoculation must be prevented as far as possible.

In abdominal tuberculosis the possibility of an infection with bovine tuberculosis must be noted, and bovine tuberculin may produce better results than the human variety. In open lesions other organisms will abound, and occasionally these have to be combated by autogenous vaccines as mentioned above. Finally, in all cases, and especially in children, the possibility of a generalised infection resulting from the use of tuberculin must always be borne in mind, and the treatment adopted with great caution.

CHAPTER XXIX

CHEMOTHERAPY

Treatment of Protozoal Infections — Quinine — Mercury — Synthetic Arsenical products—Parasitotrophic ; Organotrophic—Acquired resistance—Trypanosomiasis—Spirilla diseases—Atoxyl, Soamin—Arsacetin—Arsenophenylglycin—*Salvarsan :* Methods of administration ; its value in all forms of syphilis — Neo-salvarsan — Other diseases ; malaria, variola, blood diseases—Conclusions.

We have already seen that different infective diseases can be treated in different ways, and that no single line of treatment is applicable in all cases.

In dealing with a group of diseases not already mentioned, namely, those due to pathogenic protozoa, it is found that neither bacteriotherapy nor serum therapy are of any avail. In view of the increasing list of diseases due to protozoa it is only natural that attention should have been directed to dealing with them ; and especially so since the spread of civilisation has been accompanied by a dissemination of these diseases.

It has long been empirical knowledge that malaria plasmodia can be destroyed rapidly by quinine. Elucidation of the life cycle of the plasmodium has placed the use of quinine on a more scientific basis ; so that now, instead of pouring unlimited quantities through the intestines, it is generally sufficient to give smaller

doses, either by the mouth or preferably subcutaneously, at such a time when the young parasites are present in abundance in the blood stream—this occurs when the red corpuscles have dehisced and, clinically, at the period of rigor.

Similarly, in the case of syphilis, mercury has long been recognised as a specific form of treatment. When, in quite recent years, syphilis was found to be due to the spirochæta pallida, which later was shown to belong to the group of protozoa, it was found that mercury was a powerful spirillocide, and caused rapid disappearance of these organisms from the lesions involved. So effective is this treatment that, as Metchnikoff first demonstrated, mercury inunctions can be employed as a prophylactic—even after the syphilitic virus has been inoculated into a part—a line of routine treatment that is specially applicable to the services.

Among the earlier attempts to treat infections by direct action of bactericidal agents was the suggested treatment of tuberculosis by intravenous injection of formalin; but the resulting dilution in the blood stream that could be produced without harming the body itself was far too weak to exert any influence on the bacilli.

To Ehrlich's genius belongs the credit of showing that it is possible to attack and destroy parasites by direct action of drugs without harming the tissues of the host. This constitutes the science of Chemotherapy.

By analogy with the observation that various dyes have a selective activity and stain, *in vivo*, different tissues and cells, Ehrlich deduced that toxic chemical products could be made to have the same selective affinities, and ultimately demonstrated that " parasites only can be destroyed by materials for which they have a certain affinity, these substances being parasitotrophic."

There has consequently been produced a series of bodies which exert a direct *parasitotrophic* action against various parasites, *in vivo*, with a minimum or total absence of effect on the body of the host—the so-called *organotrophic* action. These bodies, belonging to the arsenic group, and mostly to the synthetic benzene group, are classified by Ehrlich thus—

(1) Arsenical compounds : arsenious acid, and the phenyl-arsenic acid derivatives, viz. atoxyl, arsacetin, aresenophenylglycin, and the most recent of all, salvarsan or " 606."

(2) Azo-dyes, such as trypan red, trypan blue.

(3) Basic triphenylmethane dyes, *e. g.* methyl violet, parafuchsin, malachite green, etc.

Dealing with the benzol derivatives of therapeutic import, he showed that by synthetically altering the various groups attached to the benzene ring, the action of the drug could be varied at will, and its parasiticide action increased or decreased with absolute certainty. For example, parafuchsin develops stronger action when the halogen group is appended, as do also other

substances; also by devoting special attention to the arsenic group it appeared that the action of these bodies could be varied against different parasites, as, for example, with arsenophenol. This is markedly fatal to trypanosomes, but on the introduction of iodine into the compound this trypanicide function disappears, whereas a markedly spirillocidal effect is developed.

It would be beyond the scope of this work to follow out in detail all the steps of this fascinating work, but we must take the more important of these products that have been synthesised in the way mentioned, and discuss their utility in practice.

The basis of the ultimate researches as laid down by Ehrlich was simultaneously to introduce substituents into the arsenobenzol which—

(1) Diminish the whole toxicity.
(2) Increase the spirillocide qualities.
(3) Cause a greater durability of the combination.

Arsenious acid is extremely toxic (organotrophic), but atoxyl, which was, indeed, discovered and advocated in treatment of disease long before the present era of chemotherapy, is an arsenic product of much lessened toxicity. After recognising the correct constitution of atoxyl, Ehrlich proceeded to produce other bodies of allied nature which conformed to the principles laid down by him; and these have now had so extensive a trial in curative medicine that definite opinions as to their worth can be deduced.

The success that greeted the use of atoxyl and its allies in trypanosome infections of man and animal was such that as soon as the definite spirochætal nature of syphilis was proved it was only natural that similar treatment should have been attempted against this disease. The ultimate discovery of the most powerful and least harmful of all spirillocide products, namely, salvarsan, has resulted in a revolution of the treatment of this disease in all its protean manifestations.

There are, however, a few generalisations to make before detailing the various drugs and the results of their use.

In the first place these products are not parasiticidal in the test tube, and only exert their activity in the living body.

Also it was found that in dealing with trypanosome infections, though the trypanosomes could rapidly be eliminated from their usual haunts, often they recurred after a varying interval; also if insufficient dosage was employed the parasites could develop a complete resistance to the drug—a resistance which was found to be transmitted from generation to generation of parasite, and experimentally even to the hundredth generation. Hence it would be possible to produce in a sleeping sickness area by inefficient treatment a breed of trypanosomes that would be quite resistant to the drug employed, and so add an additional difficulty in eradication of the infection.

This production of resistant strains has been

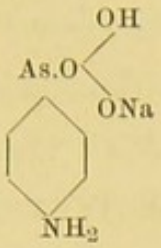
brought about with many trypanosomes against trypan-red and various arsenical products, but as yet there is no evidence to support a similar production of resistance in spirochætæ when treated with salvarsan.

Again, though an arsenic product may be germicidal to one species of trypanosome it may be inefficacious against other species. For example, the T. gambiense was readily controlled by arsenophenylglycin, whilst the T. lewisi was almost completely resistant to this drug. Hence it is necessary to use a specific germicide known to act against the parasite in question, and to use it in sufficiently large doses to obtain rapid and complete sterilisation of the host.

As regards the toxicity of these products much has been written and much has been misunderstood. With the earlier products, and particularly atoxyl and arsacetin, there undoubtedly resulted injuries to the eyes, and in as many as from 1 to 2 per cent. of cases actual blindness occurred. But with salvarsan no genuine case of blindness due to the drug itself has ever been reported, though occasionally, as Ehrlich remarked, cases of early optic atrophy progressed to complete atrophy even after administration of the drug. Also cases of nephritis have followed the use of atoxyl.

The most important of the compounds may now be detailed.

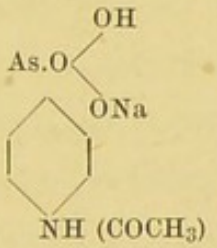
Atoxyl (monosodic salt of paramidophenylarsenic acid) contains 24 per cent. of arsenic, and is thirty times less toxic than arsenious acid. *In*



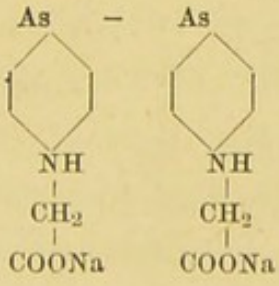
vivo it is both prophylactic and curative in trypanosomiasis, and various spirilla diseases, such as relapsing fever and syphilis. By its use the trypanosomes can be made to disappear rapidly from the blood and glands, though it is only after a course of treatment lasting several months that a permanent cure can be obtained; and then only in some cases, relapses occurring even after twelve months' interval. Nevertheless, by its use the infection can be kept in check, and hence as a prophylactic it is of extreme importance, though its toxicity must be borne in mind.

Soamin is a product of atoxyl with a molecule of water, and is less toxic.

Arsacetin (acetylatoxyl) is a substitution product of atoxyl.



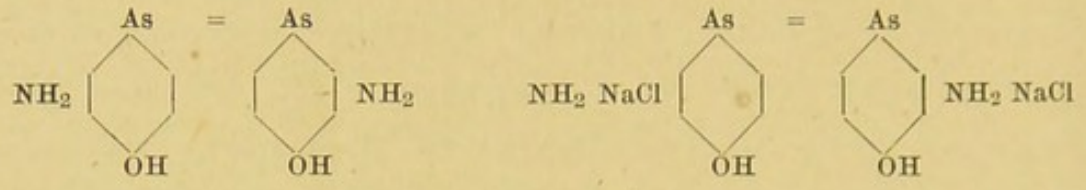
Arsenophenylglycin is even less toxic than atoxyl, and constitutes the body in Ehrlich's series



numbered 418. It has been used with satisfactory results in surra, a protozoal disease in horses.

Salvarsan

Salvarsan (dioxydiamidoarsenobenzol) consti-



tutes the substance numbered 606 in the series. As this body is insoluble, it is combined with hydrochloric acid to constitute the soluble salvarsan. It is the most recent product, and has had by far the most extensive trial, and sufficient time has elapsed to prove its worth as a powerful spirillocide of practically no toxicity. It has a rapid destructive action on the spirilla of relapsing fever, and of fowls, and on the spirochæta of syphilis and frambœsia. Trypanosomes rapidly disappear after its administration; the protozoan parasites of malaria are held in check by it; and even in variola, which may yet be proved to be a protozoan disease, curative results are reported.

But it is as a specific against syphilis that it is mostly used and best known, though even yet disputed by some.

It is efficacious against all stages of syphilis—primary, secondary or tertiary, hereditary syphilis, or even syphilis in utero, and in parasyphilitic affections.

In all these there is a marked and rapid action, best seen where the lesions are acute and the results

urgent or perhaps dangerous. The spirochætæ disappear shortly after the injection of a single dose, and the lesions heal with surprising rapidity. Ulcers diminish in size, and the scar ultimately is hardly visible; in the larynx and pharynx ulcers which have caused dysphagia and actual starvation heal so rapidly that within a few hours food can be taken again; gummata rapidly absorb, no matter where they may be situated, and even the exudate from a gummatous meningitis will disappear so rapidly as to save the life of a patient. Syphilitic pregnant women can be cured and the baby born free from infection. Parasyphilitic conditions such as tabes dorsalis and general paralysis of the insane can be improved and the destructive process held in check.

There is no question as to the superiority of the drug over mercury as regards its power of immediate sterilisation and its ability to lead to a rapid absorption of the granulomatous material and healing; nor of its superiority in the treatment of cases of extensive ulceration or of malignant syphilis where rapidity of treatment is of the utmost urgency; and still further in those cases which are uninfluenced by mercury, which either does not affect them at all or is followed by repeated relapses, or else is met by an idiosyncrasy that forbids its use.

Now the treatment of syphilis is concerned with (1) the removal of the lesions, and (2) the destruction of the infective agents and their eradication from the system.

With salvarsan, properly used, there is a rapid disappearance of the manifestations of the disease, and an immediate eradication of the spirochætes from the foci of infection. But the permanency of cure depends on the complete eradication of the infective agent from the system, the determination of which now rests, in the absence of lesions, on the Wassermann reaction (*see* Chap. XII). Cure should be accompanied by a *permanent* negative reaction provided that a positive reaction was obtained before treatment, or by a *permanent* absence of reaction in cases of primary syphilis treated before the reaction could be obtained in the blood.

The time is perhaps too short since the introduction of this treatment to definitely assert the value of it, but it might reasonably be supposed that after a trial for two years in this country and a considerably longer period abroad, some element of certainty might be allowed to enter into our conclusions.

The immediate conclusions, then, are that with a single dose of salvarsan many cases have been completely relieved of manifestations; primary cases have not developed further symptoms, and the Wassermann reaction has remained, or (in the case of secondary syphilis) become negative, and remained so over a period of two years. But in the majority of cases a single dose is followed by a relapse after a varying interval.

With two injections at a short interval the results are far more definite. Many, and perhaps the

majority of cases, and certainly of early infection, give evidence of cure, and these include many that have been kept under observation for a period of two years or more.

But a few cases of early infection, and also of the later stages, though rapidly responding to salvarsan, so that after two injections a negative Wassermann reaction obtains in a period varying from one to six or eight weeks, relapse again, and the Wassermann reaction returns even after an interval of six or eight months.

Similarly, with a group of cases of long-standing disease relapses occur, or else cure is not complete; but it must be added that many of these are cases which have also resisted prolonged and vigorous treatment with mercury.

It would appear that the severity of a syphilitic infection depends, as in other infections, on the virulence of the infective agent and the resistance of the soil. This appears evident from the varying severity of the manifestations, especially when a comparison is made between races in whom syphilis has long been endemic and in races to whom it is a foreign disease.

So, then, it might be concluded, with the provisional limits that the duration of treatment with salvarsan compels, that this drug is a specific for a large number, perhaps the majority, of cases of syphilis. We would say, further, that in those cases where the patient can be kept under observation and his blood examined at intervals, treatment with two injections of salvarsan will suffice,

but where the reaction does not become negative in from two to three months afterwards, then the course may be repeated and combined with mercurial injections.

But with all protozoal infections it would appear that combined treatment is of great value, and in the present state of our knowledge there is much to be said for the treatment adopted by those who combine two injections of salvarsan with weekly intramuscular injections of mercury cream for three months. With this course the results are most satisfactory.

A few practical points connected with this treatment must be mentioned.

Salvarsan is supplied as an acid salt in hermetically sealed capsules. It has to be prepared for injections by dissolving in sterilised freshly distilled water and normal saline, and neutralising with caustic soda until the precipitate which forms redissolves. This solution, in bulk of about 300 oz., must be injected intravenously, preferably with a syringe, but if desired with an infusion apparatus. But in all cases it is desirable to enter the vein by direct puncture, so as not to damage the vessel to such an extent as to lead to thrombosis with an additional danger of embolus. Venu-puncture necessitates above all for its satisfactory performance a sharp, properly bevelled needle, which must be pushed slowly but steadily into the vein where visible, or, in stout patients, where felt beneath the skin, after a tourniquet has been placed on the upper arm. It is very seldom

necessary to dissect out the vein and use an infusion cannula. If the solution escapes into the subcutaneous tissue it is extremely painful, and, in large quantities, causes tissue necrosis.

A specially prepared emulsion, in smaller bulk, can be employed for intramuscular injections, but these are seldom performed now. In the intravenous method the drug is rapidly brought

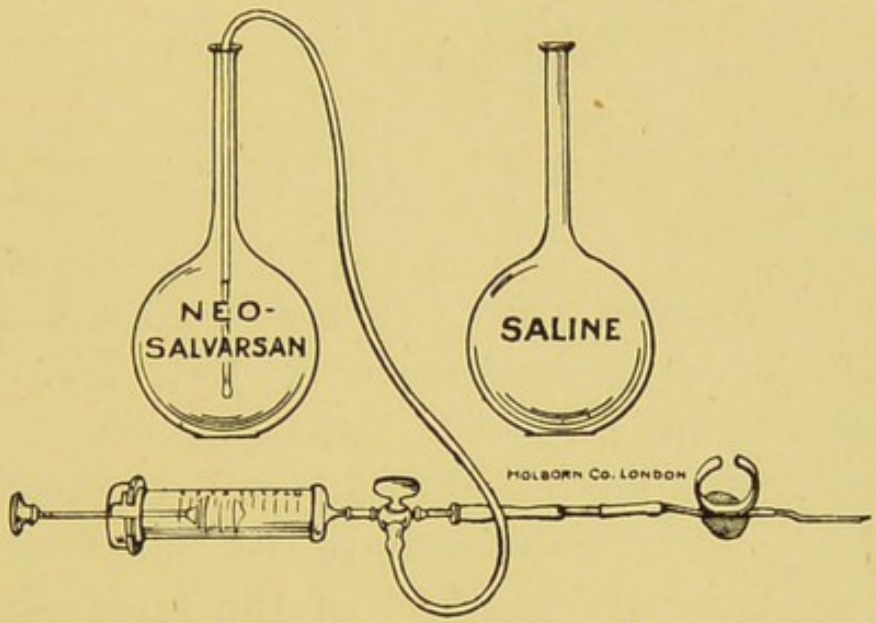


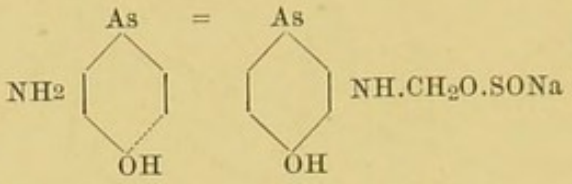
FIG. 40.—Apparatus for injection of 606. The syringe is of the Record pattern, with a capacity of 20 c.c. (Holborn Surgical Instrument Co.)

into contact with the parasites in a fairly concentrated form. It is rapidly eliminated from the system, being excreted by the kidneys in about three days. In the intramuscular method it is only slowly absorbed in smaller quantities, and remains for a long time in the muscle, whilst the treatment is most painful.

It is given in doses of 0·6 gram for an adult and 0·06 for an infant, intermediate doses being adopted between these two periods. The lethal dose for a rabbit averages 0·3 gram, so there is safety in

0·6 for an adult; these amounts have been exceeded in some cases.

Recently a variety known as *neo-salvarsan* has been introduced, consisting of a neutral sodium salt of the drug. This dissolves immediately in distilled water, and is then ready for injection. It appears to be as efficacious as salvarsan, and can be given in larger doses, 0·9 gram corresponding to 0·6 of the older drug.



The after-effects often include rigors, sickness, a little pyrexia and malaise, but these vary considerably in different patients.

The dangers have been much exaggerated. We would say that the immediate risk is heart-failure from the mechanical effect of the injection on a weak heart, such as we have seen occur once only in a confirmed alcoholic with fatty heart, liver, etc. Such a fatal issue has even occurred during an injection of normal saline. If the vein be damaged, or ligatured, the clot which forms may separate within a few hours and produce a fatal pulmonary embolism, as we have known to occur once only. And amongst these results of faulty technique must be included the production of a septicæmia. Otherwise in properly selected cases there is no danger, and the only conditions which contra-indicate its use are extensive degenerations of the central nervous system, myocarditis, and

extensive disease of the cerebral blood-vessels; but even in such cases as these we have administered it without untoward results. In syphilitic nephritis, aortitis, laryngitis and the marked cachexia and anæmia which often characterise the disease, it produces rapid improvement.

But in sucklings occasionally death has resulted from the reaction following treatment, and it is suggested that this denotes the presence of an endo-toxin which is liberated from the bodies of the killed spirochætæ in such large quantities as to cause a fatal toxæmia. And possibly the severe reaction that is seen in some cases of infection in adults may be due to the same cause.

It appears also that in suckling babes suffering from congenital syphilis a rapid disappearance of manifestations can be brought about by treating the mothers with 606, although no arsenic appears in the milk itself. This perhaps points to the production of antibodies in the mother's serum, following liberation of endo-toxins in the blood from the dead spirochætæ, such antibodies being present also in the milk. Such cases of congenital syphilis must then be further treated with 0·01 gram of salvarsan directly.

Concerning the use of salvarsan in other diseases there is little more to be added.

Trypanosomiasis, we have already mentioned. Malaria of the tertian variety can be kept in check by its use, and the cycle of events cut short, with a single dose given at the appropriate time, just before the adult parasites burst into the blood

stream. But as yet there is insufficient evidence to show that it can produce a permanent cure.

In variola, though two satisfactory cases have been reported, we can only state that in the closely allied disease, vaccina, no such good results have been obtained in a series of experiments on rabbits carried out by the author in conjunction with Monckton Copeman.

The various blood diseases have all been treated with salvarsan—in some cases with the hope that they are truly protozoal in origin. But in the leukæmias no good results have been noted. In pernicious anæmia after repeated injections there results a marked improvement, but owing to the fact that the drug remains in the body only three days, we are inclined to think that better results can be obtained by the constant administration of arsenic in the old way.

In conclusion, we would say that chemotherapy, the latest addition to medical science, is as yet only in its infancy, and the future is most alluring. Up to the present it has done much, and in addition has served to draw our attention away from the groove of other lines of treatment which, though holding an important place, have tended completely to oust the older drug therapy. Now this latter has come into its own again, and with its vague empiricism directed by true science it falls into line with serum therapy and bacteriotherapy.

APPENDIX I

METHOD OF DRAWING BLOOD FOR WASSERMANN REACTION AND OTHER SEROLOGICAL TESTS

THE lobe of the ear is cleansed and then friction applied with a piece of lint. A puncture is then

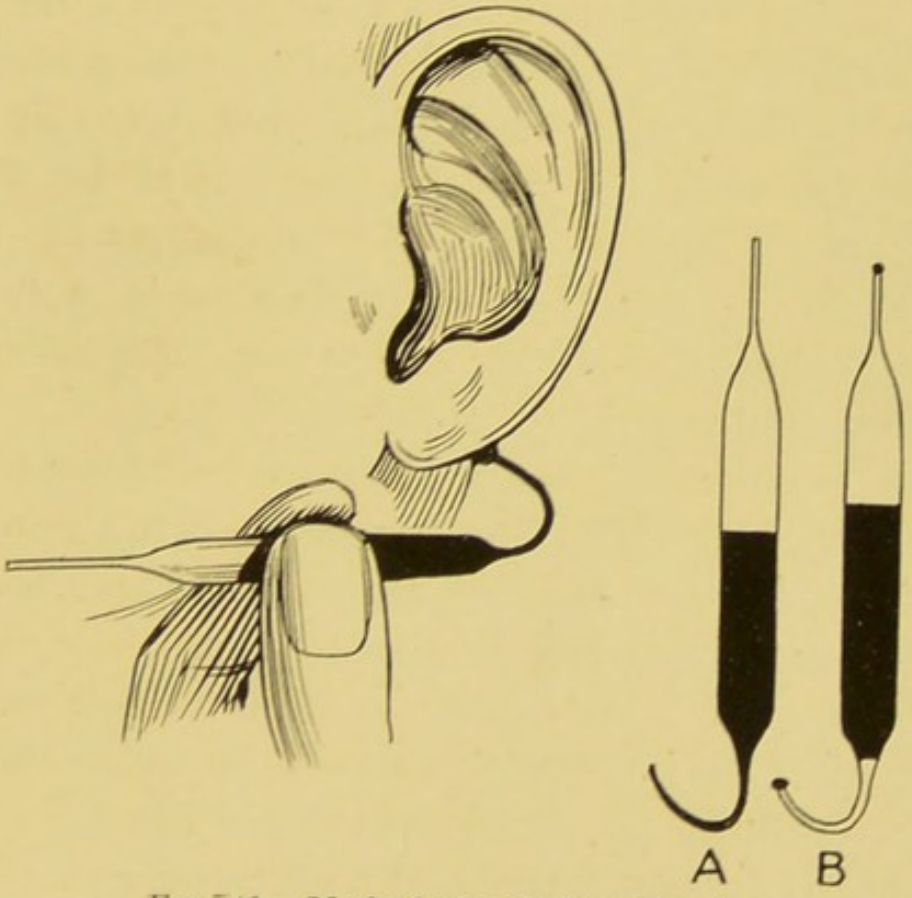


FIG. 41.—Method of collecting Blood.

made with a triangular needle, and the blood allowed to enter the tube until nearly full. Occasionally it will be necessary to "milk" the

ear in order to express the blood. After collection, the straight end of the tube is warmed and sealed in a flame, and, on cooling, the blood retracts into the bulb and the other end can then be sealed. On no account must the blood itself be heated, as this destroys the antibodies. The ends may be sealed with sealing-wax if more convenient (Fig. 41).

Technique of enumeration of Blood-elements, Vaccines, etc.

For this purpose a special counting chamber (Fig. 42) is employed. This is carefully divided into squares of known area and—when a suitable coverslip is used—of known volume. In the pattern devised by Thoma and made by Zeiss, each small square (Fig. 43) measures $\frac{1}{20}$ mm. $\times \frac{1}{20}$ mm. $\times \frac{1}{10}$ mm. in depth, so that it will contain $\frac{1}{4000}$ c.mm. of fluid; there are 400 of these squares, holding in all $\frac{1}{10}$ c.mm. of fluid.

The graduated area is on a central platform B (Fig. 42), separated by a groove from an outer platform W. A drop of the diluted specimen is placed on the central platform and the coverslip D placed in position, so that it rests on the outer platform. Great care must be taken that no fluid overflows on to the outer platform, for then the coverslip will be raised and the depth of the cell increased. After a few minutes with the blood specimens, and a varying period with bacterial emulsions, the elements sediment and can be readily counted under the microscope. A number

of squares are examined, and from the average number of elements contained in each (which

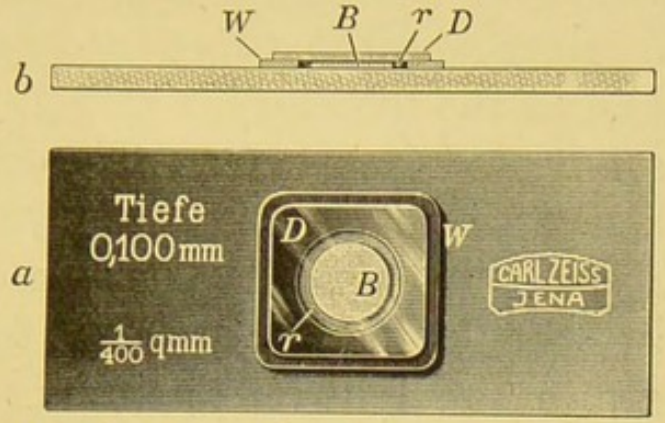


FIG. 42.—Counting Chamber; *a*, plan; *b*, section; *W* outside plate with circular aperture; *B*, inside plate; *r*, groove between the two; *D* cover-glass of special thickness.

forms $\frac{1}{4000}$ c.mm.) the number in 1 c.mm. can readily be determined.

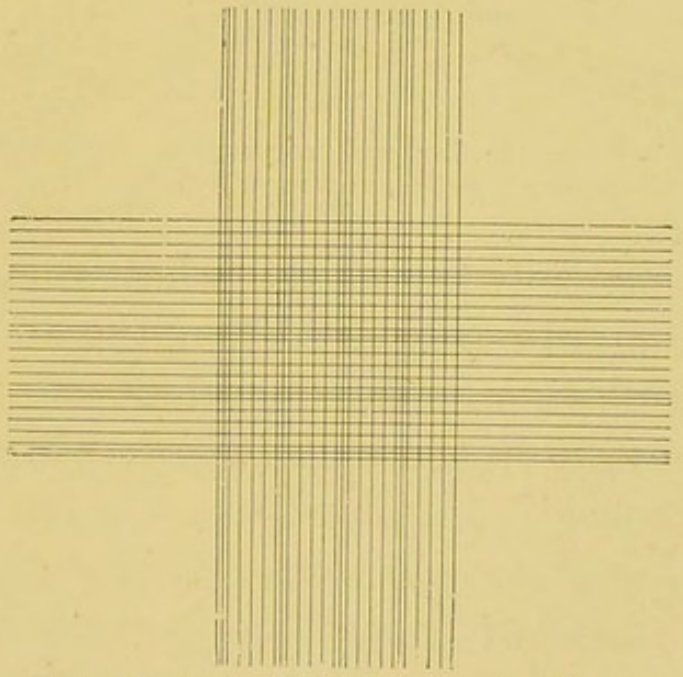


FIG. 43.—Cross-line division of Thoma Counting Chamber. × 20. (Zeiss.)

But to simplify the technique the fluids must be diluted, and, in the case of blood, with solutions which will prevent coagulation or other changes.

This dilution is carried out in a pipette graduated as in Fig. 44, so that the bulb contains 100 times the volume (or 10 times in some) of the graduated volume in the tube, or 200 times the volume taken to the 0·5 mark.

(*a*) *To count Red Corpuscles.*—The lobe of the ear is pricked after cleansing and applying friction to make hyperæmic, and blood is taken into the pipette up to the 0·5 mark. Into the tube is then drawn the diluting fluid (10% sodium sulphate)

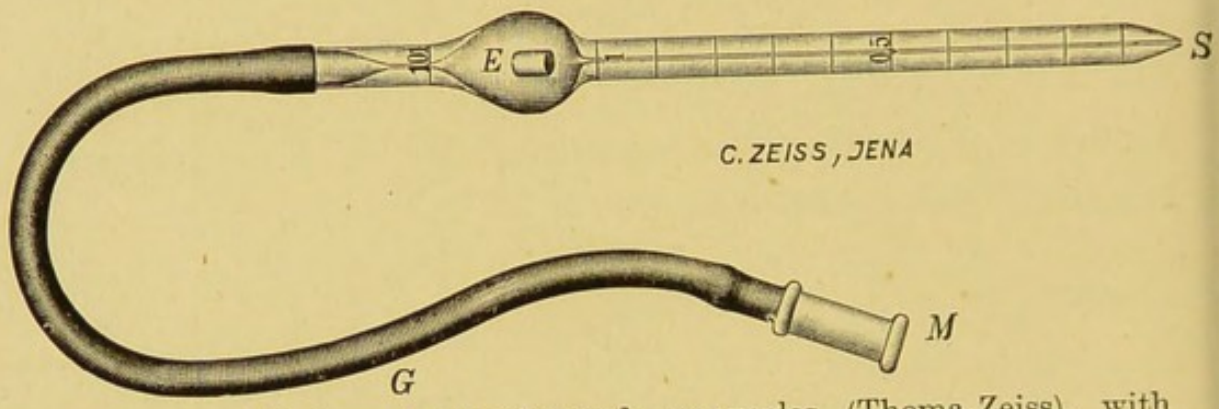


FIG. 44.—Mixing pipette for red corpuscles (Thoma-Zeiss), with rubber tube, *G*, and mouthpiece, *M*.

up to the mark 101, and the whole rotated so as to be thoroughly mixed. Then the fluid in the capillary tube is expressed and discarded, and a drop of the fluid in the bulb (which is thus diluted two hundredfold) put into the counting chamber. Eighty squares are counted, and if x represents the average number of corpuscles in each square ($\frac{1}{4000}$ c.mm.), then $x \times 4000 \times 200 =$ corpuscles in a c.mm. of blood.

(*b*) *To count Leucocytes.*—A special pipette is graduated so that the mark above the bulb is 11, and consequently the dilution is tenfold; or if

the blood be only taken up to the 0·5 mark the dilution is twentyfold. The diluting fluid consists of one-third per cent. glacial acetic acid tinted with methylene blue, so that all the red corpuscles are dissolved and the nuclei of the leucocytes are stained blue. The whole four hundred squares (representing $\frac{1}{10}$th c.mm.) can readily be counted, and if this be x, then $x \times 10 \times 20 =$ leucocytes in 1 c.mm. of blood.

(*c*) *To count Bacterial Emulsions* (*vaccines*).—The young culture on agar-agar is washed off with normal saline and shaken for some time to separate the bacteria, then diluted in the pipette used for leucocytes with a solution of—

Sodium chloride	0·1
Formalin	4
Giemsa's stain	10
Water	100

The average of many squares is taken and then—

$x \times 4000 \times 20 \times 1000 =$ bacteria in 1 c.c. of emulsion.

To estimate Hæmoglobin

Haldane's Method.—A standard coloured tube (Fig. 45) is used. This is graduated to represent percentages of diluted blood in which the hæmoglobin has been converted into CO-hæmoglobin by passing coal gas through it. Twenty c.mm. of blood are collected into an empty graduated tube containing a little water, and then coal gas passed in through the tube supplied (45) until the colour becomes permanent. Then water is added

to dilute until the colour matches the standard tube. The percentage of hæmoglobin is then read off.

Gower's Method.—In this, the hæmoglobin itself is matched in the standard tube; no gas need be added. The colour is a little more difficult to match, but it is often inconvenient to obtain access to a gas jet.

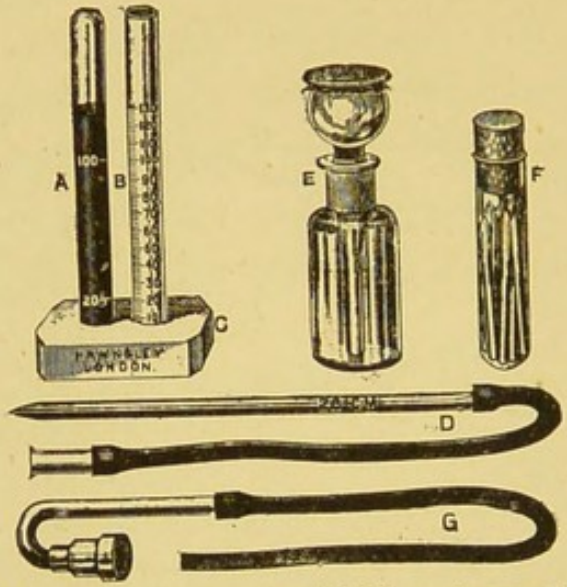


Fig. 45.—Hæmoglobinometer (Haldane's modification).

To make Blood Films

Perfectly clean slides must be used.

(*a*) *To examine fresh blood*, a drop is placed on the centre of a slide and a coverslip placed on so that the drop spreads. Under the microscope the red corpuscles ought to be discrete and circular. If they are found in rouleaux the slide is to be discarded.

(*b*) *To make films for staining*, a drop of blood is taken on to a slide, nearer one end, and the narrow edge of another slide placed near to it, this slide

itself being held at an acute angle and dragged along lightly so as to spread the blood along the central part of the slide. As soon as dry it is ready for staining, preferably by a modification of Romanowsky's stain as follows—

The film is covered with the stain (Leishman's), and, after one minute, diluted with several volumes of distilled water " until a scum appears on the surface of the stain." This is left on for three minutes, when the slide is washed in distilled water until it appears pink, when it is dried and examined.

APPENDIX II

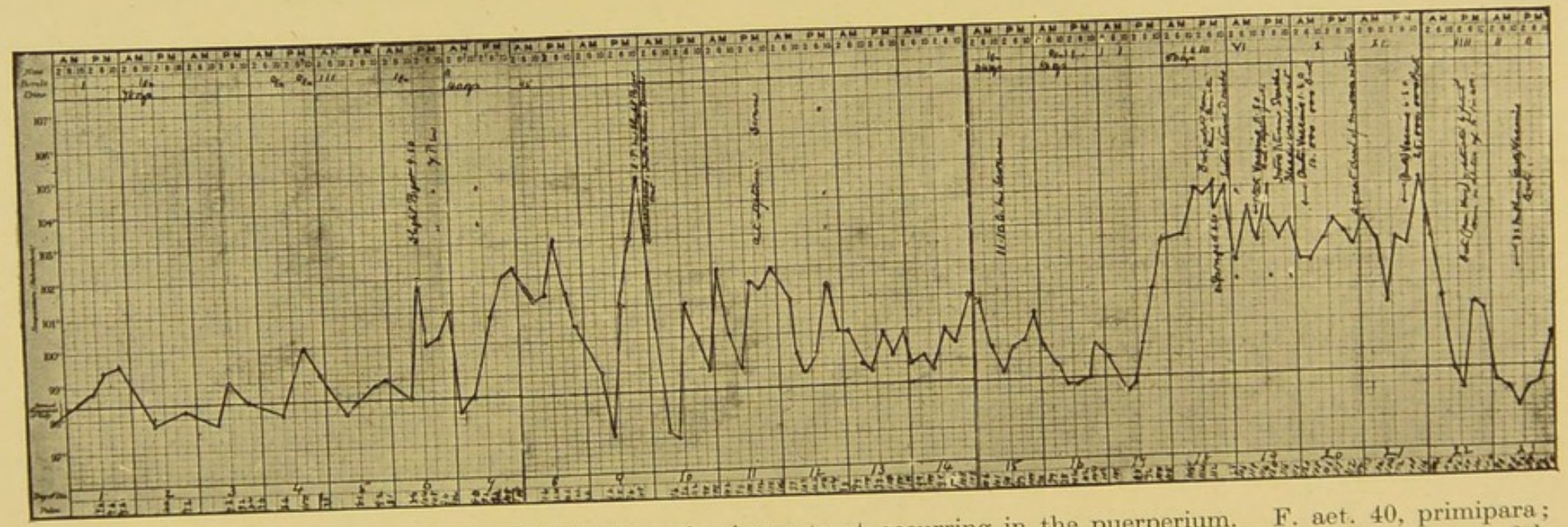


FIG. 46.—Chart of case of *B. coli* infection of urinary tract occurring in the puerperium. F. aet. 40, primipara; pyrexia began on 6th day after confinement; antistreptococcus serum produced no effect; *B. coli* found in urine on 8th and 18th days in pure culture, and this was agglutinated by patient's serum in 400-fold dilution (*B. typhosus* not agglutinated). No organisms could be cultivated from blood (18th day); leucocytes, 15,000; stock vaccines on 19th day, autogenous vaccines (*B. coli*) as follows: 10 million on 20th day, 25 million on the following evening; pyrexia rapidly subsided. Vaccines continued, and improvement maintained under them (from a case seen with Drs. Simson and Beddard).

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