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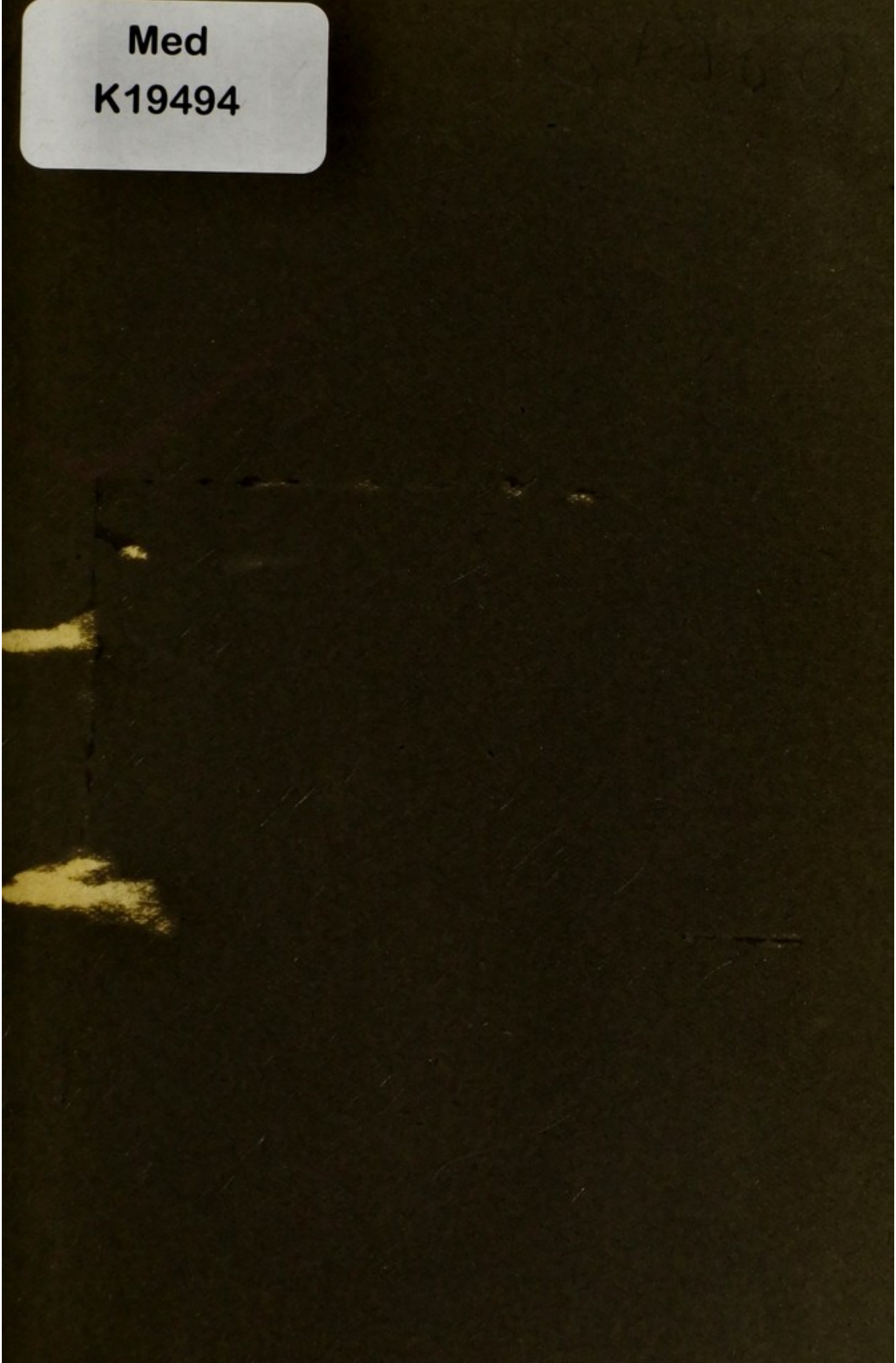

THE GENERAL PATHOLOGY

OF

INFLAMMATION, INFECTION, AND FEVER

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OF

INFLAMMATION, INFECTION, AND FEVER

BEING

THE GORDON LECTURES FOR 1902

BY

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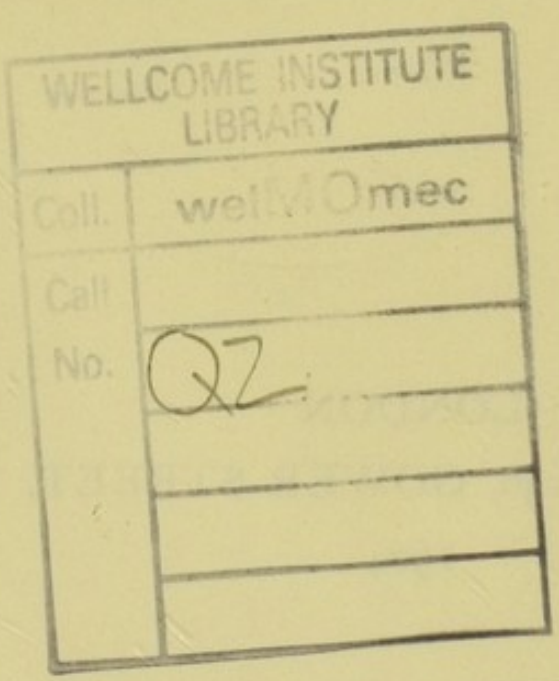

PRÆCEPTORI VENERANDO

IOANNI BVRDON SANDERSON,

D.M., D.C.L., SOC. REG. SOC.

BARONETTO,

MEDICINÆ PROFESSORI REGIO,

OXONIENSIBVS

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HORTATORI, CAVSÆ, FACI,

GRATO ANIMO

COMMENTARIOLVM SVVM

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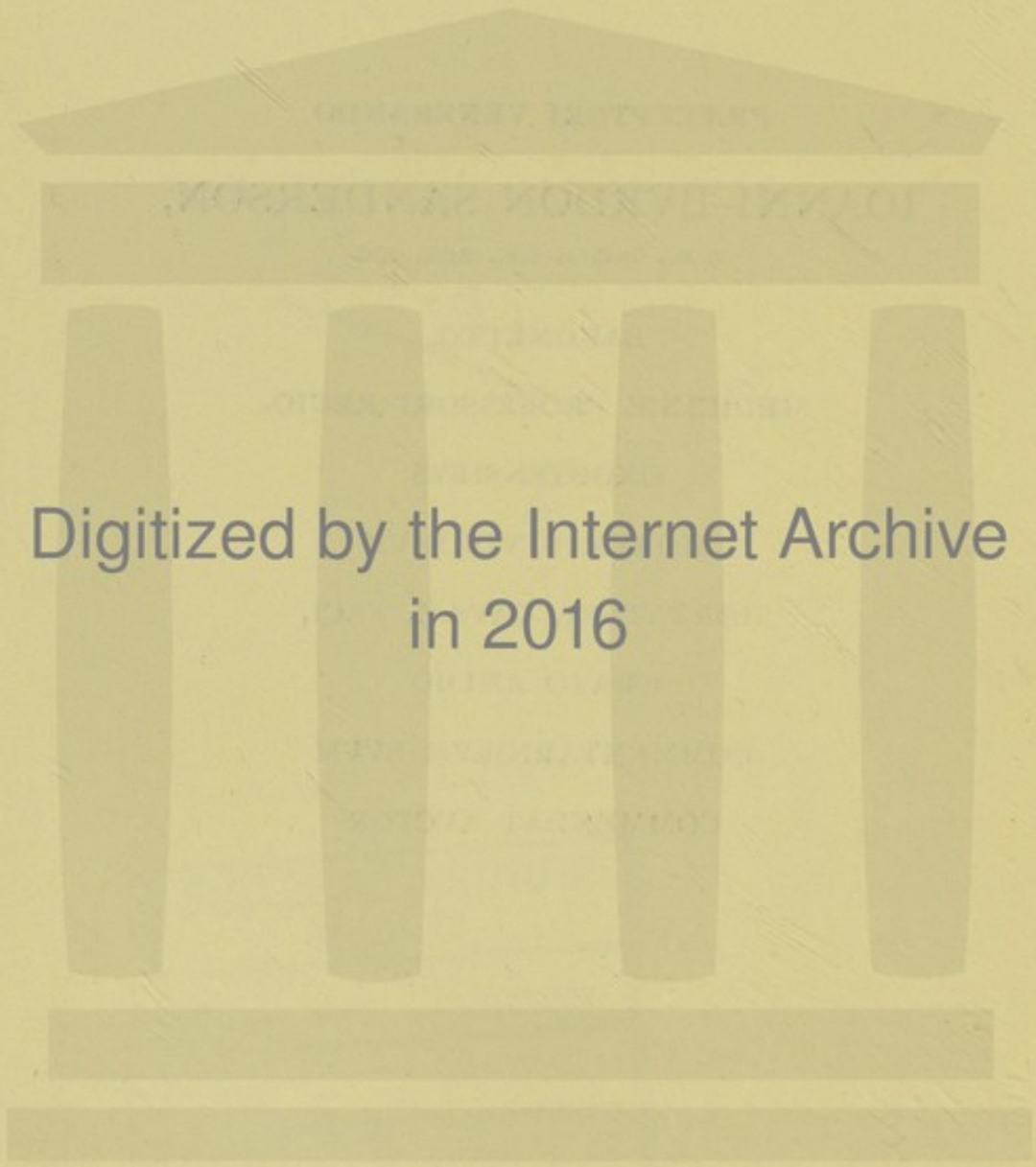

PREFACE

THESE lectures were originally published in the *Clinical Journal*. They are now reissued in book form in response to the numerous suggestions and inquiries which I have received since their first appearance. Their design was to provide such information on the subjects dealt with as is required by intending graduates in medicine at the Universities, and by others who desire a more detailed knowledge of the phenomena in question than is usually supplied in the current text-books or in routine teaching.

They constituted the first series of Gordon Lectures, delivered at Guy's Hospital under the provisions of the Deed of Endowment of the Research Lectureship and Laboratory established at that hospital by the munificence of Robert Gordon, Esq., of Brockham Park, for the advancement of the science of medicine, and the encouragement of that spirit of investigation and inquiry for which Guy's Hospital

is, by tradition and history alike, most justly famous.

Fully alive as I am to the many imperfections which are only too apparent in the following pages, I can only beg for them the lenient judgment of the courteous reader. But I hope that, however imperfect, they may prove to be of some assistance to the earnest student of pathology.

E. W. AINLEY WALKER.

University College,
Oxford,
December, 1903.

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THE

PATHOLOGY OF INFLAMMATION, INFECTION AND FEVER

LECTURE I

In the present course of Lectures I propose to begin by considering the *local* reaction to a localized tissue injury which we call Inflammation. We shall in our earlier meetings proceed to examine the phenomena which it presents, espeeially in their relation to the events of local Infection. From this we shall go on to discuss the *general* reaction to Infection in general. And, finally, we shall endeavour to explain the facts and meaning of one of the most frequent and most intimate accompaniments of both these reactions—namely, the morbid process known as Fever.

The General Pathology of Inflammation.

The term Inflammation is applied clinically to local conditions, which are usually said to be characterized by certain definite clinical signs. Those signs

have been handed down from the time of Galen, as *calor*, *rubor*, *dolor*, *tumor*, and, as Celsus very properly added, *et functio læsa*—heat, redness, pain, swelling, and impairment of function.

Of these five so-called cardinal signs, pain, and in many cases also impairment of function, is not a sign at all, but a symptom, and is not objectively determinable excepting by its effects; and *none* of them is at all essential to the process, since any one or more may be entirely absent in cases of undoubted inflammation.

Thus, as regards *pain;* after section of a nerve—for instance, the sciatic of a dog—an inflammation of the foot can be produced at least as readily as before, although no pain accompanies it. The continuity of sensory nerve tracts is therefore not essential to inflammation; and, as you are aware, in the case of the eyeball, unless special measures are taken to protect it, a most acute pan-ophthalmitis is liable to follow removal of the Gasserian ganglion of the fifth nerve for trigeminal neuralgia, although, and indeed *because*, the sensory impulses normally produced by irritating foreign matter entering the conjunctival sac have been entirely cut off.

Both *heat* and *redness*, being dependent on increase of blood-supply, are absent from the inflammations of non-vascular areas—as, for example, in experimental inflammation of the cornea, or of the tail fins of certain embryos.

Swelling is necessarily absent in the early stages of

acute inflammation of non-expansile tissue, such as bone. And both *pain* and *impaired function* may be so completely absent—in certain syphilitic inflammations, for example—that the subject is completely unaware of any morbid change. On the other hand, *heat*, *redness*, and *swelling* may all be present in a marked degree without the existence of any inflammation, as in the physiological activity of glandular and erectile structures.

It follows, therefore, that though inflammation is usually accompanied in the higher animals by these classical signs, which are both useful and necessary for its clinical description, they do not in any way assist us to a definition of the thing itself.

It is, therefore, necessary in pathology to get rid of the idea of inflammation as a *condition* marked by certain signs, and we must recognise it as a *process* or succession of conditions or changes which are usually, but by no means invariably, accompanied by the signs in question. In this way we shall include in the process of inflammation all those events which, under suitable conditions, may result in the four classical signs, pain, heat, redness, and swelling, but must seek a definition founded on etiology—that is, causation, rather than on symptomatology.

Such a definition was given by Burdon Sanderson in his well-known article in Holmes' 'System of Surgery.' He says inflammation is 'the succession of changes which occurs in a living tissue when it is

injured, provided that the injury is not of such a degree as to at once destroy its structure and vitality '; or, as he himself briefly expresses it, the process of inflammation is *the response to injury*.

Professor Adami has comparatively recently endeavoured to set aside this definition as being too narrow, and has substituted for it a definition of inflammation as the local manifestation of the attempt at repair of actual or referred injury to a part; or, briefly, the local attempt at repair of actual or referred injury. Here the last clause is introduced in order to include certain at present insufficiently explained experiments on the production of inflammation by *hypnotic* suggestion. This definition has the objection, which Adami himself foresaw, that its expression is highly teleological—that is to say, it attributes purposive action to the cells concerned, which are said to 'attempt' repair. A teleological expression is always a misfortune, and is only permissible, if at all, in general description, where it may save a good deal of circumlocution; but in a definition it is highly inappropriate. Moreover, the definition includes too much, for repair can be both 'attempted' and completed without the occurrence of any inflammatory reaction whatever. Indeed, even the definition of inflammation as the response to injury is itself in this respect somewhat too wide, since it makes no distinction of the kind of injury concerned. For it has been shown conclusively that purely mechanical injury does not give rise to inflam-

mation. This was proved by Kocher, of Berne, who found that almost any mechanical injury may be done to bone, for example, if done aseptically, without producing inflammation, an observation upon which depends the justification of osteoclasty as a surgical procedure.

Where inflammation follows mechanical injury, it is invariably due to septic infection. This was proved as follows by Chauveau : In the South of Europe it is customary, instead of castrating cattle, to simply twist the testicle, rupturing the spermatic cord. Fatty degeneration of the testicle ensues, but inflammation never follows this purely mechanical injury. But Chauveau found that if active septic material were previously introduced into the circulation, the procedure always led to local suppuration.

Mechanical injury, therefore, by itself does not give rise to inflammation. But a purely mechanical injury is in general so unusual an event that we may accept the definition of Professor Sanderson—by far the best that has been given—without further question, merely remembering the existence of the exception I have stated.

John Hunter was the first observer who carefully investigated the phenomena of inflammation, which he regarded as being brought about by vascular changes. He taught that inflammation primarily consisted in an increase in size of the bloodvessels and a formation of new vessels in the part concerned. Indeed, he drew a sort of parallel between this pro-

cess and the increase in size of the external carotid arteries, which he found to occur in stags at the period when their horns are growing rapidly. And he supported his position by the statement, which was certainly accurate, that the heat of inflamed parts never exceeds that of the circulating blood. In his book on the blood, inflammation, and gun-shot wounds, published in 1794, the year following his death, Hunter says : ' The act of inflammation would appear to be an increased action of the vessels '; and again : ' The part inflamed becomes to appearance more vascular than in the natural state, and it is probable that it is really so both from new vessels being set up in the inflamed part. . . . Besides, the vessels of the part are enlarged.'

The view of Hunter remained in general acceptation for the next fifty years. But with the discovery of the microscope and its application to histology by Malpighi came the recognition of the importance of the tissue elements in physiological and pathological processes. This was first emphasized by Sir William Bowman, then by Goodsir, of Edinburgh, who recognised the changes taking place in tissue cells in inflammation, and, finally, by Virchow, who established in his ' Cellular Pathology ' the doctrine which is now universally recognised—that all the events of physiology and of pathology alike are primarily dependent on the normal or abnormal activities of the body cells. Virchow, in fact, taught that the whole process of inflammation consisted in a succes-

sion of changes in the tissue cells of the part concerned.

Finally, we come to Cohnheim, who introduced the true experimental method of observation in pathology. This method consists in attempting to determine the relation between a number of concomitant or sequent events by varying the conditions one at a time, and noting exactly the effect of such variations upon the result obtained. This is the only accurate method of investigation. In *disease*, on the other hand, the conditions vary from the normal, several and sometimes many together, and in different directions. And the result is therefore complicated, so that we are unable to determine with certainty which of the variations present is the cause of any given effect. A good illustration of this is to be found in the increased excretion of urea which, as we shall see, occurs in Fever. Here the variations from the normal are *pyrexia* and *disorder of nutrition*, and we cannot determine from an examination of disease alone whether the pyrexia or the disorder of nutrition, or both, are to be held responsible for that increase. But in experiment as introduced by Cohnheim it is possible, by varying only one condition at a time, to see exactly its relation to the gross result.

Cohnheim applied this method to the investigation of many of the problems of pathology with remarkable success. And anyone who cares to see what can be done in this direction cannot do better than read his lectures in the New Sydenham Society's

translation, if not in the original. To him especially we owe our knowledge of the vascular changes which occur in inflammation, and which we shall discuss directly.

But first we must consider for a moment the ' reaction to injury ' in the lower animals. This has been very carefully worked out by Metchnikoff (' Pathologie comparée de l'Inflammation ') and others.

Among the Protozoa simple mechanical injury is followed by immediate repair. Thus, if a large amœba be divided by a cut, the separated parts heal up, and that part which contains the nucleus continues to grow and proliferate as before. But if the amœba receive what may be called a chemical injury the reaction is different : the structure of the protoplasm is affected, and an extrusion of hyaline globules may be brought about, resembling what is sometimes seen in cells of an inflammatory area, and possibly similar to the extrusion of granules described by Kanthack and Hardy in leucocytes in the presence of bacteria. Again, if foreign particles of matter be introduced into its neighbourhood, the amœba tends to take them up and to digest them in the acid-containing vacuole which it forms around the particle ingested. Here, then, we have already an evident distinction between the reaction to mechanical and other forms of irritation.

Coming next to the Metazoa, which have ectoderm and endoderm and mesodermal wandering cells, it is found that the reaction to injury and irritation is a

reaction of the mesodermal cells, a group which has preserved a marked resemblance to the simplest protozoon forms of life. Thus, Metchnikoff found, in studying certain larvæ, that if a sharp foreign body be pushed through the ectoderm, the mesodermal cells collect, and form a plasmodium round it. And if bacteria are introduced they are taken up and speedily digested by the wandering cells. And similar facts have been observed in worms.

In the Crustaceans also the reaction to the introduction of foreign irritating matter, such as bacteria, is a reaction of their leucocytes. And Metchnikoff, in studying a disease of Daphnia (the water-flea) due to infection with a sporing torula, showed that in this animal the spores are eaten up within the body by the leucocytes, and thus destroyed; but if too many gain access, and are thus enabled to develop into torulæ, the latter cause destruction of the leucocytes, and subsequently bring about the death of the animal itself. The reaction of the leucocytes, then, is a protective one. This is well seen in the same animal—Daphnia—after an injury to its carapace. The first thing that occurs is the collection of a mass of leucocytes at the site of injury, where they destroy whatever foreign matter may have entered through the breach, and close the path of access against further irritating substances. Then follows a reaction of regeneration or repair, and only when the injury has been repaired by the proliferation of the tissue cells is the leucocytic barrier removed.

The reaction of repair is very extensive in the lower animals. Thus, Worms replace their hinder segments after these have been destroyed, Crustaceans can restore lost claws, and lizards will renew a severed tail. But this regeneration is quite distinct from the direct response to injury. It occurs much later, and is brought about by a proliferation of fixed tissue cells in which both epiblast, hypoblast, and mesoblast may all take part. The reaction of regeneration cannot be regarded as being in any way a part of the inflammatory process in these animals. It is a subsequent, but not essentially a consequent, reaction.

If now we pass on to examine the events of inflammation in the Vertebrates, with which we are naturally more particularly concerned, we find that vascular phenomena almost invariably play a prominent and important part. It is to these phenomena that the heat, redness, and swelling which are usually associated with inflammation are due. They were first thoroughly investigated by Cohnheim in the web of the frog's foot, and nothing of essential importance has been added to his results by subsequent observers.

If the epithelium of the frog's web be slightly injured with a hot wire or by a drop of acid, and be watched continuously under the microscope, the following alterations in the circulation may be seen to occur :

1. Sometimes a very brief *constriction* of the arterioles of the part. This is probably the direct effect of the injury rather than a reaction to it.

2. *Dilatation*, first of the arteries, later of the veins, and in perhaps an hour a dilatation of the capillaries also.

3. *Acceleration* of the stream in the dilated vessels, the axial stream becoming very marked. This is followed by a gradual—

4. *Slowing of the stream* until the actual current, which has broadened out more and more, is ultimately lost. Meanwhile, the leucocytes appear to have become 'sticky,' and tend to adhere to one another and to the vessel walls in the part affected. This process and the progressive slowing of the stream may end in complete—

5. *Stasis*, though it does not always nor necessarily do so. At the same time an—

6. *Exudation* of lymph is occurring from the vessels, and—

7. *Diapedesis*, leading to the so-called 'margination,' of the smaller veins especially, with leucocytes, many of which gradually pass out to reach the injured surface, covering it eventually with a thick layer which dries to form the scab.

Gradually the circulation recommences, and by degrees returns again to normal, exudation and diapedesis ceasing. Then, within perhaps about twenty-four hours, the process of regeneration commences, the epithelium at the edges of the wound begins to proliferate and spread beneath the scab, and healing rapidly proceeds. From such observations Cohnheim came to the conclusion that the main

thing in inflammation is the succession of vascular changes, and formed the theory that this process must be due to a molecular alteration in the vessel walls. It could not be dependent on the formation of new vessels, as Hunter had supposed, for such formation does not necessarily occur, and where it does it is a *late* phenomenon.

The original experiment of Cohnheim has been modified and improved by various observers, and especially by Burdon Sanderson and Stricker (who investigated inflammation in the exposed omentum of mammalian animals), by Thomas, of Heidelberg, and by Pembrey in the mouse. Coats' modification of the frog-web experiment, in which he snipped away a small area of the epithelium with sharp scissors, had the great advantages that practically the only injury inflicted was exposure of the subcutaneous tissue to the air, and that the vessels in the tiny wound could be examined without the intervention of a dead epithelial covering.

But inflammation does not always terminate in *resolution* in the way I have described. It may go on to suppuration or to necrosis. *Suppuration* is best seen in inflammations due to the action of micro-organisms, though, as we now know, it may also be induced by means of powerful chemical irritants. Here the process goes on beyond the stage of stasis, the vessels in the centre of the affected area become filled with leucocytic thrombi, and diapedesis proceeds until the area is densely packed with white

corpuscles. Destruction of tissue and degeneration of leucocytes takes place in the central area, where the agent of injury or 'noxa' is present in greatest concentration, resulting in the production of a purulent fluid—the liquor puris—while round the circumference is a layer of closely-packed white corpuscles, and round this, again, a layer of rapidly proliferating connective-tissue cells, which form the so-called granulation tissue, itself infiltrated with leucocytes, and constituting the 'pyogenic membrane' by which the contents of the abscess are encapsuled.

These changes we shall have to treat more fully later. Meanwhile, we must now consider briefly the phenomena of inflammation in *non-vascular areas*.

The most convenient site for studying this in higher animals is in the tissues of the cornea. And very numerous are the observations which have been recorded. The most complete, perhaps, are those of Senftleben, who was the first to use the cornea for this purpose. If the central part of the cornea be lightly touched with a strong solution of zinc chloride (60 per cent.), without causing any breach of the corneal epithelium, there is seen to follow a degeneration of the cells (corneal corpuscles) in the centre of the area affected by the caustic action. The cell-bodies disappear, and only traces of the nuclei remain. Around this central area is a zone in which the cells are shrivelled and coagulated. In about forty-eight hours the process of repair begins just like repair in ordinary connective tissue. The sound

corpuscles at the margin of the injured part begin to throw out processes—'regeneration spikes,' as they are called—which gradually grow into, and eventually fill up, the spaces of the injured area from which cells have disappeared, and from these 'spikes' new corneal corpuscles develop. There is no change in the vessels at the margin of the cornea, and no invasion of leucocytes occurs—that is to say, regeneration has occurred without reaction of the leucocytes. Here there has been no inflammation, although the process is associated with the antecedent injury, and was initiated by the effects that injury produced.

If, now, the same experiment be done near the margin of the cornea—that is, nearer vessels—or if, a few hours after the central cauterization, we inflict a tiny wound by lightly scratching off a fragment of the epithelium which was cauterized with the zinc chloride, there follows infiltration of the tissue spaces with a mass of leucocytes which come in the former case out of the neighbouring vessels, and in the latter from the conjunctival fluid. And this gives rise to localized opacity—in fact, a local keratitis.

From these experiments we gain two very important conclusions :

1. That the keratitis — the inflammation — was dependent on a leucocytic immigration.

2. That the process of repair was not dependent on migrated leucocytes, but on the tissue cells.

To proceed a little further. Metchnikoff has shown that if the epithelium of the tail-fin of a

certain embryo (the axolotl) of about two weeks old, in which the tail is non-vascular, be slightly injured by touching it with silver nitrate, the following series of events occurs: (*a*) A certain number of cells are immediately destroyed; others are injured, and these become swollen up by imbibition of water. (*b*) An immigration of leucocytes occurs; but these are wandering cells of the tissue, for there is no change in the nearest vessels, and no diapedesis of their white corpuscles. (*c*) Repair by proliferation of the injured epithelium.

In the tail of the newt a similar series of changes may be seen, but here there are vascular events associated. Stasis occurs in the nearest vascular loop, accompanied by diapedesis of the leucocytes. By the following day the parts have again returned to normal. In the newt the vessels are much more numerous and much nearer to the site of injury than in the axolotl, whose tail-fin contains no bloodvessels. The newt experiment is therefore comparable to the experiment at the margin of the cornea.

From all these observations it follows that the view of Cohnheim, which regarded inflammation as being determined by molecular changes in the vessel walls, must be abandoned. It follows also that, since regeneration may occur without the occurrence of any inflammation, it cannot be regarded as a part of the inflammatory reaction. The restoration of the cornea, after central cauterization unaccompanied by any breach of the epithelial covering, proceeds without

inflammatory reaction. The same is true of injuries purely mechanical in nature. Accordingly we must regard the repair accompanied by or following an inflammatory reaction as being only an associated process, and not an integral part of inflammation as at present understood. On the other hand, it may eventually prove that both these processes are only the expression of the same general reaction or response to irritation exhibited by different cell systems of the body.

We must now pass on to a consideration of the part played by the bloodvessels in the inflammatory process.

The heat, redness, and swelling of an inflamed part are all dependent on the local changes in the circulation, which we have already described. *Redness* is due to increase of blood-supply and dilatation of the capillaries, and *swelling* to an increased transudation from the vessels. The increased *heat* is due to increased volume and velocity of the local circulation, and to this alone. The temperature of inflamed tissues *never* exceeds that of the circulating blood. This was first taught by Hunter, as the result of experiments, in which he found that the temperature of the rectum and vagina of animals was but little affected by acute inflammation artificially produced in those parts. It was proved by Cohnheim, who showed that the temperature of inflamed parts is never greater than that registered by a thermometer introduced into the rectum. If fever is associated

with the inflammation, and the general blood-temperature is raised, the inflamed part will then be hotter than the normal; but it is never hotter than the blood itself.

There is, therefore, no production of heat in inflamed areas. On the other hand, the temperature of an inflamed area may be less than that of the body generally, and *may even be subnormal.* In artificial pleurisy, for example, the temperature of the inflamed pleura may be lower than that of the healthy one. This is due, when it occurs, to a diminished blood-supply resulting from the condition of complete or partial stasis in the vessels of the affected part, which succeeds the earlier stage of increased and accelerated current. And Cohnheim showed that if one forepaw of a dog be caused to inflame, while the other is simply rendered hyperæmic by division of the brachial nerves upon that side (the arteries in consequence dilating), the latter has slightly the higher temperature, because, while the circulation in the inflamed paw becomes eventually slowed, that in the opposite limb remains accelerated. The observations of Cohnheim have been confirmed by Jacobson in experiments and with instruments of extreme precision.

I have already described the succession of vascular changes which occur in inflammation. We must now consider briefly their causation.

The preliminary brief constriction of the arterioles is probably resultant, not reactive—the direct effect

of the injurious agent, not a reaction to it—and it is quickly followed by a reactive dilatation. The increase in calibre of the arterioles is not the consequence of central reflexes, for, as I have stated previously, complete division of the nerve-trunks does not affect the succession of these changes ; and Cohnheim showed that, even when the vessels are already dilated after nerve section, a further dilatation follows if a local inflammation be induced in the affected area. The inflammatory dilatation must be either due to direct action of the irritant on the vessel walls, or, indirectly, through the agency of the peripheral nerve-endings in those walls. Between these possibilities we cannot decide on present knowledge, but it is of suggestive interest to remember that stimulation of the peripheral portion of a mixed nerve often produces at first a brief constriction, followed by lasting dilatation of the vessels in its area of distribution. On the other hand, typical inflammation may be brought about in parts whose nerve-supply has been divided.

The accelerated circulation is the direct result of the dilatation of the arterioles, since more blood necessarily flows to a part in which the arterioles are dilated than to the neighbouring parts supplied by the same artery ; and therefore if the pressure in the main artery undergoes no diminution, an increased amount of blood will reach the part whose vessels have become dilated.

The subsequent slowing of the circulation in the still dilated arteries might be attributed to any one of the three following factors: (1) An alteration in the vessel walls, causing increased resistance to the flow of blood; or (2) an increased resistance due to the great massing of leucocytes in the small veins, and also in the capillaries; or (3) to a local increase in the specific gravity of the circulating fluid, consequent on the enormous amount of transudation taking place. Probably all these factors play a part in the result. But that an alteration in the vessel walls is the chief factor follows from the experiments of Ryneck, who was able to show that stasis can be artificially produced in vessels through which an indifferent fluid, such as milk, is being circulated, but cannot be produced at all if the vitality of the endothelium be first destroyed by circulating a solution of a metallic poison.

That alterations do actually occur in the endothelial cells in inflammation is evidenced by the fact that they may be observed to enlarge, at times projecting into the lumen of the vessel, to undergo proliferation and multiply, to throw out pseudopodia, and in bacterial inflammation to take up the micro-organisms by phagocytic action. They appear also to become adhesive, so that the leucocytes, and even red corpuscles, now exhibit a tendency to stick to the vessel walls. They offer increased resistance to the circulation, and they permit the transudation of

increased quantities of altered lymph. In chronic inflammations also, according to Arnold and most other recent observers, they give rise to the new vascular loops which form in the inflammatory tissue, though this has been denied by Rindfleisch, who attributes the origin of new capillaries to the tissue cells.

LECTURE II

THE process of inflammation constitutes, as we saw in the last lecture, the reaction to injury, and is the succession of changes which occur in living tissue when it is injured, provided that the injury is not of such a degree as to at once destroy its structure and vitality.

We considered the distinction between this process and the process of repair which is usually associated with its later stages, and saw that the former is present throughout the animal series (from the very lowest forms which have a differentiation of cell-groups) as a reaction of the mesodermal phagocytic group, and is exhibited by a similar series of events even in the simple unicellular amœba. On the other hand, the reaction of repair is similarly present in all animals, and is, indeed, more marked and more extensive in the lower series. It is a process in which all the cells, whether of epiblastic, or hypoblastic, or of mesoblastic origin, alike take part, though in the higher animals it is usually very incomplete, and often represented chiefly by connective-tissue growth.

Accordingly we came to the conclusion that these two processes are quite distinct, and that repair is not included in the inflammatory reaction as at present understood, being only an associated and non-essential process; but we suggested that it might eventually prove that both these processes may be the exhibition of the same reaction to an irritative stimulation of different cell systems of the body.

On the question of the immediate cause of inflammation we have made reference to the conclusion of Hunter and his followers, that it was brought about by an increase in size and number of the vessels of the part affected; to the epoch-making doctrine of Virchow that, like all other pathological processes, it was the expression of a succession of changes in the tissue cells; and to the theory of Cohnheim, that it is brought about by certain molecular changes in the vessel walls.

We discussed the nature and causation of the vascular changes which occur in inflammation, and of the heat, redness, and swelling which are associated with these changes, and, finally, brought forward evidence to show that Cohnheim's theory of its essential nature was fallacious, by a comparison of observations on the inflammatory process in non-vascular areas with those in areas supplied with bloodvessels, and from the results obtained experimentally when fluids other than blood were circulated through the vascular system.

From the evidence which we thus obtained it follows that, though inflammation is not due, as Cohnheim thought, to alterations in the walls of vessels, yet such alterations form an important factor in the inflammations which occur in vascular areas.

Cohnheim believed that he had proved the dependence of inflammation on these alterations by the following experiment : He produced injuries in the vessels of a part by circulating through them irritating fluid. On subsequently restoring the blood-flow through the part, an inflammation of the neighbouring tissues followed. He concluded, therefore, that the injury to the vessel walls produced the inflammation. The fallacy in this conclusion lies in the fact that there is no evidence nor any probability that the solutions which he circulated remained confined within the vessels, and did not pass beyond the vessel walls, injuring the neighbouring tissues also.

A simple stoppage of the circulation combined with the application of an agency, normally quite innocuous, may give rise to inflammation. This was proved by Cohnheim in the following manner : The circulation in a dog's leg was arrested for half an hour by the application of an Esmarch's bandage, and the foot subsequently placed in water at 50° C. (122° F.), and the bandage removed. An acute inflammation supervened within some twenty-four hours.

This is to be explained as due not simply to an

alteration in the vessel walls, as Cohnheim thought, but to the fact that the vitality of all the cells of the part was so reduced by the lowered temperature, the deprivation of nutriment and oxygen, and the accumulation of carbonic acid and other metabolic products, resulting from the stoppage of the circulation, that a temperature of 50° C., usually quite harmless, became sufficient to produce a tissue injury and determine the development of inflammation.

Behaviour of the Corpuscles.—We must now examine the behaviour of the blood-corpuscles in the course of inflammation. As the circulation in the dilated vessels slows, the white corpuscles seek the sides of the vessels until the small veins become lined, as it were, or 'pavemented,' with leucocytes. Later the red corpuscles also are affected. This change is brought about in part by an alteration in the corpuscles themselves, or in the fluid plasma, and not entirely, as is often stated, by the increased adhesiveness of the vessel walls, for the former tend to adhere not only to the sides of the vessels, but to each other also. But the importance of the vessel endothelium in the process is shown by the experiment of Ryneck, already mentioned, in which stasis could be produced when an indifferent fluid, like milk, was being circulated, but could not be induced at all after the vessel endothelium had been killed by circulating for a time solutions of metallic poisons, such as the sublimate of mercury.

As stasis approaches, the red corpuscles tend to run into rouleaux in the capillaries. This formation of rouleaux is a familiar event in blood outside the body in the presence of dead or inanimate matter, and is probably induced within the vessels in inflammation by the injured condition of the endothelial cells. Ultimately the condition of stasis becomes complete.

This condition may be followed by thrombosis, but only when the capillary walls have died does that event occur. Thrombosis is an intravascular coagulation of the blood, and is initiated, as we know, by a deposition of the blood-platelets originally described by Osler. In inflammation there is always a tendency to thrombosis. Thus, if a frog's mesentery be exposed and painted lightly with a $\frac{1}{2}$ per cent. solution of silver nitrate, thrombi of leucocytes are formed in the capillaries.

The gradual slowing of the circulation leads to great engorgement of the vessels with corpuscles, which are forced in by the arterial pressure, and shortly before the stasis is complete they may be seen to oscillate synchronously with the pulse-wave, moving a little forward with each beat, and then recoiling in the intervals. But neither the slowing nor the stoppage of the circulation is the cause of the increased adhesiveness of the corpuscles. This is well shown in an experiment of Lister's which, however, had previously been used by Weber. He ligatured the vessels of a frog's leg, thus producing

complete stoppage of the circulation. It was now seen that the corpuscles in the vessels of the web moved freely among one another, and exhibited no tendency to adhere together. But when a tiny piece of mustard was applied to a part of the web, and thus a local tissue injury produced, free movement ceased in the affected area, and the corpuscles became adherent to each other and to the vessel walls. The result was an accumulation of corpuscles in the area, since any corpuscle which happened to glide in became adherent. If any corpuscle near the margin of the area chanced to escape from the zone of inflammation, it ceased to be adhesive, and again moved freely.

Stasis may be followed by complete restoration of the circulation ; but if the vessel walls succumb, and a thrombus forms, a complete resolution is improbable. The thrombosed area becomes, *ipso facto*, extravascular, and necrosis, with the formation of an abscess, is the usual termination. The changes are very well exemplified in the formation of an ordinary boil. Here we can see a fiery red areola of increased circulation, with dilated vessels and a rapid blood-flow, from which the colour can be easily pressed out, but returns again immediately upon releasing pressure. Within this ring there is a region of dull red or purplish congestion, in which the colour fades only slowly on the application of pressure, and returns slowly on releasing the compression. This is the region of dilated vessels with

diminished rate of flow. And in the centre there may be a purple area from which the colour cannot be discharged by pressure. Here is a condition of complete stagnation of the circulation, usually proceeding to thrombosis and necrosis of the central core of tissue. Even inflammatory thrombosis may, however, resolve completely.

Diapedesis. — Besides the intravascular events affecting the corpuscles, there is another phenomenon which they exhibit in the course of inflammation—namely, their passage through the vessel walls, a process usually termed diapedesis. This is exhibited first by the leucocytes, and subsequently by the red corpuscles also. The phenomenon was first observed in 1834 by Addison, and independently by Waller in 1846, though neither of them seems to have recognised its meaning. It was first studied by Cohnheim in 1867.

Shortly after the commencement of the 'pavementing' of the smaller veins with leucocytes, numbers of them may be seen to pass through the vessel walls, and come to lie outside the vessel, giving rise to the appearance known as 'margination,' and a similar process occurs in the capillaries also.

This passage of the leucocytes was thought by Cohnheim to be a passive process, for he found that stoppage of the circulation in the part by pressure on the main artery arrested its occurrence. This observation confirmed him in his view that inflam-

mation was due to alterations in the vessel walls, since he concluded that the leucocytes which left the vessels had simply been forced out through or between the altered cells by the blood-pressure. The observation was, however, faulty, since, as we have already seen, diapedesis can and does occur after complete arrest of the circulation ; and Metchnikoff observed it in the tadpole's tail after the heart-beat had been stopped by the action of curare, and the capillary circulation had entirely ceased.

The passage of the leucocytes is, therefore, an active process. They can be seen moving backwards and forwards from place to place along the vessel wall before passing through, and when outside the vessel also exhibit active amœboid movement. Whether they pass out between or through the endothelial cells is not quite certain, though it seems the more probable that they make their way through the intercellular material. There is no evidence that the leucocyte leaves any breach of continuity in the wall after its passage. It probably escapes much in the way that one soap bubble may pass through another without injury to either.

The passage of red corpuscles only begins after the commencement of the leucocytic emigration. There is no evidence that it is other than a purely passive process. The red cells are simply forced out through the vessel walls by intravascular pressure, exactly as occurs in passive hyperæmia, and escape between the endothelial cells, frequently at a point where a

leucocyte has previously passed out, and often several at the same point in quick succession.

Exudation.—Besides the passage of corpuscles from the vessels, there is in inflammation an increased escape of plasma, which accumulates in the tissue spaces of the area very much faster than it can be carried off by the lymphatics, and thus gives rise to what is called the inflammatory exudate. This occurrence is dependent chiefly, but not entirely, on the changes in the circulation. Not entirely so, because an active hyperæmia of non-inflammatory origin never gives rise to lymph formation greater than can be accommodated and carried off by the lymphatics of the part, and passive hyperæmia which gives rise to an obstructive dropsy does so by the production of an exudation of lower specific gravity than normal lymph, while that of inflammation shows a great increase in solids. There is, therefore, another factor in the process besides the alteration in the circulation. This is the altered condition of the endothelium, which in its injured state appears to allow the passage of a more copious and more concentrated lymph than normal.

Virchow, who regarded inflammation as a process consisting essentially in an increased activity of the tissue cells in the surrounding region, due to the stimulation of the injury, attributed all the inflammatory changes to an increase of local metabolism. Both the alteration in the circulation and the exudation were, in his opinion, due to this increased meta-

bolism. But such a view is quite untenable on various grounds. For increase of metabolism and accelerated tissue change could not in any way produce the essential slowing and stagnation of the circulation which occurs, and exudation is most marked precisely under those conditions in which increased metabolism is least in evidence—namely, at the beginning of inflammation, before any signs of growth and proliferation of the tissue cells are present, and in those forms of inflammation especially where rapid and extensive cell destruction is most marked. Beyond the fact that we have in inflammation two factors—increase of circulation, and an injured endothelium—both of which favour the escape of plasma from the vessels, we cannot at present go.

In certain modern text-books you may find it stated that the exudation subserves the purpose of diluting the irritant, of flushing out the inflamed area, and so forth. I must warn you against all such teleological explanations of the events which occur within the living body. No process which takes place in protoplasm does so in order to subserve a purpose. You might just as fitly say that water flows down from hill to valley to subserve the purpose of making rivers, which in turn subserve the purpose of diluting the sewage and flushing out the drains of towns along their course. All this is, of course, no explanation at all. It is worse than none, for it is most misleading, and may leave behind

it an impression that something of scientific value has been said.

The processes which occur in living protoplasm, whether physiological or pathological, are, like all other events in nature, the effects of certain causes, and eventually lead on to certain inevitable results, but there is nothing purposive about them. Processes which are unfavourable in their results tend to the destruction or deterioration of the organism, and so to its elimination in the course of evolution. Similarly, processes whose results are favourable tend to be perpetuated in the race.

We cannot speak of purpose in regard to the exudation ; it is a question of effect, not of intention ; and absolute precision of language and of thought in dealing with these questions is essential to any scientific and accurate conception of the phenomena concerned.

Though it does not subserve the purpose, the inflammatory exudate *has the effect* of diluting the irritant, if that irritant be chemical in nature, and of flushing out the area affected.

Of the causation of the exudate we cannot with our present knowledge go beyond the factors I have mentioned. We require first to understand the mechanism of ordinary lymph formation. This is a question which we cannot take up here, though on some future occasion I hope to deal with it in connection with the general pathology of dropsy ; but I may point out to you that it is still uncertain whether

the view of Heidenhain and his followers is correct, which regards lymph as a secretory product, or that so ably defended by the researches of Starling, and which considers it to be a simple filtrate. In any case, however, we must remember that even if the process of lymph formation be one of mere filtration rather than of secretion, it is carried on through the substance of an animal membrane lined with living, active endothelial cells, and must in any case be rather of the nature of dialysis than of percolation.

The lymph of inflammation differs from normal lymph not only in its greater volume, but also very remarkably in its percentage of solids. This is so much increased that the specific gravity may be almost trebled. Thus Halliburton, in some observations carried out upon the exudations in acute pleurisy and in simple hydrothorax, found the percentage of proteids in the former about three times that in the latter cases.

Inflammatory lymph also contains more corpuscles than normal, and may even contain so many red corpuscles as to acquire a faintly reddish tinge as it leaves the part affected.

The increased flow of lymph can be well observed in the hind leg of the dog, in which all the lymphatics of the foot unite into the superficial lymphatic trunks of the leg. And Cohnheim found, by placing a cannula in one of these lymphatic trunks, that when the foot was inflamed by the method which I mentioned in the first lecture, the flow of lymph was eight to ten

times greater than on the healthy side. And this occurs without any venous obstruction or other passive congestion, which are entirely absent from this stage of inflammation, although the flow of blood is even doubled. The only other condition in which a comparable volume of lymph is formed is in obstructive dropsy due to obstruction or pressure on a main vein, but in that case the percentage of solids in the lymph which leaves the part is very much diminished.

This experiment of Cohnheim's was repeated and confirmed by Lassar, who found the flow of lymph increased to eight times the normal quantity. Seeing, then, that the amount of proteids per hundred parts of lymph is almost trebled, it follows that the lymphatic circulation is carrying off from twenty to thirty times the usual quantity of proteid material.

Unfortunately, it is not possible from these facts to determine very much about the composition of the exudate as it leaves the bloodvessels of the affected area, for besides the fact that the lymph which leaves the part contains an enormous number of leucocytes above the normal, which greatly alter its percentage composition in a chemical analysis, its proteids have also been increased by the addition to it of all the substances resulting from tissue degeneration in the inflammatory area.

Osmosis.—There is another factor which I must refer to which must play a part in the production of the exudation—I mean the variations in osmotic

pressure. You know that, if solutions of two substances or mixtures of substances which have different osmotic pressures be separated from one another only by an animal membrane, a process of exchange occurs between them tending to equalize the osmotic pressure on the two sides. Now, the events occurring in the tissues of an inflammatory area must of necessity produce considerable and continuous alterations of the osmotic pressure in the tissue spaces. Such alterations are probably of great importance in the causation of the exudate, although our knowledge is not as yet sufficiently advanced in this direction to permit of any very definite statement being made upon the question.

Inflammatory exudates differ in character and in appearance with the differences in the amount of *fibrin* formed in them. This varies both with the nature of the irritant and with the situation of the inflammation, and results in the production of the exudates described as serous, fibrinous, or sero-fibrinous, according to their varying character. As regards the nature of the irritant itself, the result depends in part upon whether it is capable or not of causing extensive destruction of leucocytes ; for, as we know from the physiology of the process of coagulation, fibrin formation is probably determined by the breaking down of leucocytes. And this, we shall see, depends very largely upon whether the inflammation is of the simple variety or is infective. The fibrin factors are always present in inflammatory lymph,

though in amount which varies with the intensity of the inflammatory process. The amount of ferment present is probably determined by the extent to which the leucocytes undergo dissolution in the exudate. Hence, other things being equal, the amount of fibrin present depends on the extent of leucocytic destruction. It depends also on the extent to which the irritant at work possesses peptonizing or digestive action on the fibrin formed.

As regards its situation, the character of the exudate is determined chiefly by mechanical factors. In dense tissue—as, for instance, in the substance of a tendon—an extensive exudate is quite impossible, while in the loose synovial membrane which surrounds it everything favours the outpouring of a copious exudation in the tendon-sheath. Similarly, in a loose areolar tissue exudation is able to proceed almost without restraint until the bulk of the fluid exuded becomes great enough to raise the extravascular tension to an equality with the intravascular, or even to exceed the latter, and thus produce compression of the smaller vessels, and especially the veins.

In inflammation occurring in serous membranes the exudation is favoured both by the considerable vascularity of the part, and by the fact of the existence of a cavity with compressible contents, which readily accommodates the fluid poured out. This is well seen in serous pleurisy, whereas in pleurisy associated with massive pneumonia, in which the lung

becomes enlarged, solid, and incompressible, a great effusion is almost impossible.

The deposition of fibrin on an inflamed serous surface is comparable to the occurrence of thrombosis in inflamed capillaries, and can only occur after the degeneration or death of a proportion of the endothelial cells lining the surface of the serous membrane. Where a dense layer of fibrin lines the surface, this of itself mechanically tends to check the exudation from the vessels of the membrane.

The exudate when poured out is much less readily absorbed from serous cavities than from the ordinary tissue spaces. This follows from the law of the relation of the volume of a cavity to its surface; since, as the diameter increases, the volume of the cavity increases as the *cube* of the diameter, but the area of the absorbing surface only as the *square* of that diameter. This helps us to an explanation of the tendency to slow absorption often exhibited by large serous exudates, as well as of the accelerated disappearance of the fluid after a portion has been artificially removed, bringing the surface area once more into a reasonable relation to the volume of the fluid contained within the cavity.

Suppuration.—If the number of leucocytes normally present in an inflammatory exudate become so much increased as to convert the clear or merely blood-stained, watery exudate into a thick and slightly viscid, opaque fluid, we are accustomed to speak of the condition as one of suppuration, and of the fluid

as pus. This condition, when arising naturally, is always due to the presence of bacteria, though artificially it may be brought about by certain other means.

Purulent fluid is usually yellowish-white in colour, but may be altered in appearance by the presence of blood-pigment or of blood-decomposition products. It may be stained by other colouring matters, such as bile derivatives, or may obtain a special colour from the products of chromogenetic micro-organisms which it contains. Such is the blue or greenish pus produced by the action of the *Bacillus pyocyaneus*. It is alkaline in its reaction, it possesses a faint odour, and has a specific gravity of about 1030 (taking water as 1000), and it contains from 10 to 15 per cent. of solid matter, two-thirds of which is proteid in nature.

The special characters of suppurative inflammations we shall discuss in the next lecture.

LECTURE III

In the latter part of the preceding lecture we considered the nature and causation of the inflammatory exudate, and the factors which affect its character and quantity.

Now, if the number of leucocytes present in the exudate becomes so great as to convert the clear or merely blood-stained fluid into a thick and slightly viscid, opaque liquid, we are accustomed to speak of the condition as one of suppuration.

Suppurative inflammation, when arising naturally, is *always* due to the presence of micro-organisms, though artificially it may be brought about by certain other means. And Simon more than thirty years ago arrived at the conclusion that all naturally-occurring inflammations are more or less connected with infective processes. In this conclusion he foreshadowed the later theory of Hüter, of which I shall have to speak directly. Then it was shown by Lister that suppuration of *wounds* is always due to the entrance of infective matter from outside, a discovery which enabled him to lay the foundation of aseptic surgery on a firm and scientific basis.

Burdon Sanderson also, in 1873, concluded from a series of experiments in which he had endeavoured to produce, firstly, infective, and secondly, non-infective inflammations, that the degree of infectiveness of an inflammation depends entirely on the number of micro-organisms present, and showed that, whenever metastatic inflammations occur, they are associated with the presence of micro-organisms.

It was then held by Hüter, in 1878, that inflammation *only occurs* when pyogenetic micro-organisms are present in the lesion; and this view has been supported by some other surgical pathologists, who have endeavoured to limit the application of the term to cases where, at any rate, a majority of the so-called classical signs are present, and are associated with the suppuration. They claim, for instance, that the aseptic healing of wounds occurs without an inflammatory reaction. This is a *reductio ad absurdum* of the whole position. It is, as Professor Adami has justly pointed out, to confound the inflammatory reaction with the process of pyogenesis. It is quite impossible to draw a distinction of this arbitrary nature, for, as we shall see directly, even suppuration—pyogenesis—may be brought about entirely independently of the presence of bacteria. And, on the other hand, there is no sharp distinction either in the immediate *cause* or in the *progress* of the process between a simple inflammation and an inflammation which goes on to pus formation. The differences, such as they are, are

only of *degree*, and not of *kind*, between the two, and the one merges gradually into the other without the existence of a clear dividing-line. If a perfectly aseptic incision be made, and the wound surfaces be promptly brought together, an inflammatory exudate at once occurs, and the formation of so-called 'lymph,' or fibrin, seals the surfaces together long before any regenerative process is discoverable in the tissue cells. And this deposit of fibrin on the wound surfaces is brought about by the disintegration in the exuded fluid of leucocytes which have escaped from severed vessels, or have passed out by diapedesis, as in any other inflammation. It should, moreover, be clearly borne in mind that such an injury as here occurs is not a simple mechanical injury comparable to those which we discussed last week. For here we have, even in the most favourable case, a chemical injury or irritation from the exposure of the severed tissues to the air, which of itself, as we have seen, is quite sufficient to induce the inflammatory process ; and in the vast majority of operations there is besides the irritating action of swabs and instruments and sterile water, if not of actual chemical irritants in the form of various antiseptic fluids.

Even the formation of pus, in which the definition of Hüter found the criterion and characteristic sign of inflammation, does not require the presence of micro-organisms for its production by experimental means.

It is now nearly thirty years ago since Cohnheim first investigated the power of various liquids in producing inflammation. He used the following method: The liquid to be tested was enclosed in a sealed capillary tube. This tube was introduced beneath the skin of an animal through a tiny puncture, and was pushed along for a certain distance in the subcutaneous tissue. Some days later, when the skin puncture was soundly healed, the little tube was broken subcutaneously. All chance of a microbic infection was thus avoided, and the uncomplicated action of the substance introduced could be well observed. This method of producing inflammation by the use of what came to be called a Cohnheim's tube has been extensively employed, with the result that it has been definitely proved—especially by Grawitz, De Bary, Strauss, Leber, and Councilman among others—that various chemical substances are capable of producing suppurative inflammation, and notably mercury salts and silver nitrate among the inorganic substances, and castor-oil and turpentine in the organic series. These two observers also showed that cadaverin, an alkaloidal substance obtained from decomposing animal matter, has an inflammatory action on the tissues; and Koch has proved the same fact for the tuberculin obtained from tubercle bacilli.

Suppuration from the action of such chemical substances as I have mentioned is a purely artificial pyogenesis. It can never happen under natural

conditions, because there is no natural means by which these powerful irritants can gain access in concentration to the tissues without at the same time entrance being afforded to pyogenetic micro-organisms. The experiments are, however, of great importance as tending to the conclusion that the local accumulation of leucocytes in suppuration is the direct effect of the action of a chemical irritant.

It follows, then, from all that I have said, that inflammation is *not*, as Hüter held, dependent on infection. Nevertheless, infection plays a most important part in many inflammations, and is the invariable exciting cause of naturally-occurring suppuration.

It was at first believed that any micro-organism might cause inflammation. This view, however, was speedily disproved by the discovery that ordinary air germs and water germs were quite innocuous. The presence of particles in air was proved by Tyndal. He showed that the luminosity of a beam of sunlight passing through air is due to reflection from the surface of suspended particles, and many of these particles were found to be living micro-organisms. Similarly it was discovered that numerous bacteria exist in water. But it was found that air could be passed through the subcutaneous cellular tissue of the rabbit, or ordinary water introduced into its peritoneal cavity, without producing any inflammation. It followed that the ordinary air and

water germs were not ' phlogogenetic ' micro-organisms—that is to say, inflammatory agents. Many of the phlogogenetic bacteria may, and often do, occur in air and water, especially in the neighbourhood of towns and human habitations, but that is quite another matter altogether.

One of the earliest steps in the direction of establishing the specific nature of pathogenetic micro-organisms was taken by Ogston, of Aberdeen, in 1881, in an investigation, as the result of which he made the statement that acute abscesses always contain what he called cluster cocci, now better known by the name staphylococci. And he concluded that the cluster coccus was the specific causal agent of such abscesses.

Koch's great discovery about this time, of culture methods and media suitable for the artificial cultivation of bacteria, provided means for accurate investigation of their properties and character, and, with the application of his well-known postulates for specificity, has led to the determination of the specific causal agents in many different forms of inflammation. The first book published on the subject was that by Rosenbach, of Tübingen, in 1884.

Already, in 1876, the discovery had been made by Burdon Sanderson that from the spreading edge of erysipelas can always be obtained an exudation fluid full of cocci which are arranged in chains, and which were named by him the chaplet cocci. These are now usually termed streptococci. But it was not

till 1884 that Fehleisen determined accurately what he considered then to be the specific streptococcus of this inflammation.

These two varieties of cocci (strepto- and staphylococci) are the usual causal agents in local inflammation and suppuration, and they were once regarded as specific pyogenetic (pus-forming) micro-organisms, but we now know that many other pathogenetic organisms can, under suitable conditions, give rise to local inflammation ; and not to local inflammation only, but to suppuration also. I need only mention now the *Bacillus coli communis*, the *Bacillus typhosus*, the *pneumococcus*, and the *Bacillus pyocyaneus*. But probably *all* pathogenetic micro-organisms could, under suitable conditions, be led to cause a local inflammation, and all phlogogenetic organisms *can* give rise to suppuration.

Now, in what way do the bacteria give rise to inflammation ? There only exist two ways in which they can produce effects upon the tissues to which they gain an access. They can act either (1) mechanically as foreign particles, or (2) by means of chemical substances which they produce or contain. Their action as foreign particles is exactly comparable to that of any other kind of foreign particulate matter which is insoluble, and therefore chemically inactive, and can only be purely mechanical in nature. The injury, if any, thus produced is purely mechanical injury, and as such will not call forth the inflammatory reaction, as we have already

seen. If they gain access to the circulation they may give rise, like any other foreign particles, to blocking of small vessels, or embolism. For this to occur they must be present in enormous multitudes, and that is the limit of their possible effect, excluding every form of chemical action. The inflammation they occasion must therefore be dependent on this latter action.

The chemical substances produced by micro-organisms are very various, and are by no means fully understood or even identified. I need only mention here two very important groups, the specific poisonous bodies, or so-called toxins, and the bacterial ferments. The former cause degeneration and destruction of living cells, while the latter exercise digestive action, and lead to peptonization of proteid material, and to a further breaking down, with the production of bodies of the oxyphenyl series, which were at one time looked upon as antiseptics. This idea was largely wrong, but it had the great result of leading to the invaluable discovery of toxins and antitoxins, and the consequent initiation of modern serum-therapeutic measures. The peptonizing action of bacterial ferments may probably afford an explanation of the fact that, while the ordinary inflammatory exudations very readily coagulate, and usually undergo coagulation in the body, thus leading to a deposition of fibrin on the inflamed surfaces, the liquor puris of a suppurative inflammation will not coagulate spontaneously, since its fibrinogen has

been already peptonized within the abscess-cavity by bacterial action.

The inflammatory reaction brought about by an invasion of bacteria is therefore due to the injurious action of the chemical substances which they produce. Accordingly, their local action is exactly comparable to that of other chemical irritants, such as I have already mentioned, and to that of culture fluids from which the bacteria have been separated by filtering them through porcelain in the Chamberland filter.

The action of these chemical irritants, however, is in the majority of cases chiefly, if not entirely, local, since, as they gradually diffuse into surrounding parts, they are diluted by the tissue fluids, and their injurious action is in consequence progressively diminished. But that of micro-organisms is not thus limited, since they are capable of independent growth, and if they reach the circulation, may be carried to distant parts, where they become established and proliferate, and again produce specific harmful substances, thus giving rise to metastatic inflammations. Or, without thus becoming localized in secondary foci of infection, they may survive and flourish in the blood, producing the condition known as septicæmia, which has received the appropriate name of ' inflammation of the blood ' from several of the French pathologists.

The chemical irritants are also able to produce a metastatic inflammation in parts where they become

collected in concentration, after diffusing through the body from the local focus of origin or point of introduction, either by reason of a selective action and peculiar affinity for certain groups of cells, in which accordingly they gradually concentrate themselves, or because in the course of their destruction in the body, or in their excretion from it, they are collected into certain organs where accordingly they come to act in concentration. To give a few examples: The products of diphtheria bacilli diffusing through the body from the local lesion are excreted by the kidney, whose cells abstract them from the circulating blood. And if they reach these cells more rapidly than they can be discharged, a local concentration will occur, which may result in the production of acute nephritis. Similarly, certain products of diphtheria bacilli appear to have particular affinity for the nervous tissues, and may collect in these in quantity sufficient to produce neuritis, with the familiar results. Tetanus toxin has a selective preference for nerve cells, with which it enters into combination, and is thus accumulated in them as it passes to the circulation from the local focus of infection, until enough is present in the nervous centres to produce the picture of disease which we call tetanus. Cantharides, which is excreted by the kidney, may similarly produce albuminuria or actual nephritis when carried to that organ in sufficient concentration; and mercury may have the same effect, especially in a kidney which has been already

injured by disease. Alcohol may possibly exert a similar influence on the hepatic cells.

We may accordingly conclude, from the considerations I have put before you, that there is no *essential* difference between the inflammations which are brought about by micro-organisms and those produced by other agencies.

We now proceed to a consideration of the *rôle* played by the leucocytes in the inflammatory process.

We have already seen that the passage of the white corpuscles from the vessels of an inflamed part, and their accumulation in the inflammatory area, was an active process. What is the meaning of this phenomenon, and how is it produced ? The leucocytes appear to be *attracted* from the neighbouring vessels and tissue spaces to the affected part. And since the inflammatory reaction is brought about by chemical agencies, the attraction of the leucocytes is presumably of chemical origin. It is accordingly spoken of as *chemiotaxis*.

Phenomena of similar nature, which may be grouped with those of chemical attraction of the leucocytes under the general term *allurement*, were first observed by Engelmann, who found that if a fluid containing motile bacteria were illuminated in one part by beams of light of various colours, the rest of the fluid being exposed to diffused daylight, the bacteria were attracted by certain colours—as, for example, purple—so that they gradually collected

in the part illuminated by that particular colour, and this phenomenon he termed *phototaxis*.

The events of chemiotaxis were investigated by Stahl and Pfeiffer, and it was shown that certain substances exert attraction, while others are repellent for living protoplasm. These phases are usually now spoken of as positive and negative chemiotaxis. Moreover, it was found that living protoplasm can become habituated to previously repellent substances. Thus, a plasmodium could be trained by gradually lessening its supply of water to send out processes into a salt solution which previously had exercised both a repellent and an injurious action on it.

As regards leucocytes, it appeared from the experiments of Leber, Metchnikoff, Massart, Bordet, and others that certain chemical solutions possess attractive power for these—for instance, a solution of malic acid—while others, like quinine, exert repulsion. The same is true of certain slightly soluble metals, such as mercury and copper. Thus, Leber showed that if a fine capillary-tube containing mercury be carefully inserted in a vein it becomes rapidly filled with leucocytes, although the circulation has continued normal and no coagulation has occurred upon the tube. Further, a substance which in strong solution has repelled the leucocytes will, in sufficiently dilute solution, give the positive phase and cause attraction.

In the same way the soluble products of bacteria

exert a chemiotactic action more or less positive, according to the less or greater virulence of the micro-organism, the leucocytes approaching more readily the less virulent forms, and being but little attracted, and perhaps even repelled, by very virulent varieties. This is well shown in an experiment of Metchnikoff. If two cultures of anthrax bacilli be taken, the one virulent, the other attenuated—that is to say, of diminished virulence—and one ear of a rabbit be inoculated from each culture, an intense inflammation is set up in both the ears. But while in the ear inoculated with attenuated anthrax there is very little serous exudation, but an immense accumulation of leucocytes, in the other there is a great effusion of clear serum containing hardly any leucocytes at all.

Dead tissue similarly acts as a positively chemiotactic agent. Hence it follows that the leucocytic diapedesis of inflammation occurs as the result of the chemiotactic action of the injured tissue, and of the chemical or bacterial irritant which has caused the injury. This affords an explanation of the fact that in purely mechanical injuries in which, comparatively speaking, very few cells are actually destroyed, and in aseptic destruction of cells in parts remote from vessels, as in the centre of the cornea, no diapedesis occurs, for here the products of cell disintegration never reach the circulation in sufficient concentration to produce a chemiotactic influence, and no bacterial chemiotactic substances are present.

Thus we see that while the inflammatory exudation is conditioned—at any rate, chiefly—by the direct injury produced in the vessel walls by the action of the irritant or noxa, the determination of leucocytes to the area of inflammation is the effect of chemiotactic action exercised by that irritant, or by the products of the cell destruction which it causes.

I have said that, though a weak solution of a given substance may be positively chemiotactic, yet a strong solution may be found to exercise a reverse effect. The same fact is probably true of the bacterial products. It would then follow that at the centre of inflammation, where they are present in concentration, they may be able to repel the leucocytes, though further off, where they are weakened and diluted in the process of gradual diffusion, they will have a positively chemiotactic action. The bacterial products are in many cases also capable of destroying leucocytes which come within the area of their concentrated action.

These two factors suggest the explanation of the fact that in any inflammation due to a very virulent bacterium very few leucocytes are present in the inflammatory area, and even these are for the most part killed by the bacterial products, so that, instead of the formation of a local abscess, a spreading inflammation is produced.

Besides their action in producing chemical irritants, the bacteria present themselves as foreign bodies,

and as such they are subject to the same conditions as any other foreign particles.

Now, throughout the animal series, from the unicellular protozoa upwards, it is a property of *amœboid cells* to take up particles suspended in the fluid in which they live by a process of ingestion. Around these particles, when ingested, there is developed, as can be seen in the amœba, a vacuole, and into this is poured a fluid which Le Dantéc showed is acid in reaction, and which contains a peptonizing ferment (Miss Greenwood, Krukenberg). The particles are thus digested, or, if they are indigestible, they are subsequently extruded. To this process of ingestion Metchnikoff gave the name phagocytosis. The property of thus ingesting foreign particles is possessed in marked degree by certain varieties of the leucocytes, including the wandering cells of tissue spaces, and by certain fixed cells also, notably the endothelial cells which line the vessels and the serous cavities, to which the term *fixed* phagocytes is applied by Metchnikoff.

The wandering phagocytes attracted to the inflammatory focus by a chemiotactic influence approach the bacteria, and if they are not first destroyed by the bacterial products, they rapidly ingest the microorganisms themselves, and subsequently exert on them digestive action. In a precisely similar manner particles of other foreign matter and dead tissue undergo the process of ingestion and digestion by the phagocytes.

The fluid exudate itself may also have a destructive action on bacteria, as Nuttall showed to be the case with serum. This, as we shall see when we come to the discussion of infection, is probably brought about by ferments set free in the fluid by the destruction and disintegration of leucocytes.

Phagocytosis and the effect of chemiotaxis are well shown in the following experiment of Leber in the frog: A fine suspension of vermilion is injected into the dorsal lymph-sac of a frog, and after a short time some mercury is introduced into the anterior chamber of the eye. In a little while a bright vermilion colour can be seen in the cornea of this eye, produced by an accumulation of leucocytes which have taken up vermilion in the dorsal sac by phagocytic action, and have been attracted to the corneal spaces by the chemiotactic influence of the mercury in the anterior chamber.

I have hitherto spoken of the leucocytes collectively without distinction of kind, as if all the varieties took an equal share in the phenomena of inflammation, but this is not the case. Not all the leucocytes are phagocytes; nor, on the other hand, is the power of phagocytic action limited to leucocytes, since, as we have seen, the cells of endothelia, among others, possess a similar activity.

Differences in kind among the leucocytes were first described by Wharton Jones in 1846. His observations were followed and extended by those of Rindfleisch, Max Schultze, and others. But a new era in

the histology of blood was inaugurated by the discovery of Ehrlich of the differentiating value of the aniline dyes. He subdivided the leucocytes into five varieties, according to their *granulation* and their reaction to *acid* or *basic* stains respectively. His observations have been somewhat modified by the results of Sherrington, and of Kanthack and Hardy, who divided the wandering cells into the six following varieties :

Cœlomic and non-phagocytic, 1 and 3; Hæmal and phagocytic, 2 and 4	1. Coarsely granular, with horse-shoe nucleus	Oxyphile. Stain with acid dyes	2 to 4 per cent. of leucocytes (eosinophile).
	2. Finely granular, with polymerous nucleus		20 to 70 per cent. of leucocytes.
	3. Coarsely granular, with round nucleus	Basophile. Stain with basic dyes	None in blood.
	4. Finely granular, with trilobed nucleus		1 to 5 per cent. of leucocytes; more numerous after meals than at other times.
Phagocytic	5. Hyaline, with kidney-shaped nucleus	Non-granular	2 per cent. of leucocytes.
	6. Lymphocytes, small, with round nucleus and little protoplasm		Up to 30 per cent. of leucocytes.

Metchnikoff had previously, as the result of his researches on phagocytosis, subdivided the blood leucocytes into the following classes :

1. Lymphocytes.

2. Large hyaline mononuclear phagocytes—'macrophagocytes.'

3. Smaller neutrophile polymorphonuclear phagocytes—'microphagocytes.'

4. Eosinophile—coarsely granular oxyphile cells, non-phagocytic.

These two classifications correspond very closely in the main. We see from them that phagocytic leucocytes are those contained in Metchnikoff's Classes 2 and 3, and correspond respectively to Class 5 and Classes 2 and 4 combined of Kanthack's classification.

Besides these leucocytic phagocytes, certain other cells which belong developmentally to the same group of the mesodermal cells possess the phagocytic power. These are the 'fixed cells' of connective-tissue spaces and the endothelial cells lining the vessels and the serous cavities, the latter being simply greatly enlarged lymphatic spaces which communicate directly with the lymphatic vessels by means of so-called stomata. All these cells possess the faculty of forming pseudopodia, and of thus enclosing and ingesting foreign particulate material.

The information we have gained up to the present from our discussion of the phenomena of inflammation may now conveniently be recapitulated by summarizing briefly the events in the formation of acute

abscesses. These have been carefully worked out by various observers, and especially by Hohnfeldt for staphylococcus (*Staphylococcus pyogenes aureus*) suppuration in the rabbit.

The vascular changes proceed exactly as in simple inflammation. Then within a few hours the leucocytes are found beginning to collect in the affected area. These are at first chiefly of the mononuclear variety, but after a short time leucocytes with polymerous nuclei become more numerous, and predominate. At this stage it is seen that the massing of leucocytes, which has occurred at the focus of infection around the accumulation of proliferating cocci, is due to the collection in that region of enormous numbers of the multinuclear leucocytes, while in the boundary zone, where cocci are less numerous or absent, the uninuclear variety of leucocyte predominates.

After some forty-eight hours a well-defined local abscess has been formed, in which the following facts may be made out: The leucocytes within the abscess-cavity are almost entirely of the polymorphononuclear variety. Some of them are degenerating, and the normal tissues of the central area have broken down and been destroyed. There is no evidence of any process of repair, nor any multiplication by proliferation, either of the leucocytes or of the connective-tissue cells. Most of the cocci are by this time intracellular—that is, they have undergone phagocytosis. Towards the periphery of the

abscess they are fewer and fewer in number, though some may be found free in the lymph spaces, and others are seen to lie within the endothelial cells of the bloodvessels, having been taken up by these by phagocytic action.

Destruction of leucocytes by bacterial action, fresh diapedesis from the vessels, and the phagocytic process go on continuously, until at length the cocci are destroyed, but not until about the *tenth* day does any sign of *new formation* or regeneration of tissue appear. About this time the connective-tissue cells around the margin of the abscess may be seen to undergo proliferative changes, and to multiply, giving rise to a formation of epithelial cells which are called fibroblasts. Among these new capillaries are thrown out, and the abscess-wall assumes the character of granulation tissue, from which cocci are altogether absent, and in the spaces of which leucocytes are present only in small numbers. Cicatrization follows.

The changes which are found at different intervals after the inoculation of staphyloccoci may be more easily remembered from the following table :

At about Four Hours.—Local collection of mononuclear leucocytes ; diapedesis of polymorphonuclear leucocytes ; multiplication of the cocci.

After Ten Hours.—Polymorphonuclear leucocytes in the centre ingesting cocci ; mononuclear leucocytes in the boundary zone ; ingestion of cocci by endothelial and other fixed phagocytes.

After Forty-eight Hours.—Abscess packed with polymorphonuclear leucocytes and ingested cocci; destruction of the tissues of the central area: some cocci seen outside the abscess either free or already ingested by the phagocytes.

From Forty-eight Hours onwards.—Degeneration of leucocytes; diapedesis; phagocytosis; destruction of cocci.

Tenth Day onwards.—Proliferation of connective-tissue cells; formation of granulation tissue; cicatrization.

Another termination of the infection is, however, possible. If the bacterium introduced is highly virulent, it may produce a very rapid and widespread destruction of leucocytes in the affected area, or even, perhaps, hold them at a distance by exerting negative chemiotaxis—though this is not entirely proved at present. Hence, as it multiplies, it is not held in check by phagocytic and digestive action, but can spread freely in the exudate, passing to neighbouring parts by contiguity of tissue, and being carried on in the lymph-stream which leaves the area of inflammation. It thus becomes disseminated or sown throughout the body, and may give rise to general infection of a septicæmic or pyæmic character.

But this condition we must leave aside until we come to deal with the phenomena of general infection.

LECTURE IV

Besides the reaction which affects the leucocytes of the blood-vascular system, there are also certain changes which occur in the cells of the tissues involved in the results of the injury which has occasioned the occurrence of inflammation.

Scattered throughout the tissue spaces are numerous so-called wandering cells. These present many points of similarity to the white corpuscles of the blood, and they belong to the same great cell group, and form a part of the cœlomic class of leucocytes. These are probably the leucocytes which can be seen accumulating in the area of inflammation even before diapedesis has become well marked, and which in later stages occupy the boundary zone enclosing the accumulated mass of polymorphonuclear leucocytes in the central area.

The fixed cells of the tissues also undergo important changes in the course of inflammation, and Virchow, as we have seen, attributed the whole reaction to an increased metabolism or overaction on the part of the tissue cells. Accordingly, he

and his followers ascribed the origin of pus corpuscles wholly or partly to a proliferation of fixed tissue cells which they believed took on amœboid movement.

In support of this position numerous experiments were made by Hoffman and von Recklinghausen, among others. These observers produced corneal inflammations, and then removed the eyes or the whole heads of the animals in question, and preserved them in moist chambers. After the lapse of two or three days from this procedure the site of injury invariably showed a great accumulation of amœboid cells, exactly similar to those seen in ordinary keratitis. These, they concluded, must have arisen from the corneal corpuscles. The fallacy in this experiment is that the cornea remains attached in the normal manner to the eyeball, which itself in some of the experiments was not even separated from the head, conditions which leave it equally possible that all the amœboid cells seen in the area of inflammation had migrated to it under chemiotactic influence from the tissue spaces and vessels of the eye, and were not formed at all from the fixed tissue cells.

That this is in reality the fact, and that all these amœboid cells were actually leucocytes, is proved by an experiment of Leber. Leber *excised* the cornea of an animal and introduced into it a tiny capillary tube containing sterile septic material. The cornea was then placed within the peritoneal cavity of

another animal. On subsequent examination it exhibited round the focus of irritation introduced in the capillary tube a great accumulation of leucocytes which had invaded it from the peritoneal fluid in which it had been lying, and thus produced appearances precisely similar to those observed in the experiments of von Recklinghausen.

The views of von Recklinghausen were carried still further by the statement of Rindfleisch and others that *epithelial* cells can give rise to an endogenous formation of amœboid cells within their substance such as can actually be seen lying within the epithelial cells. These we now know are simply leucocytes which have made their way into the bodies of the cells in question. They are similarly to be seen in cancer cells. We shall, therefore, probably be justified in holding that *all* the free amœboid cells of acute inflammations are migrated wandering cells of the blood and tissue spaces.

In the fixed tissue cells themselves two opposed series of changes occur in association with the inflammatory process. These are respectively *degenerative* and *regenerative* changes. Of the degenerative changes, the greater number, and perhaps all, are not reactive, but resultant—that is to say, they are the direct effect of the injury or of the action of the irritant, and as such are not an essential part of inflammation—which is a process of reaction—but merely associated phenomena.

There are, however, certain degenerative pro-

cesses commencing or associated with proliferation of cells which are at present regarded by most pathologists as being of an inflammatory nature. These are the parenchymatous degenerations, of which a good example is the parenchymatous nephritis induced by certain drugs or in conditions of acute sapræmia.

Cantharidin, for instance, if it be given in excessive doses, may excite an inflammation of the kidney, which affects especially that portion of its substance which contains the excretory segments of the uriniferous tubules—namely, the cortex of the organ. This action we explain as follows: The cantharidin circulating in the blood in great dilution is taken up for excretion by the renal cells in question, and consequently, if it be present in the circulating fluid in such quantity as to reach the kidney cells faster than they are capable of excreting it, it becomes gradually heaped up within them, and ultimately acquires a concentration in those cells sufficient to cause injury, and thus give rise to an inflammatory reaction.

In considering the tissue changes which result from the action of irritants, two things are clearly to be borne in mind: *Firstly, that stimulation, if excessive either in degree or in duration, ceases to be stimulation, and becomes irritation or injury; and, secondly, that the same irritant,* acting for the same time and in the same degree, *may produce injury in a highly organized tissue, while only causing stimulation of less highly organized cell systems.* The former

of these propositions is well illustrated by the action of cantharidin itself, which in moderate doses stimulates the excretory renal cells, increasing their metabolism and acting as a diuretic, though in larger quantities it causes injury by excessive stimulation, and leads to cell degeneration, lessened metabolism, and diminished excretion of urine. The latter is exemplified in the so-called interstitial nephritis, in which the irritant, whatever it be, while causing atrophy and degeneration of the proper kidney tissue, leads to a stimulation and increased formation in the fibrous stroma.

The action, therefore, of an irritant on any given cell depends entirely on the degree of concentration in which it reaches that cell, and the length of time for which it acts upon the cell. This is illustrated in the formation of a corn upon the foot, which, as pointed out by Paget, is the result of intermittent moderate pressure. If the pressure be made not moderate or not intermittent, we have as the result, instead of proliferation and increase of epidermic structures, their degeneration and destruction, with the production of a sore, or perhaps the outpouring of an exudate and the formation of a blister at the injured part.

It is, therefore, reasonable to regard the proliferation associated with parenchymatous inflammations as the effect of stimulation by the irritant while it is still dilute ; and the degeneration as the result of the injury produced by its more powerful and more

extended action. And it is important to remember in this connection that the proliferation marks the earlier stages chiefly in acute parenchymatous inflammation.

The degenerations which occur are chiefly the cloudy and the fatty changes, and so-called reversionary degeneration; but the mucoid, amyloid, and hyaline forms are also seen, especially in the chronic inflammations.

Repair.

Besides degenerative changes, there is associated with inflammation the process of *repair*. This is a relatively late event in inflammation, and appears to me to mark the stage and be the result of a weakening of the irritant to the point at which it is no longer injurious, but only stimulating in its action. Epithelium is restored by the proliferation of epithelial cells which have survived, and tissue which has been destroyed in mass becomes replaced by fibroblasts, which ultimately develop into fibrous tissue and form a firm cicatrix.

Repair commences at the margin of the inflamed area where the irritant is naturally present in the lowest concentration; and it begins to appear as the inflammation subsides or passes gradually into a chronic stage—that is to say, as the injurious action of the irritant diminishes to the point where its effect is merely stimulating to those cells concerned in the repair. This is well seen in an experi-

ment of Ranvier, who endeavoured to investigate the peritonitis which resulted from the injection into the peritoneal cavity of animals of weak solutions of nitrate of silver. Such injections gave the following effects: At the end of twenty-four hours there was in the parts which had been most affected an acute inflammation, with complete loss of the peritoneal endothelium, but in the parts more sheltered, where the irritant had evidently only arrived gradually, and in great dilution, the endothelial cells, so far from being lost, showed evidence of enormously increased activity and growth, and within forty-eight hours some of them had attained a diameter of 100 μ ($\mu = \frac{1}{1000}$ millimetre) or more, and had become amœboid.

Similarly, with regard to fibrous tissue, its formation is induced by stimulating irritative action. This may be shown as follows: An open wound heals usually by granulations; but if a wound be made aseptically and be left open—that is, the sides not brought together—but be preserved from all mechanical or chemical irritation by absolute asepsis and a non-irritating covering, no granulations form. The epithelium gradually spreads over the surface from the edges, and healing occurs with a minimum of new formation of fibrous tissue. The best natural example of this is the healing which occurs beneath a scab.

The origin of the *fibroblasts*, from which new fibrous tissue is formed, has been the subject of

many researches and of much discussion. If new-formed granulation-tissue be examined with the microscope, four main varieties of cells are seen composing it. Two of these kinds are obviously leucocytes; the third consists of cells of various sizes, but mostly large, of varied conformation, but on the whole of spindle shape, and having a single oval nucleus and abundant protoplasm—these are the fibroblasts. The fourth variety is composed of moderately large cells rounded in shape, with a single nucleus, and relatively a large amount of protoplasm. It is the origin and destiny of this fourth class of cells which still remain uncertain. They are apparently large mononuclear leucocytes. Do they develop into fibroblasts?

This question of the origin of fibroblasts cannot be answered definitely in the present state of knowledge. There is no doubt that a large number of them are developed from the fixed tissue cells, the connective-tissue corpuscles of the part. It is the tissue cells, whether of epiblastic, hypoblastic, or connective-tissue origin, which present during regeneration of tissue the most marked evidence of activity in their enlargement, karyokinesis, and proliferation. And in the corneal experiments to which I have more than once already referred the tissue cells complete the process of repair without the occurrence of any leucocytic infiltration by the enlargement and proliferation of the corneal corpuscles. And the large cells belonging to the fourth

variety seen in granulation tissue are indistinguishable from a stage in the development of fibroblasts from fixed connective-tissue cells.

On the other hand, they are equally indistinguishable from large hyaline leucocytes. And Metchnikoff has actually watched the development day by day of a large hyaline leucocyte into a fibroblast in a tadpole's tail. Hence it is probable that a proportion of the fibroblasts derive their origin from these leucocytes.

Again, the cells of which I am speaking can be seen to act as phagocytes taking up degenerating polymorphonuclear leucocytes. The same is true of fibroblasts, according to Nikiforoff, and of the hyaline leucocytes as shown by Metchnikoff, Ruffer, and others. Their phagocytic action, therefore, does not assist us to decide their origin, whether from tissue cells or from the hyaline leucocytes. All that we can at present say with certainty is that fibroblasts are undoubtedly formed by the proliferation of fixed tissue cells, and probably also to some extent from hyaline leucocytes. German pathologists, however, with the exception of Arnold, all at present hold that connective-tissue cells can only arise from pre-existing connective-tissue cells.

In this connection it is important to remember the view, which has been more than once put forward, that the hyaline leucocytes differ from other white corpuscles in being derived from endothelial

cells. And we have seen already that in inflammation the endothelial cells, both of the vessels and of serous membranes, become amœboid and throw out processes, and act as phagocytes—become, in fact, very similar in appearance to the large hyaline leucocytes. The fibroblasts derived from the fixed tissue cells are also phagocytic. Thus there exists no very sharp distinction between the hyaline leucocytes, the endothelial cells, and the connective-tissue corpuscles. The leucocytes, the endothelial cells, and the connective-tissue cells are all of mesoblastic origin, and form the simplest tissues of the body, so that it is possible that they are partly interchangeable. And Metchnikoff emphasizes this relation by his application of the term ' fixed phagocytes ' to the two latter classes. How close the relation is between the other mesoblastic tissues and the leucocytes is shown by his own observation that in the degeneration of muscle fibres in the tadpole's tail the proliferated nuclei of muscle fibres become the nuclei of separate wandering cells.

Besides the production of new fibrous tissue there occurs in the process of repair a formation of new bloodvessels and vascular loops. The observations of Rindfleisch led to the conclusion that this takes place by an arrangement into parallel rows of extravascular vaso-formative cells, thus giving rise to new capillaries, which presently acquire attachment to the existing capillaries of the part. According to other observers, certain cells of the granulation tissue

become hollowed out to form new vascular channels, just as occurs in the vascular area of the chick embryo. Arnold, however, and most recent investigators deny these statements, and describe the formation of new vessels as occurring by the proliferation and projection outwards of endothelial cells of pre-existing capillary loops. There is first formed a protrusion from the endothelial cells. This becomes nucleated, and grows by the proliferation of the cells which form it. Such a protrusion eventually meets a similar protrusion from a neighbouring loop, and fuses with it, and ultimately this solid process becomes hollowed out to form the new capillary.

There is thus formed to replace the tissue which has been destroyed new fibrous tissue richly supplied with blood capillaries. In this new tissue further changes then proceed. The fibroblasts gradually become more elongated, and break up longitudinally into successive layers of fine fibrillæ, until eventually but little is left of the original cell except the nucleus and a small amount of protoplasm surrounding it. These fibrillæ undergo chemical alteration, and proceed to gradual contraction, which results in the occlusion of the majority of the new capillaries, and ultimately there is produced a firm and almost bloodless, hard cicatrix.

This is the process which invariably occurs in the healing of a wound. Where healing is by primary intention the amount of injury and irritation of the

tissues is extremely small, and the formation of new fibrous tissue is very slight indeed. In healing by granulations, on the other hand, the new formation is considerable, and increases in amount with increase in the duration and degree of irritation present. Thus it is least in an aseptic wound which is allowed to heal beneath non-irritating coverings, greater in one irritated by pent-up exudation or by irritating dressings, and greater still in one subjected to the action of powerful chemical reagents, or attacked by septic processes.

The process of regeneration leads in chronic inflammations, where the irritant is just sufficiently powerful to induce continuous degeneration in more highly organized cell systems, but only strong enough to stimulate connective-tissue growth, to the production of inflammatory fibrosis and fibrous hyperplasia.

Relation of the Nervous System to Inflammation.

As regards the relation of the central nervous system to the inflammatory process, we have already seen that its action is not essential, since an inflammation can be produced, and indeed is caused more readily, and runs a more rapid course, in parts whose nerve supply has been divided than in normal tissues. And Metchnikoff has followed inflammation in the tail of a tadpole, which had been curarized to such a degree that its heart had ceased to beat, a dosage

under which all efferent motor impulses must have been completely blocked.

The time relations also are not those which should undoubtedly present themselves if inflammation were dependent on a nervous reflex, for Cohnheim showed that if, for instance, croton oil be rubbed upon a rabbit's ear, quite half an hour may elapse before any evidence of inflammation appears, although when it then arises it assumes a most acute and very active type.

Whether the central nervous system can directly modify the liability of a part to inflammation independently of vascular changes which it may originate, or can control the type of inflammation which arises, is a more difficult question. The existence of special trophic nerves is, at any rate, very problematical, and is certainly not proved. Indeed, the evidence tends in a contrary direction. The tendency of paralyzed limbs, and of parts below the site of injury or disease in complete transverse lesions of the spinal cord, or of the eye after removal of the Gasserian ganglion, to rapid and destructive inflammations affords no evidence of the existence of a trophic action of the nervous system. They are sufficiently explained by the diminished circulation, and by the loss or diminution of sensation which result, by which the vitality of the tissue is lowered, and the perception and removal of injurious agencies prevented. The paralyzed limb, kept warm and protected from pressure, and the eye, kept covered to prevent the

entrance of foreign particles into the conjunctival sac after removal of the central ganglion, do not become inflamed. The increased liability to inflammation is therefore not directly the result of the removal of accustomed trophic influences.

Nevertheless there are a number of cases which are extremely difficult to explain except on the hypothesis of direct nervous influence. Such are the cases of inflammation affecting the part supplied by one branch of a nerve associated with definite inflammatory phenomena in other areas of distribution of that nerve—the case of so-called sympathetic panophthalmitis—and, last and most important, the occurrence of herpes zoster, which is probably always secondary to inflammation of the posterior root ganglion of the nerve supplying the affected area of skin.

All this, however, need not necessarily mean more than that a variety of changes in the innervation of a part, and in its vascular conditions, may so lower its resistance and vitality that its susceptibility to inflammation becomes sufficiently increased for the ordinary irritations arising from normal contact with the outside world to excite an inflammatory reaction. And all these cases of associated inflammation occur in exposed parts. The nephritis sometimes following catheterization or operation on the urethra, which has been quoted as an inflammation of nervous origin, is, of course, always due to septic agencies.

Cases have been recorded of the apparent produc-

tion in susceptible subjects of a condition of inflammation by hypnotic suggestion. The suggestion to the hypnotized patient that a red-hot iron had touched the hand was followed by the production of all the local appearances of a burn. Here the inflammatory reaction, if such it be, appears to have been definitely originated by centrifugal nervous impulses, which it would seem had acted in the direction of an injurious local irritation.

However this may be, there is no doubt that the central nervous system exerts a powerful influence in controlling the origin and course of inflammation through the action of the vaso-motor nerves. Thus we have seen that, after the division of the nerves supplying a given region, an inflammation which arises in it runs a more rapid course than in the normal animal. Moreover, this may be in part the result of actual changes in the vessel walls as well as alterations in their calibre, for it has been shown by Gergens and Rütimeyer in the frog that after destruction of the spinal cord the vessels allow a greater transudation than the normal, and even permit the passage through their walls of solid particles of colouring matter introduced into the circulation.

An illustration of the influence of the vaso-motor nerves on inflammation is seen in the following experiment of Samuel on the rabbit's ear: If the sympathetic nerve supply—*i.e.*, the vaso-constrictor fibres—be divided in one ear, and the auricular nerves—the vaso-dilators—in the other, the vessels

of the former become widely dilated, those of the latter constricted, from the unopposed tonic action of the undivided nerves. If now both ears be plunged in water at 54° C. for a short time, and then removed, the reactions they exhibit differ very markedly. The ear in which the vessels are already dilated from the removal of constrictor impulses becomes still more hyperæmic, and acute inflammation supervenes. This rapidly passes on to a complete recovery, while in the ear of which the vessels are constricted no hyperæmia occurs, but stasis is induced, and the condition may go on to gangrene.

These results have been confirmed by Roger in a modification of the experiment in which one ear retained its normal nerve supply, while in the other either the constrictor or the dilator fibres were divided. Both ears were then inoculated with the same dose of the streptococcus of Fehleisen. If the constrictor had been cut, the erysipelas resulting from the inoculation appeared more quickly, and ran a more rapid course in the ear concerned than in the normal ear, while in an animal in which the dilator fibres had been severed it developed much more slowly than in the intact ear, ran a more protracted course, and led to loss of tissue from necrosis.

But although the controlling influence of the vaso-motor system is so definitely manifest, we cannot look upon the vascular changes of inflammation as a vaso-motor reflex, since section of all the nerves does not prevent the usual sequence of the vascular events,

though it accelerates them by liberating the vessels from the sway of central controlling influences.

Whether the changes are dependent on a peripheral reflex due to a stimulation of the peripheral ganglion in the vessel walls is a more difficult question, and does not at present admit of definite answer or dogmatic statement. But three considerations are of interest in this relation. First, were the dilatation a peripheral reflex, occurring in the local ganglion, one would expect that it would overcome the condition of tonic constriction following the section of the dilator nerves in the experiments already quoted, and this is not the case. Secondly, the evidence, so far as it goes, tends on the whole in favour of the view that the peripheral ganglia of the vascular system subserve sensation rather than the supply of motor impulses. And in any case they are not believed to act as reflex centres. And, thirdly, there is definite evidence, as shown by Klebs, that the capillary walls, at any rate, are endowed with independent contractility, so that they are capable of altering their calibre in response to stimulation entirely independently of nervous influences. And it is possible, though not proved, that the muscular walls of the arterioles possess a similar power of independent regulative action.

Summary.

Inflammation has been divided according to its *most prominent features* into different varieties—serous, fibrinous, suppurative, ulcerative, productive, and the like; according to the *tissue affected* into parenchymatous or interstitial; and according to its *causation* into simple and infective. It has been said to vary with the *nature* of the tissue involved—the *position* of that tissue on a free surface or otherwise, for example—the *nature of the irritant*, and the *intensity of the irritation*.

Some of these distinctions are useful for descriptive purposes, and from the clinical aspect, but all are purely artificial. There is only *one kind* of inflammation, and the differences observed in different cases depend exclusively on the extent to which one or another feature of the process becomes prominent. The actual process is the same in all. It is therefore more correct to use the term *degrees* of inflammation, rather than varieties. For all the events observed depend exclusively upon the factors which we have already treated—namely, the degeneration of injured tissue, the exudation, the migration of leucocytes, the formation of fibrin, and the peptonization caused by the action of bacterial ferments, where such are present, which occur in the reaction of inflammation—and on the associated reaction of regeneration, which follows as the inflammatory events subside.

Thus *serous* inflammation is the type where the intensity of the irritation is comparatively slight, giving rise to exudation with the minimum of migration and breaking down of leucocytes, and consequently hardly any formation of fibrin in the clear fluid ; or, on the other hand, an inflammation due to a very virulent micro-organism where the leucocytes are rapidly destroyed in the exudate, their substance, together with any fibrin which is formed, being speedily peptonized by the bacterial ferments. In the latter case, however, the fluid resulting is more usually *sanious* in character.

Fibrinous inflammation may be described as one in which the action of the irritant is more intense than in the case of serous inflammation. A much greater number of leucocytes are broken down, and a considerable amount of fibrin formed.

Productive inflammation is the name given where the marked feature is the subsequent new formation of fibrous tissue. Here the irritation is slight, but long continued. In *suppurative* inflammation the irritation is both intense in action and prolonged in time. Occurring on a free surface, it is spoken of as *ulcerative* inflammation. Marked positive chemiotaxis and more or less peptonization of the exudate occur.

Of the influence of *position* as affecting both the vascular phenomena and the amount and character of the exudation (by mechanical conditions) we have already spoken.

Parenchymatous inflammations are such as affect chiefly the essential tissue elements of an organ—as, for example, the epithelial cells of kidney tubules—while the term *interstitial* is applied in cases where the connective-tissue basis of the organ appears to be primarily affected.

The *way* in which the nature of the irritant and its degree of intensity affect the resulting inflammation has already been discussed. We also saw that if the irritant be of particulate nature the phagocytes will tend to take it up, and to digest and destroy it if it be digestible. Besides this anti-bacterial action of the phagocytes, there is developed a bacteriolytic power in the fluid exudate, so that even exudates in which the leucocytes have been destroyed by the infective agent may still possess considerable bacteria-killing power.

Of the *systemic changes* associated with or accompanying local inflammation the great majority are due to the absorption of toxic products from the area of inflammation. These we shall more conveniently consider under the heading of Local Infection, while inflammatory fever will be included in our discussion of fever in general. Two facts remain to be mentioned : First, that in acute local inflammation, especially when the inflammatory exudation is considerable, a condition of apoplasmia or diminished fluidity of the blood results from the great loss of fluid from the circulation. The resulting increase in the specific gravity of the blood may last for sixty

hours or more from the onset of the inflammation, as was shown by Sherrington. The same observer proved that frequently a leucocytopenia—that is, a diminution in the percentages of leucocytes—occurs in the early stage of many inflammations. This is not necessarily accounted for, as at first supposed, by a destruction of leucocytes associated with the onset of the inflammatory reaction, but may be due to their collection in some special area of the circulation, especially in the lungs, as shown by Muir and others. The stage of leucocytopenia is rapidly followed by a marked increase in leucocytic count, which may appear within as little as an hour of the production of the local injury.

The *termination* of inflammation may be by complete *resolution*—a *restitutio ad integram*—which is the most favourable and the most frequent termination. Or it may end in *molar death* of tissue, as distinguished from the molecular destruction which occurs in suppuration, and this is termed *necrosis*. Or, thirdly, it may lead to a considerable growth of new connective-tissue, as in so-called *productive* inflammations. On the other hand, it may not terminate at all, but pass into a lasting stage of chronic inflammation.

If now we ask ourselves the question, What is inflammation ? we have seen that of the older theories the view of Cohnheim, that it is due to molecular changes in the vessel walls, must be abandoned ; and equally that of Virchow, that it consists

essentially in overactivity of tissue metabolism as the result of local irritation.

We have seen that it is the reaction to tissue injury by a *chemical*—that is, a not-purely-mechanical—irritant, and that the tendency of the whole process is to effect the removal and destruction of the irritant concerned. Hence, Metchnikoff has described it briefly as the 'endeavour' of protoplasm to digest the irritant.

If we review the process in vascular and non-vascular areas in the same animal and in different tissues, or follow it throughout the animal series, we are met by one, and only one, invariable event, which is the reaction of the phagocytic cells. This, and this only, is the constant character and sign of the inflammatory process.

Avoiding definition, we may therefore summarize the phenomena of inflammation as *the process which occurs in living tissue when it is injured by the action of an irritant, and which invariably tends to the removal and destruction of that irritant.*

LECTURE V

The General Pathology of Infection

By the term *infection* we mean the entrance into the tissues of living micro-organisms. If the micro-organisms are capable of living and multiplying in the invaded tissues they produce disease. Such disease is called *infective* disease; and the micro-organisms which give rise to it are said to be *pathogenetic* micro-organisms.

If the infective agent is either continuously, or from time to time, or, again, at certain definite periods, discharged from the body of the infected subject—in the secreta or excreta, by desquamation from the surface, or otherwise—the disease will be *infectious* as well as infective—that is to say, it will be transferable from the infected to the healthy subject—as, for example, in diphtheria. The organism may then be spread about—disseminated—by air, by water, or by food, and cast-off clothing and the like, if it be capable of a continued existence outside the living body under ordinary conditions. Or, if it be incapable of growth and life except within the tissues

or secretions of the body, the disease, of which it is the causal agent, will be *contagious* only; that is to say, it will be only capable of being spread by contact transference from the diseased to unaffected individuals—as in the case, for example, of gonorrhœa.

Contagious diseases, then, can only be acquired by contact with the affected subject, or with quite fresh infective material from his body; while in the other infectious diseases the contagium vivum or virus may reach the unaffected individual through the agency of air or water, or some other means of spreading.

The distinction which I drew just now between the terms 'infective' and 'infectious' must be clearly borne in mind from the outset in the discussion of infection. The former term implies that *micro-organisms* are the *causal* agents in the disease in question; the latter simply that the disease is *transferable*, and therefore tends to appear in epidemics. Some infectious diseases have been proved to be infective; in a number of others there is considerable evidence of infective origin, though exact proof is lacking; while in the rest the direct evidence is at present altogether wanting, though from analogy they are assumed to be infective also. And this assumption forms a working hypothesis, which we shall find convenient for our purpose here.

That certain diseases are infectious had been known from very early times, but the cause of their infectiousness remained entirely undetermined. An

infectious disease was seen to be endemic in one region, in another only epidemic ; to spread from the endemic centres along lines of travel, becoming epidemic in its course, now in one place, now in another ; to pass with almost lightning rapidity from individual to individual, and from town to town ; to die away again, only to be followed after months or years by a new outbreak, and again another. It was seen to favour centres of insanitation and overpopulation ; to vary in severity in successive epidemics, and without apparent cause ; to undergo seasonal variations where endemic ; to pass by touch, by the breath, by food, by objects handled by the sick, it might be only months or years before, and even to follow the exhumation of bodies of those long dead of the disease. But the cause of its infectiousness remained unknown.

All the evidence, however, already pointed in the direction of a *particulate* infective agent, and, indeed, of one able to multiply, and that with great rapidity and almost without limit—in fact, of a contagium vivum. This was the view expressed in 1671 by Kircher, who employed the phrase 'contagium animatum.' It had long been foreshadowed in the opinion of the old Roman writer Varro, who attributed marsh fevers to the bites of small, invisible flies. And you will remember the still more ancient theory that a particular evil power, by name Beelzebub, was specially solicitous for harmful flies, and was their god.

Paracelsus also came quite near the truth in his conception of what he called the ' seeds ' of a disease, an expression which still clings in popular language. But it remained for Leeuwenhoek to lay the first foundations of microbiology by his discoveries in the microscopic world. Other investigations followed, and new facts were ascertained, and gradually a natural history of the unicellular plants developed ; but it was long before their causal agency in the decompositions of organic substances was determined. Conclusive proof of this was first supplied by Pasteur in his work on the phenomena of fermentation and of putrefaction, published in 1857.

It was Davaine who was the first to clearly recognise the rôle of micro-organisms in disease. He proved the fact for anthrax. Then Villemin, in 1865, following the earlier experiments of Klencke (1843), found that he could produce tuberculosis in animals by the inoculation of tuberculous material, and came to the conclusion that the virus of this disease was comparable in its mode of action with those of other infective diseases. This conclusion was strenuously opposed from many sides, but was confirmed by Armanni in 1873, and by Cohnheim and Salomonsen. The nature of the tuberculous virus itself, however, remained unknown.

In 1876 it was shown by Burdon Sanderson that in erysipelas the fluid taken from the spreading edge always contains large numbers of micrococci

arranged in chains; and Ogston found, in 1881, the constant presence in acute abscesses of what he termed the 'cluster coccus,' thus demonstrating the definite association of certain kinds of micro-organisms with particular diseases. In 1882 the discovery of the tubercle bacillus was announced by Koch, and shortly afterwards he published his extended series of masterly researches on tuberculosis, and made known his culture methods, which at once elevated the study of bacteria from the position of a natural history to that of natural science.

By the application of these methods and of the postulates laid down by Koch, our knowledge of bacteria and of their relation to infective processes has rapidly increased, and a new science of Bacteriology has been developed. In its relation to bacteria in general, their forms and characters and general biology, the science of bacteriology is a branch of botany, and of no greater interest in medicine than any other of the natural sciences; but as concerns the relation of bacteria to disease, the study of the action of micro-organisms in the living body and the reaction to their growth and metabolic products forms an important section of the science of Pathology, and is of constantly increasing value.

Of the micro-organisms at present known which produce disease in animals, only a very few belong to the animal kingdom, notably the parasites of malarial fevers; the vast majority are vegetable micro-organisms, and are usually, though somewhat

inaccurately, spoken of as bacteria. They belong to the Mycetes.

The Mycetes are subdivided into the following groups :

1. Hyphomycetes, or moulds, which are composed of a mycelium bearing hyphæ, by means of which the reproductive processes are carried on.

2. Blastomycetes, or budding fungi, in which the new members are budded off from the parent cells.

3. Schizomycetes, or fission fungi, which multiply by fission.

To the first class belong the actinomyces, or ray-fungus, and the moulds associated with certain skin diseases, such as favus and ringworm ; *the second class* possesses few, if any, pathogenetic species, though certain pathogenetic torulæ have been described ; while the *third class* comprises the great bulk of the micro-organisms of disease. For the special description, general biology, and distinctive characters of these bacteria, I must refer you to your lectures in bacteriology, or to Muir and Ritchie's text-book ; they do not especially concern us here.

In their relation to the tissues of the living body, the micro-organisms may be divided into the parasitic and the saprophytic groups, parasitic being such as can live and develop in the living tissues, while the saprophytic can live outside the living animal in dead animal tissue, or on vegetable substances, or even on inorganic matter. Each of these

groups may again be subdivided into two, giving the four following classes :

Parasitic Forms.—(1) Obligatory parasites, which can *only* live in living tissue. (2) Facultative saprophytes, which *can* continue to live outside the living body.

Saprophytic Forms.—(3) Facultative parasites, which, while normally saprophytes, *can* exist in living tissue. (4) Obligatory saprophytes, which *cannot* exist within the living animal.

The chief importance of this method of classification lies in its bearing on the question of infection, and on the distinction between such diseases as are *infectious* in the general sense, and such as are *contagious* only in the narrower meaning. The micro-organisms concerned as causal agents in the latter or exclusively contagious infections belong entirely to the first class—the obligatory parasites—which can *only* live under the conditions found in living tissue. This contact infection was spoken of by the late Professor Kanthack as 'direct' contagion, to distinguish it from what he denominated 'indirect' contagion. Diseases which can be 'indirectly' contagious in Professor Kanthack's sense as well as 'directly' contagious I have included under the general term *infectious*, confining the term 'contagion' to its literal sense of contact.

Those diseases in which the infective agent leaves the diseased subject in a condition in which it can *immediately* infect a healthy person I shall call

'directly infectious' and 'directly contagious' diseases respectively, reserving the terms 'indirectly infectious' and 'indirectly contagious' for those diseases in which the agent of infection is not directly transferable nor capable of directly reproducing the disease, but only mediately transferable through the body of an intermediate host.

This is merely a matter of terms, but it seems preferable to use the word 'contact' in relation to the *subject* of disease, whether man or animal, rather than to the *causal agent* of the disease in question. Used in the latter sense, the term 'directly contagious' would have to be applied to all infections, since acquirement of the disease implies a direct contact with the infective agent and its entrance into the living tissues of the body.

It must not be supposed from what I have said of the obligatory parasites that their faculty of living within the living tissues, and only there, is in any way dependent on the fact that those tissues are *alive*, except in so far as this implies merely the presence of physical and chemical conditions not otherwise obtainable in nature, and which are necessary to their existence.

For, as we shall see later, there are continually in action in *living* tissue certain processes which are definitely and often markedly inimical to bacterial life. All that is meant is that it is only in living tissue that the bacteria in question can obtain those conditions of temperature, moisture, and nutrition

in general which are essential to their life and growth.

In a number of cases we are already able artificially to provide conditions sufficiently similar, though still enormously removed from those which actually exist within the body, to enable us to cultivate bacteria which are, or have been, looked on as obligatory parasites, so that what is in nature an obligatory parasite can be grown in the laboratory on artificial media ; while in other cases gradually increasing knowledge and skill have shown that organisms once quite impossible of cultivation, or only grown with difficulty after prolonged and careful trial, and hence at first regarded as obligatory parasites, can actually exist and multiply outside the body under quite ordinary conditions. Thus the tubercle bacillus, which Koch only eventually succeeded in growing on inspissated blood-serum, and which took years to force to grow on agar, has actually been shown by Sander to be capable of growth on baked bread or boiled macaroni, in potato-juice or ordinary potatoes, and even tap-water, under normal conditions ; while certain of its allies have their normal habitat upon a common grass, the so-called quaking-grass.

It follows, therefore, that, as our knowledge advances, the class of the obligatory parasites is being continually reduced in number by the relegation of its members one by one to the group of facultative saprophytes ; while, on the other hand, those which

remain admitted as obligatory parasites in nature are proving more and more amenable to improved artificial culture methods under such approximation to their normal habitat as can be made in the laboratory.

The facts which I have here referred to briefly bear closely on the question of the spread of the infective maladies, and the means by which that spread may be prevented, or at least checked. Regarded from this aspect these diseases may be divided into groups and classes more or less definitely separable from each other, according to the nature and life-history of the infective agent.

For the following division I am indebted partly to the late Professor Kanthack's article in Clifford Allbutt's 'System of Medicine.'

Group I., in which the infective agent never leaves the body of the infected animal, or does so only in a condition in which it is incapable of immediately infecting another animal of the same species. Examples of this are to be seen in the spirillum of relapsing fever and in the malarial parasites. Such diseases are only indirectly infectious after the passage of the infective agent through the body of an intermediate host. They are to be met either by removal from the region in which they are endemic, or by hygienic means directed to the destruction of the intermediate host. Isolation of the sick will not affect the spread of the disease.

Group II., in which the infective agent leaves the

body of the infected animal in a condition in which it *is* capable of immediately infecting a healthy individual. Such diseases are directly infectious. They may be treated in the following classes :

Class 1.—Diseases due to obligatory parasites. In these the infective agent cannot continue to exist outside the animal body ; they are accordingly purely contagious. Absolute isolation of infected subjects would eventually result in the total disappearance of the diseases in question.

Class 2.—Diseases due to facultative saprophytes. In these the infective agent can exist outside the living body, though it does not usually do so. Here again isolation will be of advantage, but the main object must be disinfection of the secreta and excreta of the infected subjects, since these contain infective agents capable of life and growth outside the living animal.

Class 3.—Diseases due to facultative parasites. In them the organism is a natural saprophyte. Prevention of disease can, therefore, only be attained by rendering its natural habitat no longer suitable. Isolation is of little preventive value in regions where the infective agent is disseminated as a saprophyte.

Those micro-organisms which are capable of invading the tissues of the body and there producing morbid processes are spoken of, as I said at the commencement, as *pathogenetic* forms. But, besides these, the body surfaces, internal and external, are

normally inhabited by a great variety of bacteria. Some of these are capable under suitable conditions of taking on pathogenetic action—as, for instance, the ordinary colon bacillus; others are invariably harmless under normal circumstances, and are pure saprophytes. Others, again, are possibly not merely harmless, but actually useful to the organism, especially such as have their normal habitat on the digestive surfaces. For it has been shown that plants, at any rate, do not thrive when grown on absolutely sterile nutritive material, and probably the same will be found true for animals. Such different forms of life as live together for their mutual advantage are spoken of as *symbiotic* organisms.

Pathogenetic bacteria are not sharply marked off from harmless forms by any well-defined division. This could not be expected, for the power of invading living tissue is a factor of two variables, and therefore variable itself. These factors are the activity of virulence of the bacterium in question. and the resistance of the organism concerned. Thus it happens that one and the same bacterium may be pathogenetic for one kind of animal, but not for another of a higher resistance, as in the case of frogs, which are resistant against anthrax, and fowls to tetanus infection. Or the bacterium may be pathogenetic for a given animal at one time, but not at another, as the resistance of the animal varies. This is the case with tuberculous infections, or with infection by the *Bacillus pyocyaneus*. Again,

the activity of the bacterium itself may vary, so that it is at one time pathogenetic, at another not so. Or it may be, when taken by itself, entirely harmless, but become capable of harmful action when associated with another, possibly equally non-pathogenetic, organism. In the same way the action of a bacterium which is usually pathogenetic may be prevented or counteracted by its association with another organism. The meaning of many of these facts will become clearer when we consider the nature of the action of bacteria, and the reaction to them which occurs within the living body.

I have stated that all bacteria which are capable of continued life and growth in the living tissues are pathogenetic to the animal concerned, and by their presence and their products will inevitably cause disease. Certain remarkable observations have, however, been recorded recently which, if confirmed, go far to controvert this view. For though all previous observers who have worked on normal organs have declared the tissues of healthy animals to be invariably sterile, Ford, working under the direction of Professor Adami, claims to have found, in rabbits, guinea-pigs, cats, and dogs, that not less than 70 per cent. of the organs of animals killed during normal health show the presence of living bacteria in their substance when examined in the usual way with all precautions. Those experiments, if confirmed, will very considerably modify our view of the extent to which symbiosis plays a part in normal animal life.

But at present they can hardly be accepted as conclusive.

However this may be, the fact remains that the effect of the growth of *abnormal* organisms in the body tissues is to produce disease. If such disease presents a character and course such as distinguish it clearly from all other known diseases, and is invariably associated with the presence of a particular micro-organism, and no other, then the disease is spoken of as *specific*, and the infective agent which produces it is called the specific organism of that disease.

Professor Koch laid down the conditions of specificity for a bacterium in the form of his three famous postulates :

1. That the bacterium in question, and no other, is *invariably* present in the typical lesions of the disease concerned, and of no *other* disease.

2. That it can be *cultivated* from the diseased animal on artificial media through several generations.

3. That when suitably injected into healthy animals it gives rise to the *reproduction of the characteristic picture* of the disease, and can be *again recovered* from the lesions of the infected animal.

If these postulates are fulfilled, the bacterial specificity of the disease is proved. It has been so proved for anthrax, diphtheria, tetanus, gonorrhœa, malignant œdema, plague, tuberculosis, glanders, and

actinomycosis. Of the other infectious diseases, in some the proof is altogether wanting, while in the rest it is still incomplete. Thus in typhoid fever, influenza, and mycetoma (Madura disease) the successful animal experiment has not been hitherto established, though, as regards typhoid fever, both Remlinger and Chantmesse have produced a disease with intestinal symptoms and marked infiltration of the Peyer's patches in animals by means of the *Bacillus typhosus ;* and I have myself, both in the rabbit and the guinea-pig, obtained by injections of the same bacillus a continued fever of some weeks' duration, associated with variable diarrhœa, a loss of appetite, lassitude, and great wasting, and showing post-mortem an ulcerated condition of the small intestine and cæcum strongly suggestive of the typhoid ulceration seen in man.

In relapsing fever and in leprosy only the constant presence of a particular organism has been established, all attempts at cultivation having failed, though in relapsing fever it has been shown that the blood of diseased subjects is capable of reproducing the disease in monkeys when injected. In the case of leprosy, experimental inoculation has entirely failed to reproduce disease in man wherever the subject was above suspicion of already harbouring the disease in latent form.

In a number of other diseases of infective origin which present clinically a definite identity, no *one* bacterium can be said to be the causal agent, since

a variety of different micro-organisms can be found in different cases, and sometimes more than one in the same case. Such are the pneumonias, cholera, all suppurative inflammations, endocarditis, meningitis, and the like.

Finally, there remain a number of infectious diseases which are as yet only assumed, not proved, to be infective, such as rabies, syphilis, yaws, mumps, whooping-cough, and all the exanthemata.

This is the position of our present knowledge with regard to the *bacterial specificity* of the infective diseases. But we can go a step further than this in establishment of specificity. A pathogenetic micro-organism which gains entrance to the living tissues can only act upon them in one of the two following ways—namely, either by chemical or by mechanical interference with their functions. The second of these means is, in the vast majority of cases, of very slight importance, if of any. In very few conditions is the multiplication of bacteria so enormous as to produce a mechanical effect—such, for example, as a bacterial embolism within the living animal—nor is the distribution of secondary foci of infection usually such as could be produced by a mechanical action of the micro-organisms. Even where the multiplication of bacteria is great enough to cause mechanical effects, these are in general overshadowed by the more important chemical action of the bacterial products. Such mechanical effects as do occur are usually secondary

to this action. Thus emboli, which are only rarely, and then probably only in capillaries, formed entirely of masses of bacteria, are very frequently produced by fragments of thrombi formed under the chemical action of bacterial products on the blood and endothelium of vessels, and gradually softened and dissociated by the action of the micro-organisms which grow and multiply in them.

The pathogenetic action of bacteria accordingly depends almost entirely on their power of forming harmful substances, to which the symptoms and phenomena of disease are due. Hence we require, for complete demonstration of the specificity of any given disease, to prove not only its bacterial specificity, but also that of the bacterial products. This proof can only be obtained by separating the bacterial products and producing the disease concerned by their inoculation in the absence of the micro-organisms themselves.

Unfortunately, this presents exceptional difficulties. The conditions under which the toxic substances are formed within the living body are not easily determinable, and are extremely difficult, or, in many cases, at present impossible to obtain in artificial cultivations. *Chemical specificity* has, however, already been established for three bacterial infections—namely, for diphtheria, tetanus, and anthrax. This was due first and chiefly to the work of Sidney Martin, whose results have been confirmed by several observers. It has been shown that the

poisonous substances which can be obtained from cultures of these organisms are identical with those found in animals dead of the disease in question, and that both will, if injected into healthy animals, produce identical lesions.

Specific harmful substances produced by micro-organisms are usually spoken of as toxins. We may therefore say that a disease is proved to be specific when both its bacterial and its toxic specificity have been established. The conditions for specificity may accordingly be briefly stated as follows :

1. A particular micro-organism, and no other, must be invariably associated with the disease in question, and with no other disease.

2. It must, when transferred to healthy, susceptible animals, produce the disease in them, and be again discoverable in their tissues.

3. It must, if capable of cultivation artificially, produce the same disease when such a culture is inoculated in a susceptible animal, and must be again recoverable from the tissues of the animal inoculated.

4. The toxic substances obtained from artificial cultures, and from the tissues of diseased animals, must be in chemical and physiological agreement.

Since the harmful action of pathogenetic micro-organisms is exerted through the agency of chemical substances which they form, it is of the first importance to inquire into the nature of the chemical products of bacterial metabolism. Of these, unfor-

tunately, only very little is known. The subject of bacterial chemistry is in its infancy, and is surrounded by peculiar difficulties, so that it is even more backward than the sister branches of pathological and physiological chemistry.

Among the numerous substances which may be obtained from cultures of bacteria I may mention briefly the following—namely, *gases*, such as carbon dioxide, hydrogen sulphide, and ammonia ; *acids* of the fatty and oxy-acid series, such as acetic, lactic, and butyric acids and their *amides—e.g.*, leucin, etc. ; bodies of the *aromatic series*, such as tyrosin and phenol ; *indol*, pigments, ptomaines, toxalbumins, ferments and enzymes, and the products of fermentation. Many of these are common to a considerable number of bacteria ; others are more or less specific, or confined to a small group of organisms.

The gases, fatty and oxy-acids, aromatic substances and pigments do not appear to be endowed with any specific harmful action.

The *ptomaines* were originally thought to be the specific bacterial poisons. They are basic substances, which were first investigated by Brieger, who compared them to the vegetable alkaloids, and considered them to be the specific toxins of bacteria. They are, however, not alkaloids, but amines, and are produced especially in putrefactive processes. They are not invariably poisonous, nor do all pathogenetic bacteria produce such bodies. Frequently they are only present in bacterial cultures in quite small

amounts, and they do not in general, when injected into animals, produce the specific lesions of the disease in question; accordingly they are no longer looked upon, even by Brieger, as specific toxic substances.

The immediate interest in these bodies was considerably diminished by the discovery by Hankin and Sidney Martin of *toxic albumoses* in bacterial cultures. Brieger and Fränkel also separated toxic albuminous bodies from diphtheria cultures, and applied the term *toxalbumins;* but Martin showed these bodies to be really albumoses. Working with definite solutions of albumins as culture media, he proved the formation of toxic albumoses in the case of anthrax, ulcerative endocarditis, diphtheria, and tetanus. This was especially important in view of the fact that the poison of snake-venom had been shown by Weir-Mitchell to be a peptone, or, more correctly, as was later proved, an albumose. And Martin's own experiments showed the active principle of abrin, a poison derived from jequirity seeds, to be also an albumose.

It has, however, been proved by Buchner and by Uschinsky that bacteria can still form their toxins when grown in culture media which contain no albuminous material; and Brieger and Boer have separated the toxins of diphtheria and tetanus from broth cultures in a form in which they do not give any of the reactions of proteids at all. Hence it seems probable that the toxic substances are not

albuminous in nature, but only intimately associated with these albumoses, with which they tend to be precipitated from their solutions. The chemical nature of the toxic substances themselves is quite unknown at present.

The fact that bacteria cultivated in solutions of albumins give rise to the formation of albumoses proves that they exert a digestive action on the nutrient media. They therefore act as organized ferments, and in the case of the diphtheria bacilli, at any rate, produce an enzyme which was found in diphtheritic membrane by Roux and Yersin and by Sidney Martin. Martin, indeed, regards this enzyme as the true diphtheria toxin, which, by its action in the living body, gives rise to secondary toxic albumoses, and these in turn to the symptoms and the lesions of diphtheria.

But on this point it is at present impossible to make a definite statement, since all attempts to isolate such enzymes in a pure condition have hitherto entirely failed.

It has been usual to divide bacterial toxins into extracellular and intracellular varieties, according as they are or are not discharged by the bacteria into the surrounding medium. On the enzymic theory, extracellular toxins would be such as are formed outside the body of the bacterium by the action of its secreted enzymes, not excreted ready formed by the bacteria. But, as we have seen, the existence of such extracellular enzymes is, at any rate, still

uncertain ; and the analogy of other organized ferments favours the view that even the extracellular toxins have been formed within the bacterial body, and then excreted. Thus, in the case of alcoholic fermentation, alcohol has been shown to exist within the cells of the yeast during activity. It is therefore formed within the cell and afterwards excreted, and not produced by extracellular action, as was formerly believed.

The toxins of diphtheria and tetanus are those best known as belonging to the class of extracellular toxins—that is, such as are discharged by the bacteria into the surrounding fluid. In actual practice, however, the distinction between extra- and intracellular toxins should not be very sharply drawn, since in any culture of bacteria numbers of individuals are continually dying and become broken up, thus liberating any intracellular toxic substance which they may contain.

But whatever ultimately proves to be the method of formation, and the nature of the specific toxins, their action in susceptible animals, at any rate, is to produce the particular disease with which they are associated.

LECTURE VI

At the end of the last lecture we were considering the disease-producing products of bacteria.

Now, different species of animals vary in their *susceptibility* to any given disease, and of the members of the same species some are more susceptible than others. Animals whose susceptibility to a given disease is greater than the average for their species are said to be *predisposed* to the disease in question. Similarly, certain species may be predisposed to a particular disease, as in the case of guinea-pigs and inoculation tuberculosis.

Predisposition in a species is obviously an hereditary character, and must be dependent on peculiarities of the cell processes proper to the animals concerned. An individual predisposition may be similarly intrinsic and dependent on cell properties, either hereditary or acquired, or it may be extrinsic and accidental—the result of circumstances which act injuriously upon the normal tissue processes, lowering the resistance of the body.

Predisposed animals tend to become infected and

to succumb to the disease, and thus fail to propagate, while the less susceptible escape. The natural action of disease is, therefore, to improve the physical standard of the species by the survival of the fittest only. In the case of man, the natural tendency to physical improvement along this line is, to some extent, continually thwarted by the efforts of the physician, whose duty it is to preserve the unfit in life as long as possible.

After recovery from an attack of an infective illness susceptibility is found to have disappeared, and remains absent for a longer or shorter period. The insusceptibility acquired may last throughout a lifetime—as is usual in small-pox, for example—or may speedily be lost, as in pneumonia and influenza.

This observation that one attack of an infective malady can to a greater or less extent protect from subsequent infection by the same disease is probably one of the oldest in medicine, and its practical application is of some considerable antiquity. During the plague at Athens it was recommended by Thucydides that the care of those attacked should be the duty of the convalescents, since they would not thereby acquire the infection.

Again, the custom of variolation against small-pox was already old in 1717, when Lady Montagu first introduced it into Western Europe from Constantinople, where it was then a usual procedure. And long before that date, in India and in China it had been the custom to seek a similar protection by

means of insufflations of the powdered material of dried small-pox scabs.

Similarly, we are told that certain tribes on the West Coast of Africa have been for many generations, and still are, accustomed to expose their children to the contagion of frambœsia, which runs a more favourable course in early life. And even among European mothers a similar course of conduct is not unknown with regard to the infection of rubeola.

These practices, though venerable, were purely empirical, and it is only within the last few years that we have begun to have some knowledge of the intimate processes concerned. These processes, and the conditions which affect them, we must now examine.

If a number of animals of different species be subjected to the action of the same infective agent, some only are found to be susceptible to its influence; others invariably remain indifferent. And of the members of a susceptible species exposed to an infection by an epidemic of a given disease some only will acquire the disease, while others, under apparently identical conditions, escape attack. Among the latter are included those which, by recovery from a previous attack, were rendered insusceptible. But there remain a number which have not thus been rendered insusceptible, but which can none the less successfully resist infection. And yet of these a certain portion may in a later epidemic prove susceptible, and even highly so.

The condition special to such individuals or species as show themselves either continuously or on occasion insusceptible to a specific virus is called immunity to that virus: it is the converse of predisposition.

This condition is only relative, not absolute. It is the function of two variables—the resistance of the organism and the virulence of the infective agent; accordingly, it varies with their variations. Hence, by increasing the virulence of a particular bacterium we may enable it to be successful in attack upon an animal which could previously resist it, or by sufficiently attenuating the same property we may deprive the bacterium of its power to invade a previously susceptible animal, which is thus found to be immune to the attenuated virus. Again, the virulence of the infecting agent remaining constant, we can increase the resistance of the animal —without reference to specific treatment—by increasing in any manner its general health and well-being, or, on the other hand, can lower it by any procedure which will lower the general level of the normal metabolic processes. Very numerous experiments have been made in this direction. Thus, Canalis and Morpurgo found that in inanition pigeons become susceptible to anthrax; Fermi and Salsano showed that at abnormally high temperatures chickens are easily attacked by tubercle; and Pasteur and Wagner observed that when subjected to low temperatures the same animals became less

immune to anthrax. Similarly, immunity may be diminished by anæmia, deprivation of water, dyscrasias of the blood, fatigue, nerve-poisons, extirpation of organs, general diseases (such as diabetes), bad food, and many other causes.

Immunity, then, is a purely relative condition. It is therefore easy to understand why an individual who has successfully escaped one epidemic of disease may, on a subsequent occasion, show himself susceptible to the same disease, either because his own resistance has become lowered, or because the virulence of the bacterium in question has been heightened.

The grade of insusceptibility which pre-exists in any individual or species to any given infection we speak of as a natural immunity to that infection. Its production and perpetuation in the species are to be referred to the action of natural selection and the survival of the fittest in the struggle for existence, just as are the other physiological and morphological distinctions which demarcate different species from each other. Like other race peculiarities, it varies in the extent to which it is developed in different individuals of the same species.

In contrast to the natural immunity of individuals or species—the refractory state, as it was called by Buchner—is the acquired immunity of convalescents from acute infection, which, being due to an individual reaction, is of necessity peculiar to the personality concerned. This form of immunity was

naturally the earliest to attract attention, and, as I have already told you, attempts were made to procure immunity against small-pox, then the most terrible scourge of Western Europe, by imitating the method of Nature—that is to say, by variolation.

The means employed consisted in inoculating with material from the ripe pocks of persons ill of the disease, with the object of inducing a mild attack, and of thereby removing the chance, then almost a certainty, of subsequent more severe infection. But the results which followed were both variable and dangerous, for not only were the cases thus produced themselves infectious and capable of spreading the infection, but they were liable on occasion to develop the virulent disease from such inoculations, and death at times resulted. The procedure, therefore, was unsatisfactory, and failed to gain a general acceptation.

It remained for Jenner to lay the foundation of all later progress in protective treatment by his most thorough and fruitful study of vaccinia, as the result of which, after more than twenty years of patient labour, he first employed in 1796 his method of vaccination, and two years later published his discoveries which made small-pox, then only less terrible in its devastation than the Black Plague of the preceding centuries, a preventable disease.

The protection thus afforded was at first believed to be complete and permanent, but this has proved

to be in part an error. The vaccination needs to be renewed at intervals in order to maintain complete protection. But it has been abundantly established that where the inoculation is thoroughly performed and properly repeated at suitable intervals—as, for example, in the Prussian army—variola has become unknown.

Little progress was made from the position reached by Jenner's labours until the latter half of the last century. The first advance was due to Nägeli and Buchner, who systematically investigated the question of immunity, and placed its phenomena in relation with the process of spontaneous recovery from acquired infections. They were speedily followed by Pasteur, who first prepared suitable vaccines for inoculation, and thus was able to procure in fowls immunity to fowl cholera. Then, after a short delay, came the remarkable discovery of Behring, that the blood-serum of animals which have acquired immunity against a specific microbe is protective for other animals not otherwise immune.

The immunity thus induced by the injection of serum from immune animals was, however, found to differ from that which follows vaccination or recovery from disease in being only of a brief duration. It was named *passive* immunity by Ehrlich, in contrast to the *active* form produced by the reaction of the animal itself in an acquired infection.

Besides these forms of immunity, Ehrlich and

others have further shown in certain cases the existence of inherited immunity in new-born offspring of those animals which have themselves acquired active immunity against a given disease. This inherited immunity is quite distinct from the hereditary immunity of a whole species to a particular infective agent, which, being naturally transmitted by the parents, is spoken of as a natural immunity. It is, as we shall see, transmitted by the mother only.

Accordingly, we have to consider the following varieties of immunity :

Natural (hereditary) immunity.

Acquired immunity : (*a*) Active, by recovery from inoculation or natural infection ; (*b*) passive, by protective substances.

Inherited immunity : from actively immune mother.

So far we have seen that in the process of recovery from an infective disease there is developed an immunity to that disease ; further, that the immunity of any given animal to any given disease, whether it be natural or acquired, can be increased or diminished by events which modify favourably or unfavourably the general activity of metabolic processes. And it had been found in the course of the researches awakened by the opposition to the homœopathic school of Hahnemann and his disciples that one and the same agent may act now favourably and now unfavourably, according to the amount or dose

in which it is employed. These investigations led, with other observations, to a conclusion of extreme importance, clearly enumerated among the first by Hueppe, Arndt, and Schulz, that every agency which can in a certain concentration kill or injure the cell-protoplasm of a living body will, in a smaller concentration, and on the other side of an indifferent point, act to the advantage of that protoplasm by rousing an increase of its activity.

This principle is fundamental both for experimental and for clinical medicine. It holds alike for the bacterial products and for chemical substances, and forms the basis of all useful treatment. It is this question of the concentration of the virus which determines whether infection shall provoke acquired immunity, or from the failure of the immunity reaction end in death. We have already had a good example of these facts in the phenomena of localized bacterial inflammation where, in the focus of the inflammation, cell-necrosis is predominant, while at a distance, where the toxins have become diluted, cell-proliferation is the marked feature.

Following this principle of the concentration of the causal agent in disease, Pasteur, in 1880, found that the bacterium of fowl cholera could be artificially reduced in its infective and intoxicating power, or, as we usually say, attenuated, so that on inoculation it produced not general infection and speedy death, but merely local and reactive inflammation. And animals thus treated were found to have become

immune to the unattenuated micro-organism. These results were soon confirmed by numerous observers, who made use of a variety of methods of attenuating the bacteria which they employed. Among the methods used the most interesting was that of Duguid and Burdon Sanderson, who discovered that the passage of a bacterium through the body of one animal often results in the attenuation of its virulence for a different species.

The immunity produced by such inoculations is specific, and in general affords protection only against the particular species of bacterium employed; and, indeed, it is not merely specific, but is also, to a great extent, peculiarly *special* against the *particular variety* of the bacterium concerned which has been used for the inoculation, as was shown originally by Herbert Durham for the bacillus of enteric fever.

Though immunity was thus produced by the employment of attenuated cultures, yet it was thought that some degree of remaining virulence was essential, until Hueppe showed, in 1887, that cultures which have entirely lost their pathogenetic properties can still induce immunity to the fully virulent bacterium. But it appeared most clearly from all the experiments that the infective agent used to induce the immunity reaction must always (leaving aside a few particular exceptions, to which we shall return) be of the same character—that is to say, of the same species as that against which the

immunity is desired. The immunity produced is therefore of specific, or, more correctly, isopathic, character.

After immunity has been induced by means of an attenuated micro-organism, it can be further increased by subsequent inoculations with more and more virulent varieties of the same organism, until a condition of extremely high immunity is finally obtained.

The first and most successful application of these facts to medicine was made by Pasteur, in 1885, in the case of rabies, with the result that the mortality among persons subjected to the infection from the bites of rabid dogs has been reduced in France from 16 per cent. to below $\frac{1}{2}$ per cent. It consists briefly in the consecutive inoculation of the patient with material from a series of spinal cords of increasing virulence until a condition of immunity has been produced. The spinal cords employed are those of rabbits killed by inoculation with a virus of a fixed and maximum activity, and are prepared for use by drying them for different periods and thus producing greater or less attenuation of the infective agent present in them.

Haffkine endeavoured to employ a similar method of protection by successive vaccination with two cholera cultures, the one attenuated, the other of exalted virulence, during the cholera epidemic in India in 1893 and 1894, though with only moderate success; and Wright has applied the method of

vaccination against typhoid fever with excellent results.

After it had been shown by numerous researches that, in the case of many bacteria, pathogenetic action is due to the toxic action of soluble products which they liberate into the surrounding medium, it was discovered that immunity could also be produced by the injection of these substances apart from the bacteria, or by the injection of bacteria which had previously been killed.

There appeared, however, to be a striking difference between the immunity obtained by the injection of filtered culture fluids or of dead bacteria and that produced by the inoculation of toxins artificially separated from bacterial cultures, in that immunization with the former was protective only against the bacteria, and not against their separated toxins, while the latter protected against toxins, but did not confer immunity against the bacteria themselves. This discrepancy was due to the fact that, as we have already seen, the toxins as at first prepared were not in any sense the true bacterial toxins, but were artificial substances produced by chemical decompositions due to the action of the powerful chemical reagents used in their preparations. They were poisonous bodies, it is true, but they stood in no particular relation to the bacteria whose products they were said to be. Accordingly, immunity to these could not protect either against the bacteria or their natural products.

With the discovery of true bacterial toxins, such as the toxin of diphtheria as first prepared by Boer in 1896, and that of tetanus isolated by Brieger, Sidney Martin, and others, this difficulty disappeared, and it was proved that immunization against the specific toxins of these organisms confers immunity not only against those toxins, but against the bacteria themselves. The reason of this is easily to be understood. The bacteria in question produce their pathogenetic action through the agency of soluble toxins, which they secrete into the surrounding medium. If, then, an animal becomes immune to the toxins, the bacteria have no further means of injuring it—that is to say, it is immune to the bacteria as well.

If, on the other hand, an animal be immunized against a bacterium freed from its soluble toxins—by filtration through porcelain, for example—it does not usually acquire immunity against those toxins, but only against the bacterium itself. This is because by the conditions of the experiment the animal is trained to rapidly destroy the bacteria introduced. Accordingly, upon inoculation, they are killed before they have had time to elaborate and secrete more than a very little toxin in the body, and the animal, not having been subjected to the action of much toxin, will obviously not be found immune to it, if it be subsequently injected in large quantity. Thus, animals immunized to tetanus spores were found by Vaillard to still remain sus-

ceptible to tetanus toxin, since the tetanus spores which the animals received contain no toxin, but only form it after they have germinated into tetanus bacilli.

We have, therefore, the following results :

Injection of	*Immunity to*
Soluble Toxins.	Toxins and Bacteria.
Bacteria.	Bacteria only.

What I have spoken of as the soluble or excreted toxins are usually called the extracellular toxins of bacteria. Besides these, there are often present toxic substances in the bodies of bacteria—the intracellular toxins. To these is due the harmful action of the bacteria themselves, apart from excreted products ; and immunization against a bacterium means immunization against these substances, which become liberated on the death and destruction of the micro-organisms. Since, however, in any culture of bacteria, some are constantly dying and becoming broken up, a culture medium, even when freed from all bacterial bodies by filtration, will contain some, though it may be only little, of the intracellular materials, as well as of the extracellular metabolic products. This inoculation, therefore, will induce immunity to the bacteria as well as to their excrete products.

Among the pathogenetic micro-organisms some exert their action chiefly, if not entirely, through

the extracellular toxins—as, for instance, those of diphtheria and tetanus—while many others act in the main in virtue of their intracellular constituents, as in the case of cholera and typhoid, among others.

Besides the methods which I have already dealt with, specific immunity may be induced by the injection of the serum of an immunized animal (immune-serum), which can confer passive immunity upon the animal injected. This great discovery was due to Behring and Kitasato, who showed, in 1890, that the blood-serum of animals actively immunized against tetanus or diphtheria has a qualitative or specific protective power for other animals, whether it be injected before the toxin, with it, or only at a later period. The classical research of Behring forms the basis of our modern serum-therapy, and has resulted in the saving of many thousands of lives each year.

The power inherent in such sera of protecting against their corresponding toxins was described as antitoxic, and is attributable to the action of a body or bodies present in the serum known as anti-toxin.

The immunity, which is produced by means of antitoxin, in contradistinction to that produced by vaccination with the bacterium itself, is of only comparatively brief duration. The protective substances injected, if not employed in the destruction of their corresponding toxin, are excreted in the urine and

otherwise disposed of by the animal body, and the immunity which has been conferred is quickly lost.

The immunity conferred by antitoxic serum appears at once on the injection of the antitoxin. It requires no lapse of time for its development; it must, therefore, of necessity be independent of any correlated action or reaction of the body cells. Accordingly, it was named by Ehrlich *passive* immunity, in contrast to the *active* form evoked by cellular reaction to the injection of bacteria or their products, and it is believed by him to consist merely in a transference to the animal injected of certain protective, immune substances, and is not in any sense whatever histogenous.

Up to this point we have spoken of all such sera as antitoxic sera. It is, however, more convenient and preferable to confine the term 'antitoxic sera' to those sera which are especially active against toxins, applying the name 'antimicrobic sera' to such as have their action on the bacteria themselves, and using the general term of 'immune sera' to include the two.

The methods of producing an immunity hitherto discussed are of specific nature, and result in a specific protection. There are, however, certain non-specific means by which immunity can also be induced. So long ago as 1877 Pasteur had noted that, if animals susceptible to anthrax be inoculated with a mixture of this bacillus and other bacteria, the anthrax is unable to produce disease, and many

similar discoveries soon followed. And it was shown, for example, that inoculations with the *Bacillus pyocyaneus* can evoke immunity to anthrax. These observations led to the enunciation of two different views in explanation. The first was due to Hueppe, who held that the result was due to stimulation and increased activity of the normal protective processes or substances of tissue cells. The second, that of Klein, was that in cases of this kind the bacterial toxins were identical, and consequently inoculation with one variety of bacterial products resulted in protection also against the other. To this question I shall presently return.

It was, moreover, shown by various observers that in many cases cultures of pathogenetic bacteria could be destroyed by the agency of saprophytic forms. Hence arose an endeavour to seek a cure for the bacterial diseases in a therapeutic use of saprophytes. Cantani was the first to venture on this method of bacterio-therapy, using bacteria of putrefaction in an attempt to induce the healing of tuberculosis. He was followed by many others, among whom I need only mention Coley, who introduced the injection of bacterial products in a solution known as Coley's fluid for the treatment of inoperable malignant growths. Here, also, any result that is attained must be attributed to a non-specific stimulation of the normal protective processes. In what such stimulation may consist can, to some extent, be gathered from a consideration of the

results of inoculation with heterogeneous—that is, non-bacterial—substances.

Already, in 1888, Wooldridge had found that he could, by the injection of ' tissue fibrinogens,' obtain protection against anthrax. Then it was found that similar protection followed inoculation with digestive ferments in the case of cholera, with spermin, with emulsin, with cinnamic acid, and numerous other bodies, and finally with such simple substances as culture-broth or normal salt solution.

Now, Issaeff has shown that the uniform result which follows these injections is the production of remarkable leucocytosis, and that the appearance and duration of the immunity coincides with occurrence and persistence of the leucocytosis. And Bordet has found by other methods that at the same time phagocytosis of bacteria is much increased coincidently with the increase of leucocytes.

All the methods, then, which give rise to non-specific protection have this in common—that they produce a marked leucocytosis. So far as information goes, they have no other common factor. There is, therefore, evidently some close relation between the two events—leucocytosis and the destruction of bacteria (bacteriolysis).

This observation is of great importance for the phagocytic theory of immunity, of which I shall speak directly. With it may possibly be correlated the clinical success attending laparotomy for early peritoneal tuberculosis, and the production of a local

congestion by Biers' method in tuberculosis of extremities. It probably also bears upon the doctrine of Rokitansky that lung tuberculosis is rare in conditions associated with lung congestion, but common in those leading to chronic anæmia of that viscus.

So far we have seen that acquired immunity can be artificially induced by the following methods :

1. Specific : (*a*) Bacterial inoculation ; (*b*) inoculation of bacterial products ; (*c*) inoculation with specific immune serum.

2. Non-specific : (*a*) Inoculation with other bacteria or their products ; (*b*) with heterogeneous material.

The specific acquisition of immunity by natural disease is evidently the same process as occurs after inoculations in the laboratory, and leads to the appearance of the same protective substances in the serum of the convalescent. In the same category comes the inherited immunity of which I have already spoken. This is transmitted only through the mother, and is acquired *in utero* by the fœtus. *Passive* immunity can also be transmitted to the offspring by the mother's milk if she be rendered actively immune.

We must now proceed to a consideration of some of the more important theories which have been advanced in explanation of the phenomena of immunity. Of these, the earlier suggestions only need a cursory reference.

The view of Pasteur, commonly spoken of as the

Exhaustion theory, was that bacteria in their growth within the body require the use of, and eventually use up or exhaust, some pre-existing substance of the body which is necessary to their growth and propagation. This substance having been exhausted, the body ceases to afford a suitable culture medium for their cultivation, and is in consequence immune.

With the discovery of Behring that immunity can be *transferred* from an immune animal to the unimmune by transference of serum, this theory became at once untenable.

Similarly, the *Retention* theory of Chauveau, according to which the immunity following inoculation or disease depended on the retention in the body of some hypothetical bacterial product inimical to the growth of the bacterium in question, and thus protective from a fresh invasion, although in harmony with the observation that the excreta of bacteria, as of other animals, are in general deleterious to their well-being, was yet entirely unable to explain how an immunized animal, after bleedings amounting in a brief period to more than the total normal blood-content of that animal, could still continue to possess and yield an immune serum of practically undiminished power, though this was shown to be the case by Ehrlich.

More fortunate was the *Adaptation* theory of Grawitz, which attributed the phenomena in question to a gradual adaptation of the body to resist the injurious action of the invading micro-organisms.

This view of Grawitz may be looked on as in a measure the parent of the modern cellular theory of immunity.

Coming, then, to the more recent views, we are concerned with three chief theories of immunity :

1. The Cellular or Phagocytic theory of Metchnikoff.

2. The Humoral theory of Grohmann (1884) and his supporters (Flügge, etc.).

3. The Humoro-cellular theory of Bouchard.

These we shall now consider in their order and mutual relation.

Cellular Theory.—So long ago as 1864 Traube and Geschleiden showed that the animal body quickly disposes of bacteria introduced into it by artificial means. Such a power must depend in essence more or less directly on the protoplasmic functions and activities of the body cells.

Again, the local reaction to local bacterial infection, just as to other causes which lead to local injury of tissue without involving its immediate destruction and death, was seen to consist in the process of inflammation which we have already discussed. Now, in this process, as we have seen, the wandering cells of the body collecting at the focus of infection are found to be engaged in actively attacking the invading micro-organisms. Certain, also, of the fixed cells of the tissues possess this so-called phagocytic power, and play their part in the reaction concerned. Accordingly, Metchnikoff was led, in 1883, to the con-

clusion that on the functions of the phagocytes depend the essential elements of protection. To this class of phagocytes belong the following varieties of cells, as Metchnikoff believes: Macrophage (large mononuclear) and microphage (polymorphonuclear) leucocytes of the blood, wandering cells of the tissues, connective-tissue corpuscles, endothelial cells, cells of the spleen pulp, and the sarcoplasm of voluntary muscle fibres. This group of the phagocytes can be traced downwards through the animal series to the earliest forms in which differentiation of function first appears among the cells of the organism, and still lower the same properties are exhibited by cells of yet undifferentiated function, and, finally, by the simple unicellular protozoa themselves. We have, then, here a cell reaction invariably present and universal throughout the animal kingdom from the lowly protozoa up to man, and which might well serve as the natural basis of immunity. The production of immunity would then consist, as Metchnikoff believes, in the gradual heightening and extension of this natural reaction.

Next followed the discovery of Stahl and Pfeiffer, made originally on unicellular plants in 1884, of the phenomenon of Chemiotaxis, and it was found that the determination of phagocytes towards the centre of infection was the result of chemiotactic influence or allurement exercised on them by the soluble products of the bacteria in question.

It was not clear, however, whether the bacteria

taken up by phagocytes were killed by them, or whether they had first been killed by other agencies, and only subsequently ingested by the phagocytic cells like any other inert foreign substance. And it was held, in opposition to Metchnikoff, that only dead bacteria were thus attacked by leucocytes. Lubarsch then proved that living bacteria are actually taken up, and, indeed, in immune animals are taken up more quickly and in greater numbers than are dead ones.

But it was now seen, on the other hand, that the bacteria thus ingested by the white cells are not invariably nor necessarily killed by them. Thus, Trapeznikoff showed that the spores of anthrax may live on within the leucocyte until the latter dies or is killed, and then proceed to develop and produce their usual effects ; and similar facts are true for tubercle bacilli and the giant cells of tubercles.

Further, Grohmann had shown in 1884 that cell-free blood possesses the power of destroying bacteria introduced into it. This was confirmed for anthrax by Fodor in 1887, and Nuttall in the following year published a whole series of experiments on the defibrinated blood of certain animals which he showed possessed a bactericidal power for anthrax.

LECTURE VII

We considered last lecture some of the older theories of the nature of immunity, and discussed the earlier evidence bearing on this question. Thence we passed on to a consideration of the more modern views. Here we began by an examination of the Phagocytic theory which was held by Metchnikoff, and of the evidence on which that theory rested.

We saw, however, that though invading micro-organisms may be taken up by phagocytes, they are not necessarily destroyed, but may survive and multiply within them. The phagocytes may thus themselves be killed, and the bacteria again set free into the blood and tissues to continue their invasion. It follows that the phagocytic process does not of itself insure the destruction of bacteria.

Moreover, as I told you, it was shown that cell-free blood possesses a bacteriolytic action. Accordingly, the Phagocytic theory of immunity, on which the destruction of bacteria was entirely due to their ingestion by the phagocytes, became untenable.

The observations which threw doubt upon the

view of Metchnikoff led Grohmann to the enunciation of the so-called Humoral theory. This held that the destruction of bacteria is dependent on the action of certain substances existing in the body-fluids, and not upon the phagocytic process.

The question was now taken up by Buchner and his pupils, who confirmed the observation that the body-fluids may exert bacteriolytic action both in the living animal and *in vitro*. Moreover, Buchner showed that blood which had been frozen and thawed, and the leucocytes thus broken up, was almost as actively destructive of bacteria as normal blood, although, of course, no phagocytic action could now occur. On the other hand, its power was rapidly diminished if it were slowly heated, and was entirely lost at 55° C. Accordingly, he was led to attribute the protective action of the body-fluid to a purely chemical action of certain substances existing in them in solution, and which he termed 'alexines,' and regarded as being of the nature of active ferments.

Buchner found these alexines to be extremely labile substances—to be, as I have said, exceedingly susceptible to the action of heat; to lose their power if substances favourable to the nutrition of bacteria were added to the solutions, or if the sera of different animals were mixed together; to require for their action the presence in solution of certain salts; and to be performed in the serum, from which they disappeared on the precipitation of its proteids with alcohol.

Many of the later experiments, however, gave contradictory or indefinite results, while Metchnikoff and his followers were continually producing further evidence to support the cellular theory. Thus they found that anthrax spores, freed from all anthrax toxins, and inoculated in the rabbit, are rapidly destroyed by phagocytic action, and the animal remains unharmed. But if the spores be introduced, enclosed in a collodion capsule by the method of Sanarelli, and thus protected from direct attack by phagocytic cells, they develop to bacilli which produce their usual toxins, and presently bring about the death of the animal concerned.

Yet many facts remained incapable of satisfactory elucidation on the phagocytic theory, while, on the other hand, the results obtained by its supporters, as much as those advanced by its opponents, rendered the purely humoral theory of immunity quite insufficient. Hence arose the view, attributable more especially to the influence of Bouchard, and which is usually spoken of as the humoro-cellular or cellulo-humoral theory. This theory forms to-day the only really tenable position on the general question.

The process involved consisted, on the view of Bouchard, in the simultaneous action of two forces: the bactericidal power of serum and the phagocytic activity of the leucocytes. Before the latter force could come into play there must occur in the acquisition of immunity a chemical alteration or modification of the blood-plasma. Certain bacterial products

were supposed to produce this alteration in the composition of the body fluids by gradual changes, which they brought about in cell-nutrition. The altered fluids then reacted on the bacteria in such a way as to destroy their power of resisting the attack of the phagocytic cells.

Metchnikoff had himself, in 1889, been driven to the admission that at least a part of the bactericidal action *in vitro* is attributable to substances present in the serum, but these he claimed were yielded to it by the leucocytes destroyed in the process of coagulation of the blood, and separation from it of the serum. On this question a whole series of monographs have appeared, commencing with the observations of Hankin and of Kanthack and Hardy in 1892, and carried on by Loewy and Richter, von Fodor, Denys and Lecelf, Havet, Buchner, Bordet, and many others. Into these it is impossible to enter fully, but the results may be summarized as follows :

The fresh blood or serum of an immune or an immunized animal possesses a bacteriolytic action, and this action is greatest when the animal concerned presents a condition of marked leucocytosis, and is diminished when the leucocytic count falls below normal. Again, if sterile pleural exudates rich in white corpuscles be artificially produced—for example, by the injection of plant globulin into the pleural cavity of a rabbit—they are found to be possessed of high bacteriolytic power, even for bac-

teria on which the blood of the same animal exerts only a small, if any, bacteriolytic action. And it was shown that the bacteriolytic action of these exudates is associated with the presence in them of enormous numbers of leucocytes; for if these corpuscles be rapidly separated from the fluid by filtration the bacteriolytic action disappears, but is at once restored on their replacement. If, on the other hand, the leucocytes are not removed, but merely broken up and disintegrated in the fluid by the process of freezing and then thawing it again, bacteriolytic power remains.

Accordingly, we have the following conclusion: that leucocytic fluids possess bacteriolytic power outside the animal body; and cell-free fluids may exhibit similar action, but only actually appear to do so when they presumably contain the products of disintegrated leucocytes. Bacteriolytic power is therefore evidently in close association with the reaction of the leucocytes.

In the passive immunity induced by the injection of immune serum, Metchnikoff also claims a considerable share for phagocytosis, holding that the action of the serum consists to a large extent in a stimulation of the leucocytes and a consequent increase of their activity and numbers, such as we have seen can be induced in a less special manner by the injection of a great variety of indifferent substances. Pfeiffer, however, who found that anti-cholera serum possessed no antimicrobic power *in*

vitro, but became rapidly bactericidal after injection in the living animal, showed that in the intraperitoneal experiment the injected cholera vibriones are not infrequently almost entirely destroyed before the appearance of any considerable number of leucocytes can be determined. Hence, he arrived at the conclusion that the serum owed its activity to the agency of other cells than leucocytes, and probably to the endothelial cells lining the peritoneal membrane. But in this connection it must be remembered that the endothelial cells also belong to Metchnikoff's group of phagocytes, being classified by him as of the class of the ' fixed ' phagocytes.

In intimate relation with the questions of bacteriolysis and immunity to bacterial infection are the phenomena of immunity to toxins.

At the lowest level in the scale of existence we already find certain forms of life that are unharmed by toxic substances which prove markedly and rapidly fatal to other forms. And here again we can by appropriate methods induce immunity in the susceptible forms. The bacteria themselves afford excellent examples of this principle. Thus the bacillus of fowl cholera is destroyed by a solution of corrosive sublimate in a dilution of 1 to 25,000, while Friedländer's pneumo-bacillus is naturally immune to this solution, and is only killed when the dilution is reduced to 1 to 15,000. Again, Trambusti found that the latter bacillus could be accustomed—that is, immunized—to the

presence of sublimate to such an extent that it could still exist in the presence of a concentration of 1 to 2,000. In the same way Effront was able to immunize yeasts, and Haffkine to adapt the infusorian *Chilomonas paramœcium* to exist in strongly alkaline solutions. And many other investigations have given similar results.

An interesting example of the essential difference between this toxin immunity and bacterial immunity is found in the observations of Metchnikoff on certain larvæ which are immune to cholera toxin. Such larvæ, he found, support a dose of toxin which proves rapidly fatal to the frog. On the other hand, if living cholera culture be injected the larvæ die of general infection with doses from which frogs invariably recover. In the latter case, the leucocytes of the frog attack and render harmless the bacteria, while those of the larvæ fail to achieve a similar success.

After the remarkable discovery of Behring, already mentioned, of the antitoxic properties of immune serum, an explanation of the facts observed was naturally sought in the supposed occurrence of a pre-existing antitoxin in the blood of the animals in question. But numerous investigations absolutely failed to show the existence of such bodies in the naturally immune, so that Behring was able in 1896 to formulate the statement that the blood of naturally immune individuals possesses no specific antitoxic properties.

The accurate investigation of toxin immunity dates from the discovery by Roux and Yersin, in 1888, of true bacterial toxins. Their observations, and others to which I have already briefly referred in speaking of the bacterial products, have helped to throw much light on the difficult question of bacterial antitoxins. It has been further shown that antitoxins similar in their properties, in their specific character, and in their general action to the bacterial antitoxins, can be obtained by the inoculation of toxins of non-bacterial origin. Such were the antitoxins obtained by Ehrlich against the powerful toxic bodies ricin and abrin.

As regards the mode of action of such antitoxins, the view originally put forward by Behring held that the process at work consisted in a simple neutralization of the toxin, and was a purely chemical phenomenon. This position was supported by Roux and Vaillard in a series of experiments on the antitoxin of tetanus. Buchner, however, came to the conclusion that the antitoxin in some way inhibits the toxin in the organism without actually causing its destruction, for he found that mixtures of the two substances can be prepared which are harmless for mice, but prove fatal to the more highly susceptible guinea-pig. Behring, on the other hand, urged that in the mixtures of Buchner a true neutralization of the toxin occurred, but that with the proportions taken there remained over a certain amount of the toxin which had not been neutralized, and which,

though insufficient to injure mice, was still enough to cause the death of guinea-pigs.

The principle involved in this interpretation is one of the greatest importance to a clear conception of the events concerned in the causation of protective processes—namely, that whatever be the infective agent, or the toxin, and whatever the animal employed, there must always exist a certain minimal dose, quantities less than which fail to produce the usual infective or intoxicating action—that is to say, that in all cases the *basis* of immunity is already present in the animal. Moreover, Ehrlich, Cobbett, and others have definitely proved that the reaction of toxin and antitoxin—the neutralization of the former by the latter—can take place just as well in test-tubes as in a living animal, and therefore necessarily must be a purely chemical event. And recently Arrhenius and Madsen have clearly shown that the relations of the two are strictly quantitative.

We have in this relation to keep most carefully and constantly in mind the clear and well-established difference which exists between anti-bacterial and antitoxic action in endeavouring to explain the process of protection. This distinction is most clearly marked, and all the evidence goes to show that the protective processes concerned are essentially divergent.

One and the same bacterium may be at one time a harmless saprophyte--say, in the human pharynx

—while at another it may gain local access to the tissues, and, producing there its toxins, give rise to an intoxication ; or, again, it may, under suitable conditions, be induced to cause a general infection of the animal. But any given bacterium must at a given time fall under one or other of these groups as regards an individual animal. And the condition of the serum after infection is found to exhibit corresponding properties. Thus, if the bacterium falls into the second class, and can only gain a local hold upon the tissues, it there produces toxins which diffuse throughout the organism and give rise to the formation of an antitoxin. On the other hand, if it acquire invading power superior to the natural resistance of the phagocytes, and cause a general infection, there will appear, in animals which tend to make recovery, a new induced reaction directed to the micro-organisms themselves. The serum, then, is found to have acquired anti-microbic action in addition.

Of these two properties—antitoxic and antibacterial — we shall consider first the antitoxic action.

In speaking of the protective substances of immune sera, and of the views of Buchner, I used his term ' alexines ' to denote these substances. This, as perhaps appearing to involve the acceptance of a definite but ill-supported theory, we shall now relinquish in favour of the inelegant but more general term of ' anti-bodies,' or ' anti-substances,' retaining

the name ' antitoxins ' to connote the anti-bodies of toxic substances. These anti-bodies have been in recent years most carefully investigated, more especially by the school of Ehrlich—himself the most brilliant investigator of the day.

The true bacterial toxins being in themselves difficult to prepare, and from their instability and complicated nature still more difficult to investigate, much of the evidence with regard to antitoxic sera has been obtained from the results of observations on other and more accessible substances which give rise to a similar formation of anti-bodies. Among these I may mention more particularly certain vegetable poisons, such as ricin and abrin, the venom of snakes and scorpions, and certain enzymes, notably rennet ferment.

The evidence obtained from these and similar sources we shall now examine.

If a bacterial toxin be injected in successive and increasing doses, it gives rise to the formation of an antitoxin by the animal. The action of the antitoxin so produced is found to be specific—that is to say, it acts in general only against its own specific toxin. This *qualitative* action led at first, and naturally, to the view which was proposed by Buchner, that antitoxin was in some way derived from the injected toxin. And certain observations of Klemperer and others seemed to support the theory. The position was, however, shown by Ehrlich to be quite untenable on the following

grounds : Firstly, that we can, by the introduction of a given dose of toxin, obtain a quantity of antitoxin able to neutralize the original amount of toxin a hundred thousand times and more. And, secondly, that the active toxin immunity induced will last for a considerable period—in some cases for years, or even for life—while passive immunity, which follows the injection of an antitoxin, is quickly lost ; whereas if antitoxin consisted merely of a modified toxin, its length of stay within the animal body could not be affected by its manner, whether of production or of introduction, but would depend solely on its amount.

Moreover, Roux and Vaillard showed that an actively immunized animal, whose blood had acquired a constant antitoxin content, rapidly regained this antitoxin level after repeated and copious venesections, even after the last remaining traces of the toxin originally injected must long have been abstracted from the blood in consequence of the frequent and free bleedings.

That the formation of antitoxin is essentially a *cellular* reaction is further proved by the observation of Salomonsen and Madsen that the antitoxin content of the blood could be increased by the administration of substances such as pilocarpin, which are known to stimulate the secretory activity of the body cells, but could not possibly affect the injected toxins.

As the result of observations such as I have men-

tioned, Ehrlich was led to the opinion that these substances cannot be other than ordinary normal products of the cellular metabolism. Their production by the animal can be explained upon the following supposition, which forms the one and only necessary postulate of this theory—namely, that certain cells susceptible to the action of a given toxin contain particular elements or atom-groups, more or less independent and detachable, which possess a strong affinity for that toxin.

Now, so long ago as 1885 Ehrlich had come to the conclusion, in considering the oxygen requirement of the organism, that the protoplasm of every living cell must of necessity contain numerous groups of such elements, destined in normal metabolism to attract and store nutritive substances which, as we know, circulate in the blood in very weak solution. To these hypothetical groups of elements he gave the name of lateral chains or side-chains. Such chains could evidently also take up from the blood any toxic body for which they happened to have a strong affinity. Thus, nerve cells whose side-chains possess a very strong affinity for tetanus toxin abstract it from the circulating blood and incorporate it by their hypothetical side-chains.

Now, toxin thus fixed maintains its attachment to the cell concerned for a considerable period of time. There must therefore be in the side-chain a group of atoms in which one atom-complex—spoken of as the haptophore group—corresponds

to the toxin and fixes it in much the same way as a key fits its lock.

But once this process of fixation has occurred, and the haptophore group is anchored to the toxin, the lateral chain is no longer free to exercise its usual function of attaching molecules of nutritive material ; it becomes, so to speak, cut off from the physiological functions of the cell in question. The cell, therefore, to regain its normal functions, must constantly produce new chains. Now, for such regenerative processes there is a general law, which Weigert formulated, according to which there occurs not compensation merely, but always *overcompensation* for what has been lost, so that more side-chains will be produced than had been previously fixed by toxin.

If, now, the new chains thus formed are constantly being charged with fresh supplies of toxin by repeated and increasing fresh injections, a constant locking up and loss of side-chains will go on, which is continually compensated for and overcompensated, and the cells become thus habituated to the production of a great excess of these particular elements. Finally, so many chains are formed as actually to become prejudicial to the metabolism of the cell, which accordingly gets rid of them into the blood like any other waste or prejudicial product.

The chains set free into the blood compose and are the antitoxin, which by its strong affinity fixes the toxin then or subsequently present in the cir-

culating fluids, and thus prevents its reaching organs which it otherwise attacks and injures.

This is the theory of Ehrlich. It is hypothesis, and not established fact; but it provides us with a view to work from which is eminently logical and satisfactory. It rests on a recognition of the fact that processes akin and quite analogous to the formation of an antitoxin go on continually in the living body, and form a necessary part of normal physiology, and that the majority of intermediary metabolic products provoke a formation of new lateral chains in certain groups of cells, either in moderate amount, or, it may be, in quantity sufficient to give rise to an excess, which is discharged into the circulating fluids as waste matter. Thus, the blood-plasma must normally contain numerous substances which have resulted from the elimination of side-chains by various tissue cells.

Analogous reactions can undoubtedly be artificially induced in the laboratory by means of various non-poisonous substances, and even with ordinary nutritive materials.

This view exhibits the production of immunity to toxin in the animal body as a process holding a position exactly parallel to that presented by the habituation of a bacterium or a protozoön or plasmodium to nutritive media containing substances normally prejudicial to their life and growth, and as depending on a gradual modification of the intimate physico-chemical processes of its metabolism.

The great beauty of this hypothesis lies in the fact that it at once explains (as Ehrlich himself has claimed) all the apparently marvellous and unique characters of the antitoxins. Thus, their specific action, though they are not derived from the toxins, results from the fact that the condition and cause of the toxic action of the toxin lies in the special affinity of its haptophore for the haptophores of certain lateral chains of the cells which it attacks, for these are the lateral chains which constitute the antitoxin. Similarly, we find here an explanation of the relatively great production of antitoxin which results from a methodical immunization, and of the fact that the later injections only serve to increase the formation of antitoxin which is going on, as well as of the fact that the antitoxin content of the blood regains its former level after most copious and repeated bleedings. The theory also gives a reasonable explanation of the essential differences already noted between the active and the merely passive acquisition of immunity.

That toxin actually does become anchored to the cells in the way which Ehrlich has supposed was shown by Wassermann, who found that tetanus toxin mixed up and triturated with normal brain substance loses its toxicity by becoming 'fixed.' The lateral chains are adapted to the selection and fixation of nutritive substances, and toxins which excite the formation of antitoxins are, strange as it may appear, absorbed by the cell as though they con-

sisted of simple nutritive material. Their toxicity is not due to the same atom-group as that which is attracted by the lateral chain, and which is called the haptophore, but to an entirely different atom-complex of the toxin molecule, the so-called toxophore. For Ehrlich showed that toxins whose toxophores have been destroyed by artificial means, and which accordingly no longer have a toxic action, can still give rise to the formation of specific antitoxins, and this has been confirmed by Ritchie. The toxin molecule, therefore, is regarded as containing two different groups of atoms, the one toxic in character, and called the toxophore, the other harmless, but possessing a strong affinity for the side-chains concerned, to which accordingly it links the toxic molecule.

From this it follows that for the production of a given antitoxin the only elements essential are the proper haptophores injected in sufficient quantities. Hence any and every substance, whether toxic or indifferent, which possesses the same haptophore will, on injection into animals, give rise to the formation of the same antitoxic substance, and this in turn will be protective not alone against the substance used for its production, but against every toxin which may happen to possess the same combining haptophore. This is the explanation of the reason why, though antitoxins are specific in their action, yet cases do occur in which a particular antitoxin may be found to have protective action against quite

other toxins than the one which actually gave rise to its formation (tetanus antitoxin against snake-venom, etc).

The purely chemical nature of the reaction, and the quantitative relation existing between a given toxin and its antitoxin, was definitely proved by Ehrlich, who has shown, for instance, that the agglutinating action of ricin on the red corpuscles of blood is capable of quantitative neutralization by its proper antitoxin. Similar facts have been established by a number of observers for various other antitoxic substances. The most decisive of these observations were those made by Morgenroth on anti-rennin and the rennet ferment, where, in the absence of all protoplasm whatever, the purely chemical nature of the action of the anti-body is beyond question.

That the formation of such anti-substances is simply due, as Ehrlich holds, to an accentuation and increase of normal metabolic processes is shown by the discovery of Röder and Hammarsten that normal horse's serum frequently contains a powerful anti-rennin, formed under the action of the rennet ferment, which has been absorbed from their own stomachs in the process of digestion.

The action of an antitoxin is to neutralize or chemically saturate its toxin; it does not destroy the toxin. For a toxin which has been made inactive by the addition of its proper antitoxin can be restored to its full potency by an exposure of

the mixture to a temperature sufficient to destroy the antitoxic molecule. This usually occurs at about 68° C.

The lateral chains of cells, which have the power of taking up such substances as are provided with a proper haptophore, are now spoken of by Ehrlich as the cell-receptors. And since the normal products of metabolism, which are thus taken up for the nutrition of cells, are very numerous, the number and variety of these receptors must be very great indeed. But every substance which can find a suitable receptor in the living body will give rise to the production of its corresponding anti-body, if suitably injected in sufficient quantities to cause excess formation and the splitting off of new receptors from the cells affected. Accordingly, a very great variety of different anti-bodies may be formed by the same animal. A good example of this is to be seen in the results which follow the repeated injection of bacterial cultures. Such a culture contains, besides the bacteria themselves, a number of different products of bacterial activity, and each of these which finds within the living animal a suitable receptor gives rise to the formation of its corresponding anti-body. Thus, while the infection of a single chemical substance or a pure toxin results in the production of a univalent serum in the animal injected—that is, a serum containing a single anti-body only—the injection of mixed fluids like bacterial cultures leads to a multivalent action of the serum, which now contains

a number of anti-substances in correspondence with the substances injected. Such are the antitoxins, anti-ferments, agglutinins, coagulins, and the like, which may be coexistent in a given serum.

Moreover, if we inject into an animal a fluid containing cells or bacteria, these must be broken up and dissolved in the body fluids before the *intracellular* substances which they contain can come to act upon the body tissues and provoke the formation of the corresponding anti-substances. And if the cells be injected in a living condition, they must first be killed or die before these processes can be initiated. The anti-bodies then formed will be the antagonists, *not* of the living cell, but of their dead materials. Accordingly, though they prevent and neutralize the harmful action of bacterial products or of cellular derivatives, they do not kill the bacteria or the cells injected. Indeed, the immune sera, as they are usually called, frequently form admirable culture media for their own bacteria, although in other cases they may appear to have some inhibitory influence on bacterial growth.

It follows, therefore, that the events I have described in speaking of the production of anti-bodies, while they give rise to the formation of substances protective for the organism concerned against the action of extra- and intra-cellular bacterial products, do not in any way lessen bacterial virulence or kill the bacteria themselves. Accordingly, these events alone could never serve to put an end to the invasion of

bacteria, which, as was shown by Pasteur, undergo a progressive increase of their virulence by a successful residence within the body, were they not assisted, and, indeed, curtailed, by the intervention of another and more complex process. This is the process of bacteriolysis—that is, the destruction and solution of the micro-organisms themselves—which will form the subject of our next discussion.

LECTURE VIII

In the last lecture we discussed the formation and the action of antitoxins. We must now pass to the consideration of the anti-microbic processes within the living body.

In this relation we must first examine the function of the phagocytic cells. Here we are indebted first and chiefly to the laborious and distinguished work of Metchnikoff. This masterly observer, following the guidance of his own discoveries in comparative pathology and physiology, came, as we saw, to look upon the phagocytes as the essential agents in protection against living micro-organisms.

But his views received by no means general acceptation, and where his observations were not open to question, yet his interpretation of them at least was strongly combated.

Out of this opposition to the purely cellular theory of anti-bacterial action, at first conceived by Metchnikoff, there arose the humoro-cellular theory of which I spoke to you. This, in its turn, reacted on, and has considerably modified, the views of Metch-

nikoff himself. It maintains that at least a part of the bacteriolytic power of animals which have been immunized to a particular bacterium is dependent on chemical modifications of their blood-plasma, which now contains anti-bacterial substances. These substances, as we shall see, are almost certainly derived from leucocytes, and Buchner and his followers maintain, from their experiments, that they are really of the nature of a leucocytic *secretion*, but the evidence in favour of this view is quite unsatisfactory. Metchnikoff, on the other hand, attributes the presence of these bodies in the plasma or in serum to their *liberation by the destruction of leucocytes* occasioned by the action of bacteria in the body, or by the process of preparing serum. And such a view regards their origin as similar to that usually ascribed to fibrin ferment in the process of coagulation. The view of Metchnikoff has recently received additional and very strong support from the discovery of Gengou and Bordet, that plasma separated by a special method from the corpuscles without destruction of leucocytes occurring possesses no bacteriolytic power at all. It follows, therefore, that the leucocytic substance which destroys bacteria is not secreted by these cells into the plasma as a normal process, but only reaches it when it has been set free by a destruction of the leucocytes themselves.

In order to obtain some further evidence, we may next consider what takes place within the bodies of

infected animals. Now, when bacteria are introduced into the body of an animal naturally immune to the bacteria in question, they are seen to be rapidly taken up by leucocytes by a process to which Metchnikoff originally gave the name phagocytosis. Cells which possess the property of ingesting foreign particles are spoken of as phagocytes. They include the following groups : (*a*) All the leucocytes except the coarsely granular varieties, mast cells, and lymphocytes ; (*b*) the phagocytic wandering cells of the tissues ; (*c*) endothelial cells, the cells of the spleen pulp, and connective-tissue corpuscles ; (*d*) in rare cases nerve cells (in lepra) and the sarcoplasm of muscle. The first two groups form the free phagocytes, the others being spoken of as ' fixed.' Their property of taking up bacteria has been already dealt with in our discussion of the inflammatory reaction.

The phenomenon of phagocytic action occurs invariably in animals which are immune or have been immunized, and is a regular event wherever an infection runs a course favourable to the animal infected.

If bacteria be introduced by artificial means into the peritoneal cavities of immune animals, it *sometimes* happens that a considerable number are destroyed by extra cellular action in the peritoneal fluid, and not within the bodies of phagocytes. This fact was first observed by Pfeiffer in 1894 on greatly attenuated cholera vibriones, and is called Pfeiffer's phenomenon.

Metchnikoff, however, showed that if in this

experiment one employs a vibrio of normal virulence, phagocytosis becomes very marked. And this has been confirmed for many other micro-organisms.

It follows, therefore, that the phagocytic action is of great importance in relation to protection. And this was proved quite clearly by the discovery of Sanarelli that anthrax spores, protected from this *direct* cellular attack by being enclosed in a collodion capsule, developed into highly virulent anthrax bacilli within the body of an animal which easily destroyed spores not protected from the phagocytic action.

Metchnikoff, therefore, holds that the essential element in anti-bacterial immunity is phagocytic action, and that the destruction of bacteria is due to the action of bacteriolytic substances contained within the bodies of the phagocytes. He sees the origin of anti-bacterial substances, which may be present in a fresh serum, or in peritoneal effusions, in the extensive dissolution of leucocytes and attendant liberation of their anti-bodies which occurs when blood is shed, or as a consequence of intraperitoneal inoculations.

Now, before phagocytosis can occur, the phagocytes must first come into contact with the bacteria, either by bodily approaching them or by extension of their protoplasmic processes, or possibly, on the other hand, by attracting the bacteria to themselves. Accordingly, the determining factor of the phagocytic process is to be sought in the phenomenon of

chemiotaxis. This process I explained in our discussion of the rôle of leucocytes in inflammation. And it has been observed that, where immunity exists against a given bacterium, that bacterium exerts a positive chemiotactic influence upon the leucocytes of the animal in question. This, then, is the visible reaction which distinguishes immune or immunized animals from those which are highly susceptible to the bacterium concerned. Thus, Metchnikoff showed so long ago as 1884 that in unprotected rabbits injected with anthrax bacilli the micro-organisms multiply rapidly and remain for the most part free, while in a rabbit immunized to anthrax they are quickly ingested and digested by the phagocytes.

In the fact that even in the unprotected animal a few, and presumably the less robust, bacilli are similarly dealt with by the phagocytes, we find the basis of the immunity which can be artificially induced by the appropriate measures. And this we see is a precisely similar process, as De Barry pointed out, to the habituation of plasmodia, and the accompanying reversal of the negative chemiotaxis to substances normally unfavourable to their metabolic processes.

Hence it appears that anti-bacterial immunity depends on the degree to which the phagocytic process is developed against the particular bacteria in question. And these bacteria are taken up alive in full possession of their normal virulence.

But the serum of an animal which has been immunized against a given bacterium has been proved to be protective for other animals against an infection by the same bacterium. The same we saw was true of antitoxic sera. But while the neutralizing action of an antitoxin can and does take place equally well outside the living body as within it, these so-called anti-bacterial or anti-microbic sera, which, on injection into animals, lead to the destruction of bacteria in the body, exhibit no such action on the same bacteria in a test-tube—that is to say, antimicrobic sera have in general no bacteriolytic power. I say in general because, as I shall show you later, they do possess such power in marked degree when absolutely fresh from the body of the animal.

Professor Pfeiffer, starting from this observation that anti-microbic sera possess outside the body no bacteriolytic action, attributed their activity within the body to the intermediation of cells. He found, however, that, on the introduction of bacteria such as the cholera vibrio into the peritoneal cavity of an *immunized* guinea-pig, these micro-organisms were destroyed by a process of agglomeration, swelling up, and fragmentation without the intervention of a phagocytic action. The phagocytes remained entirely absent or only began to appear when the extracellular process was already well advanced, and such bacteria as were taken up he held to be already dead or dying.

This observation, which we call Pfeiffer's phenomenon, was confirmed and further investigated by numerous pathologists. They found, moreover, that the same phenomenon occurs in unimmunized animals if immune serum—that is, the serum of an animal which has been immunized—be introduced into the peritoneal cavity with the vibriones.

It was next shown that if such immune serum in an inactive condition—that is to say, incapable of killing the bacteria in a test-tube—be injected into the peritoneal cavity of a guinea-pig and samples subsequently removed at intervals, it is found after, say, twenty minutes to have undergone such modification that it has now become actively bacteriolytic, and can destroy the vibrios *in vitro*.

On the results of these and similar experiments Professor Pfeiffer based his theory that the protective substances which kill bacteria are modified and active forms of certain anti-bodies present in the immune serum. The former in their active condition are, according to him, exceedingly unstable substances, and easily destroyed. The organism, therefore, stores them in the plasma in a modified and inactive, but highly resistant form, from which it reconverts them when required by means of cellular action. And in the intraperitoneal experiment this action is ascribed by him to the endothelial lining of the cavity.

Metchnikoff, on the other hand, continued to lay stress on the degree of phagocytosis which he found

still to exist in all these cases, and attributed the origin of the protective bodies found in serum entirely to their liberation by destruction of leucocytes. The phenomenon of Pfeiffer is less marked, and phagocytic action the more evident, the greater the immunity which the animal possesses, and in highly immune animals bacterial destruction is entirely phagocytic. Moreover, Pfeiffer's phenomenon is more or less peculiar to the peritoneal cavity, which always contains large numbers of leucocytes liable to be rapidly destroyed by an injection ; and Mesnil showed that in the subcutaneous tissues the reaction is entirely phagocytic. The same is true of the intraperitoneal experiment itself after the injection of certain fluids (otherwise indifferent) which produce leucocytosis.

Again, Bordet showed that normal peritoneal fluid can render active an inactive immune serum *in a test-tube* (Bordet's phenomenon). Here leucocytes are the only cells which can possibly be present, and there is no question of a modifying action of protective bodies by the endothelium.

Taking the question broadly, it appears that the two great schools of Metchnikoff and Pfeiffer differ not so much on the facts of the phenomena observed, which are in general, and with only minor variation, fully confirmed by both, as in the construction and meaning which is put upon them.

Both now believe the protective substances to be produced by cellular action, though for the one the

cells chiefly concerned are the leucocytes, while for the other the endothelial elements have the greater importance. The endothelial cells, I may remind you, also belong to the phagocytic group of Metchnikoff. Both schools admit the occurrence of phagocytosis, though differing as to its relative importance, and both agree that anti-bacterial sera have no activity against bacteria outside the living body. But while Pfeiffer holds that its protective action when injected into animals is due to the agency of cells which modify and energize its *precontained* protective bodies, Metchnikoff maintains that this result is rather due to its stimulating action on the phagocytes themselves.

On this latter view the protective action of immune sera is of a similar kind, though specialized, and of a much higher degree than that which is produced by the injection of such various indifferent substances as I have mentioned under the methods of immunization.

Whether the breaking up of phagocytic cells, with the resulting liberation of the protective substances which they contain, is simply due to the effect of the injection only, or is occasioned partly by the action of special bacterial products which attack these cells, is not at present certain. But for one bacterium, at any rate (staphylococcus), Van der Welde has proved the formation of a special anti-leucocytic product, which he calls leucocytin. And this discovery affords an explanation of the observa-

tion of Muir that in his experiments large numbers of the leucocytes which had ingested staphylococci and destroyed them yet subsequently died and degenerated themselves, and were removed by hyaline leucocytes and the large endothelial cells described by Durham.

We saw in the preceding lecture that a positive chemiotactic influence on the phagocytes is the essential antecedent of their phagocytic action on a given bacterium, and it was proved by Everard, Demoor, and others that as immunity increases in an animal this attraction of its leucocytes by the bacteria in question steadily increases. Again, it is said that a very virulent bacterium may actually exert a negative chemiotaxis, though when attenuated it acts positively. This shows most clearly the relation of virulence to infectiveness, and of the latter to a diminished phagocytic activity of the leucocytes.

Some pathogenetic micro-organisms practically never succeed in general invasion of the animal body, but only act by means of toxins locally produced. And in such cases it is found that the bacteria in question have a strong positive chemiotactic action on the phagocytes, and hence only succeed in gaining *local* foothold in the organism in regions somewhat sheltered from the free access of leucocytes—as, for example, on the surface of the pharyngeal mucous membrane in diphtheria. Here the animal is to a great extent immune to the bacterium, although highly susceptible to the action of its toxic products

—that is, it possesses anti-bacterial immunity, but not antitoxic.

The same distinction holds experimentally, for animals immunized to a bacterium often remain susceptible to its extracellular toxins. This is to be explained as follows: The amount of toxins introduced in each inoculation of the bacterial culture is quite small, and insufficient to induce the formation in the body of an antitoxin. Meanwhile, the phagocytes acquire the power of rapidly destroying the bacteria injected, and thus prevent them forming further toxins in the animal body. This phagocytic power increases as the immunity progresses, and the bacteria are more and more rapidly destroyed at each injection. Accordingly, they never have an opportunity of forming toxins in the animal, whose serum therefore gains no antitoxic action.

That the explanation just suggested is the true one follows from the fact that if such animals be subsequently treated with the toxins they are found to yield an antitoxic serum, and to now possess not only bacterial, but also toxin immunity.

Now, on the injection of bacteria in a relatively immune animal there occurs not only chemiotaxis of the existing leucocytes, but also rapid increase in the leucocyte formation, resulting in the production of leucocytosis. This occurs also in the course of the acquisition of immunity during immunization. The process has its seat in the bone-marrow, and is

the result of stimulation of the marrow cells to an increased proliferation by the chemiotactic action of bacterial products, as was shown by Ehrlich, Goldscheider and Jacob, Muir, and others.

The visible element, then, in a bacterial immunity is the ingestion of the infective agent by the phagocytes and the increase in number of the phagocytic cells to meet bacterial invasion. Now, these bacteria are taken up alive and fully virulent. This has been proved by Sanarelli and Cantacuzène, who further showed that if the vitality of the phagocytes be lowered in any way—as by the action of cold or the administration of opium to the animal—the ingested micro-organisms at once proceed to multiply within the body of the phagocytes, which they kill, and, thus becoming free to multiply, lead to the death of the animal, which was previously immune.

We therefore need to seek an explanation of how the bacteria are killed in immune animals after their ingestion by the phagocytes. Here we require to turn from the consideration of the biological to that of the more evidently chemical factors in bacterial immunity. This is an exceedingly difficult and complicated question, though it has been greatly simplified by the discovery and preparation of the so-called anti-cellular sera, which are homologous in their action with the anti-bacterial sera, but are for several reasons easier to investigate.

It has long been known that the blood of an

animal undergoes rapid and complete destruction when injected into the circulation of an animal of a different species. On the other hand, it had been discovered that the blood of certain animals is poisonous for other species when injected—as, for example, that of eels, of snakes, of toads, and of the hedgehog. And Calmette showed that animals can be immunized against such toxic action just as against the toxic products of bacteria.

Belfanti and Carbone then arrived at the important discovery that the blood of horses, which has no toxic action when injected into rabbits, can be made toxic for these animals by the repeated injections of rabbit's red blood-corpuscles into the horse. The activity thus acquired by horse's blood was found to be specific in its nature—that is to say, the blood was only poisonous for rabbits, not for other animals. This property was shown by Bordet to depend on processes analogous to those occurring in the formation of anti-microbic sera. And similar specific changes have been demonstrated following the injection of various other elementary cells—for instance, different kinds of epithelia, leucocytes, spermatozoa, and kidney cells, and so on. The sera thus produced are spoken of as anti-cellular sera.

The anti-sera for red blood-corpuscles are called *hæmolytic* sera. If a fresh specimen of such a serum be allowed to act upon the red corpuscles of the animal for which it is specific, it rapidly produces their solution. This is occasioned by the action of

two substances which it contains, and which were first identified by Bordet.

Pfeiffer had already stated that anti-microbic sera similarly contain *two* bodies necessary to bacteriolytic action. To these the name of *immune body* and of addiment or *complement* were respectively applied by Ehrlich.

Fränkel and Sobernheim had further shown that if an actively bacteriolytic anti-cholera serum be heated for a time at 60° C., it loses its bacteriolytic power entirely ; and Bordet found that its activity can be restored by the addition of fresh normal serum, which by itself had no bacteriolytic action. Bordet accordingly came to the conclusion that one of the substances in question—namely, the complement—is present also in fresh normal serum as well as in specific immune serum, but that it is readily destroyed by moderate heat ; and that the other substance—immune body—which is more resistant, is not, in general, present in the serum, but is a specific product formed during the process of immunization. He established the same facts for hæmolytic sera.

Buchner had already found that hæmolytic action is destroyed at a temperature of 56°C. Bordet now gave the explanation of this fact by showing that the immune body, which is special to the specific serum, is not injuriously affected by such temperatures, but that the complement, a body present also in the sera of unimmunized animals, is more unstable, and is rapidly destroyed by heat.

These observations attracted much attention, and gave rise to numerous researches by Ehrlich and Morgenroth, Metchnikoff, Bordet himself, and many others. The experiments carried out by these investigators, and more especially by the two first named, have resulted in the addition of the following facts to our knowledge of the composition and the mode of action of these sera :

1. The immune body and the complement exist side by side, but ununited, in the immune serum.

2. The immune body, which is specific, has a strong affinity for the red corpuscles, and rapidly unites itself with them even at a temperature as low as 0° C. It may thus be separated from the complement (which at this temperature remains unattached) by means of centrifugalization and washing of the corpuscles.

3. The complement is only taken up by the corpuscles at a higher temperature, and only then if the immune body is also present. In the absence of this body it is never taken up at all by the red cells.

4. Neither of these bodies alone can cause solution of the red corpuscles ; both must be present and be taken up before a hæmolytic action is produced.

Hence Ehrlich came to the conclusion that, since the immune body is readily taken up, but of itself produces no effect in the absence of the complement, while the latter by itself produces no hæmolysis, and is not even taken up by the red cells, the process of

hæmolysis, when occurring, must be due to an action of the complement through the agency of the immune body.

Bordet put forward a somewhat different explanation of the facts observed. He holds that the immune body so changes the red corpuscles that these themselves now bind the complement, which thus causes their solution—that is to say, the complement becomes attached not through an intermediate link of immune body, but independently.

Ehrlich, however, showed that there appears to be a direct connection between the two substances which cause hæmolysis, since, if the complement of an immune serum be destroyed by heat, leaving the immune body intact and isolated, the former can be readily restored by the addition of serum from a normal (unimmunized) animal of the same species, but is not *necessarily* replaced on the addition of serum from another species.

An explanation of these observations has been offered, based on an extension of the side-chain theory which I previously described.

On this hypothesis the immune body is a lateral chain or cell-receptor, which is produced and discharged into the blood in the same manner as is an antitoxin or the other anti-substances. It is supposed, however, to have two haptophores, instead of only one, as was the case with antitoxins. One of these haptophores is endowed with high affinity for the red corpuscles, of which it constitutes the

specific anti-body, while the other possesses a similar affinity—though somewhat less, since it does not anchor the complement at low temperatures—for the complement.

It was next shown by von Dungern that the specific immune body and the complement are not present in equivalent masses in an immune serum. Thus, he succeeded in increasing the hæmolytic action of his rabbit's sera more than thirtyfold by simply adding complement in the fresh serum of a normal rabbit. In other words, the hæmolytic serum here contained no less than thirty times more immune body than complement. And hence it follows that the two bodies are not produced in combination, and so set free into the plasma, since in that case they should appear in serum in equivalent amounts. And Dungern came to the conclusion that, while the immune body is a product of immunization, the normal complement is not permanently increased at all during this process.

Ehrlich and Morgenroth have proved that the processes at work in the reaction take place quantitatively—that is to say, the red corpuscles employed in the experiment take up just so much immune body as is needed for their complete solution, and no more. They further showed that the ferment-like working complement is not in every case the same for all the hæmolysins which can be produced in the same animal or the same species, since they found sometimes in the same animal, besides the

thermo-labile complement which is destroyed at 56° C., a more resistant thermo-stabile form which can withstand this temperature for several hours.

Buchner and his pupils had already investigated the hæmolytic properties of *normal* sera. These also are destroyed by moderate heat, and exhibit in other respects conditions closely akin to those existing in the artificial hæmolysins. For these sera also Ehrlich proved the presence of an intermediary body analogous to the immune body found in the serum of an animal which has been specifically immunized.

As regards the complement, Ehrlich and Morgenroth found that this may be replaced in a large number of instances, though not in all, by the fresh normal serum of an animal of a different species. It therefore is not a specific body, but a normal blood constituent. Into the question of its origin and nature we shall enter later on. Meanwhile, we must examine next the conditions governing the formation of the immune body.

Now, on the side-chain theory of Professor Ehrlich, the only necessary condition for the formation of an anti-body to any substance which may be injected is the existence in some group of cells within the body of suitable side-chains or cell-receptors which can take it up. And such receptors, when discharged into the plasma, are actually the anti-body in question.

Considering, then, the great number of the organs and tissues of the body and the manifold variety of

their metabolism, such side-chains, which by supposition are the normal agents in the nutritive exchanges, must exist in the most extraordinary diversity in the body cells, and also on occasion in the blood itself. And hence the blood must undergo in respect of the side-chains discharged into its plasma both constant and considerable variations. This is proved, moreover, by the observations that a normal horse's blood may at one time contain a considerable amount of antirennin, at another none, and that dog's blood may be at one time highly hæmolytic for blood of cats, while at another it exhibits no such hæmolytic action.

As regards any substance injected into a living animal, three possibilities alone present themselves: First, it may find no suitable receptor in the body cells; secondly, suitable receptors may be present; or, thirdly, with the presence of suitable receptors, there may also be present in the body in other cells a group possessing the same haptophore as the injected substance. For simplicity let us call the chemical group which is injected the male receptor, and the group which takes it up within the body the female receptor. Then the three possible cases are as follows: Either (1) the animal contains no female receptor; or (2) it does contain the female receptor, and this alone; or (3) it contains both the female and the male receptors.

And this third case, in which there is the simultaneous presence in the animal of corresponding

male and female groups, is probably of very frequent occurrence in the economy of the animal, and has to do with the dependence of certain cells for nourishment on the products of certain other cells within the body. This occurrence, for example, might explain the relation of the testicle to the prostate, and of the ovary to the mamma, so familiar clinically, but so little understood. It is exemplified in the proved coexistence of the rennet and the anti-rennet groups in the same animal.

Such receptors may be called 'reciprocal,' the term 'singular' receptor being used in cases where the corresponding or male group is not already present in the animal. The three cases, therefore, may be given as follows: (1) No receptor present; (2) female receptor present only—singular receptor; (3) reciprocal receptors present—both male and female groups existing in the body of the animal. In the first case, evidently, no anti-body can be formed, since there is no receptor to take up the injected substance. In the second case an anti-body will be formed, and there is no particular condition limiting its quantity. This is exemplified in the formation of antitoxins. In the third case an anti-body is also formed, but this on its appearance in the plasma will be taken up by the reciprocal receptor, and consequently will never be found free in very large amount in the blood-plasma. And this was actually shown to be the case for antirennin.

These possible cases have been carefully worked

out by Ehrlich and Morgenroth for hæmolysins, but I have only time to give you a brief summary of their results, which were obtained on goats.

If a goat be injected with the blood of other goats, it forms a hæmolysin for their red corpuscles. This may be called an isolysin to distinguish it from lysins formed against the red blood-corpuscles of animals of a different species from the one injected, which are called heterolysins. A goat can thus form isolysin for the blood of each and every other goat whose blood is suitably injected. The isolysins formed are not identical, but different, and none of them is hæmolytic for the red corpuscles of the goat which forms them—that is to say, the animal will not form hæmolysin for its own red corpuscles. The isolysin formed is therefore not an autolysin for the blood cells of the animal concerned. Indeed, no formation of an autolysin has ever been observed, and from this it follows that animals do not contain receptors which could aid in the destruction of their own tissue cells. Again, the injection in an animal of the hæmolysin of its own red corpuscles leads to the formation of another anti-body, an antilysin ; and hence it follows that, even should an animal possess the power of forming lysin for its own cells, this lysin would be quickly neutralized by the production of the corresponding antilysin.

As regards other anti-cellular sera, the facts, so far as they have been established hitherto, fully confirm these observations on the hæmolysins.

The experiments throw a valuable light on the formation of anti-bodies in general and of antitoxins in particular, since they show that wherever susceptibility to the action of an injected body exists, owing to the presence of suitable receptors in the cells on which that body exercises its specific action, there exists also of necessity the basis of immunity in the power of splitting off those reecptors from the cells in question, and discharging them into the plasma as an anti-body.

In the absence of such receptors from these cells, whether they be present or not in other cells of the body, the animal will evidently exhibit a natural immunity to the *specific* action of the toxic substances injected, because the latter is not taken up from the blood-plasma by the cells in question. Thus the toxin of tetanus, which acts especially on cells of the central nervous system, and is taken up by those in a susceptible animal, is found to be totally absent from the nervous tissues after its injection into animals naturally immune.

If the naturally immune animal possess a suitable receptor for the toxin in other cells than those for which it is specifically toxic, these will remove it from the blood and store it up, as is the case for tetanus toxin and the liver cells of scorpions, which are naturally immune to tetanus.

And such receptors will produce an antitoxin, although the animal is naturally immune. Thus, Metchnikoff showed that crocodiles, which are

immune to tetanus, but whose blood normally contains no tetanus antitoxin, produce an antitoxin of considerable value after injection with the tetanus toxin.

Since any given anti-body simply represents the female cell-receptor of the injected substance which has been discharged into the plasma of the animal concerned, it follows that all substances whatever which are endowed with the *same* haptophore, and therefore have an affinity for the *same* receptor, will on injection lead to the formation of the *same* anti-body. A given anti-body, therefore, will be protective against all toxic substances which possess a common haptophore. This fact suggests a simple explanation of the observations which I previously mentioned, in which inoculation with one micro-organism or its toxins was found to be protective also against certain others.

The immune bodies formed against bacteria have the same relations as any other of the anti-substances. So far as evidence goes, they are produced under precisely similar conditions.

LECTURE IX

For the destruction of bacteria or other foreign cells which gain an entrance into the body of an animal the interaction of two substances is necessary—namely, the immune body and the complement.

The former of these substances—the immune body—is, as we saw in the last lecture, a specific product formed under similar conditions to those which regulate the production of the anti-bodies in general.

In contrast to the immune body, the complement, or addiment, as it is sometimes called, is not a specific product, being already present in a normal serum. Though not specific, Ehrlich believes it special in the sense of belonging peculiarly to the serum of the animal in which it is found. And it is not indifferently and universally replaceable, though in many cases it is replaceable by the complement obtained from animals of other species than the one used for experiment.

Further, for one and the same serum the complement is not necessarily the same for all the anti-cellular and anti-microbic reactions possible to that

serum. Thus, Ehrlich has proved in certain cases the existence of two complements in goats, the one extremely labile and destroyed rapidly by a temperature of 56° C., the other still resistant at a temperature of 65° C.

By its action the complement produces the disintegration and solution of the cells which it attacks, and exhibits characters akin to those of the class of bodies which are known as ferments. Professor Ehrlich has put forward the following view of its position and function in the normal animal: The complement is a ferment produced and discharged into the blood by certain cells—which are not further specified—to serve the purposes of general cell-metabolism. The body cells possess a group of side chains which exhibit strong affinity for the complement. The complement is therefore taken up out of the plasma by these so-called complementophile side-chains, according to the requirement of the moment. It thus enables these cells to carry on their normal metabolic processes by its power of splitting up the large nutritive molecules extracted from the blood, and thereby rendering their assimilation possible.

Now, starting from the position of Pfeiffer—that both the substances necessary for protection are present in an immune serum in an inactive form, and become active on injection into the body of a living animal, though, as I told you, the complement is present (when present at all) in limited and much

less amount than is the immune body—it is evident that it should be possible to supply sufficient of both bodies to insure protection by giving large enough injections of the serum. But this is not the case, for Roux and Vaillard showed in severe tetanus infections that an animal treated with immune serum in large quantities may rapidly succumb, although it has received such an excess of serum as to render its blood and body fluids capable of protecting other animals against a moderate infection with the same bacterium. And the same facts were proved by Pfeiffer, Wassermann, and others in the case of various other bacterial infections.

And seeing that of the two protective substances the immune body is obviously present in sufficient quantity—since the serum of the dead animal is found to have protective power for others—Ehrlich attributed these phenomena to a deficiency of the complement. Accordingly, he was driven to the conclusion that the complement injected in the protective serum is useless to the animal concerned ; in other words, that, with certain not too numerous exceptions, an animal can only make use of its own complement, which is limited in quantity, or, at the most, of complement derived from other animals of its own species.

The exceptions, therefore, became of great importance, for only by a careful search could there be found for each particular species of animal that foreign complement which could suitably replace

the deficiency of its own proper complement, and bring about the destruction of the invading micro-organisms. And more especially for serum-therapy in man Ehrlich regards this search as of prime value for the immediate future.

I am myself unable to agree with the theory of the extreme specialism of the complement to its own species of animal. That this view is by no means satisfactory is shown by the following facts: In every observation of Pfeiffer's phenomenon made by means of the immune sera of other animals in the peritoneal cavity of the guinea-pig, the school of Pfeiffer holds that the inactive complement of this serum is rendered active by the agency of the endothelial cells. That is to say, that a foreign complement can be made use of by the guinea-pig so that it can now, even after its removal from the peritoneal cavity, exhibit its activity against the bacterium concerned. Again, Wassermann has shown that in infections of the guinea-pig a satisfactory complement, both for the animal and for the immune body of dog's serum, which he used for the specific protection, is present in fresh serum of the ox—an animal belonging to a species widely different both from the guinea-pig and from the dog. Ehrlich himself has also found a number of exceptions to the law which he proposed. And I have shown that in the case of guinea-pigs treated with horse's immune serum for typhoid infection suitable complement can be supplied from the fresh serum of the rabbit, ox, and pig.

Complement, therefore, does not seem so special to the species as Professor Ehrlich thought. The deficiency of complement observed in animals infected with large doses of bacteria, and treated with specific immune sera, is the result, not of an inability of the animal to employ the foreign complement, but of the fact that the specific immune serum injected *contains no complement* of any kind at all, but only the specific immune body.

The complement is not simply inactive in the immune serum, as was taught by Pfeiffer, but it is absent. It is so extremely labile that it disappears with great rapidity when the blood is shed. And I have watched this disappearance of the complement from the fresh blood of animals from the actual moment when the blood is shed until its presence is no longer recognisable. After its disappearance it can be replaced from the fresh serum of various other species, whether the experiments be made in test-tubes or in the body of a living animal.

I have already told you what is the view of Ehrlich as to the nature and origin of the complement, which he considers to be a normal metabolic ferment formed by certain cells by which it is discharged into the plasma, there to circulate until such time as it is taken up by other cells, which it assists in carrying on assimilative processes. This view, however, has now become untenable on various grounds. These we shall next examine.

Just as we saw to be the case in the destruction

of bacteria, so in hæmolysis of red corpuscles which have been introduced within the body of an animal Metchnikoff has shown that phagocytic action plays a definite and increasing part with increase of the animal's immunity, until, when full immunity has been acquired, the phagocytic method of destruction may be almost universal and exclusive.

The school of Ehrlich also now admits that the destruction of bacteria or other cells can take place intracellularly within the phagocytes as well as extracellularly in the body fluids. Now, such intracellular destruction must either (1) pursue a course entirely different from the extracellular, or (2) it must be occasioned by the same substances as cause the extracellular lysogenesis. And in this case the necessary immune body and complement would, on Ehrlich's theory, have to be taken up by the phagocytes from the blood-plasma to enable them to carry out the process of destruction.

1. The former of these two alternatives would lead to the remarkable position that the animal body, while possessing a basis of protection in the natural biological process seen in the universal tendency to phagocytic action, yet has resort in the acquirement of immunity to the development of a purely chemical reaction in addition—that of the immune body and the complement; and, not content with this, develops and increases equally the more complex biological method of ingestion and destruction by the phagocytes, with the result

that at a period when the chemical reaction has reached a maximum it is actually found to be entirely superseded by the intracellular method of destruction—that is to say, that the bacteria or other cells injected are taken up from body fluids admittedly capable of causing their solution and destruction to be destroyed by other methods by the phagocytes. This is absurd, and renders the immunity reaction meaningless.

We are, therefore, forced to the conclusion that the two processes of intra- and extra-cellular destruction are not different from each other and independent, but that they are identical in nature.

2. The question then arises, Do the phagocytes really obtain the complement and immune body which they require to bring about the lysogenesis from the blood-plasma in which they circulate? If this were so, phagocytosis would present itself merely as an epiphenomenon in the process of protection of no especial value, and of no particular importance. And it would be impossible to explain why, as immunity increases, living and active bacteria, for example, can be shown to be more and more eagerly ingested by the phagocytes, and then destroyed, when this result could be obtained as easily and more conveniently by their remaining in the plasma, which contains (on Ehrlich's view) both immune body and the complement.

But as a matter of fact, the serum of animals which are naturally immune has been shown to

contain no recognisable amount of immune body, and yet in these the phagocytic destruction of bacteria is exhibited in its most active form. It follows that the phagocytes must themselves contain the receptors which in immunized animals are discharged into the plasma as the immune body, and which are necessary to initiate lysogenesis.

It might, however, still be possible that the complement is a free ferment, which the phagocytes obtain from plasma. Let us examine this possibility.

We have the following facts : Anti-microbic serum possesses *in vitro* no bacteriolytic action, but it does contain the immune body ; the other necessary substance—the complement—is therefore absent. Such serum is bacteriolytic when freshly obtained from the living animal ; the complement, however, is very labile, and soon disappears. It may be restored by the addition of fresh normal serum (Bordet) or of leucocytic fluids (Hahn) ; and Bordet showed that a definite relationship exists between the mass of leucocytes added and the degree of bacteriolytic power obtained ; that is to say, the amount of complement is in relation to the number of leucocytes added. Again, Denys and Havet discovered that a bacteriolytic pleural exudate loses its activity entirely on the removal of its leucocytes, but that its power can be immediately restored by merely putting back the leucocytes.

Moreover, I have found the following facts: (1) That a deficiency of complement in guinea-pigs can be made good not only by the injection of fresh normal serum, but also by an extract of fresh blood-clot from which the serum has been separated. Complement, therefore, is present in the clot as well as in the serum. (2) That serum when it first begins to separate from the clot contains only a little complement, but that this rapidly increases in amount during the first few hours after the blood is shed if the serum which is separating be left in contact with the clot, while if the serum be removed into a separate vessel no increase in the amount of complement occurs. And Bordet and Gengou have recently proved that plasma which has been obtained by special methods that prevent the breaking down of leucocytes in the shed blood contains no complement, and has no lytic action on bacteria at all.

From all these observations it follows that the complement is not a ferment circulating freely in the plasma, as was held by Ehrlich, but is exclusively a phagocytic product, only set free into the circulating plasma or the serum by the disintegration of the phagocytes themselves.

The intimate relation of the complement to leucocytes has been established in a different manner in some experiments by Dr. Beaton and myself. Rabbits were immunized to a particular bacterium; their blood then contained the immune body for this

micro-organism. They were then treated with another bacterium in order to produce leucocytosis. This did not affect the immune body for the first bacterium, which remained approximately constant in amount ; but it was found that the bacteriolytic power of the blood varied from day to day exactly with the number of leucocytes present, and reached its maximum exactly at the height of the leucocytosis caused by the injection of the other bacterium. The amount of complement present accordingly depends entirely on the number of the leucocytes. Complement, therefore, is, as Metchnikoff maintains, the ferment of the phagocytic cells.

Where the animal is immune or has been immunized the complement performs its functions of bacteriolysis within the body of the phagocyte, which is its normal situation, after the bacteria have undergone ingestion ; but where the animal is more susceptible and phagocytes are destroyed by the bacteria it is set free into the plasma, and can there also carry out bacteriolysis. It only acts, however, as I have told you, after the immune body has attached itself to the bacteria.

This immune body, as we saw, is also present in the phagocytes. Whether the animal is naturally immune or not depends, in my opinion, only on the amount in which it normally exists within these cells. The effect of an immunization is to stimulate these receptor groups, which multiply and become split off into the plasma as free immune body.

The formation of the immune body by the leucocytes is proved by the following observations : The experiments of Deutsch, confirmed in general by the results of Metchnikoff, Wassermann, and others, led him to the conclusion that in bacterial infections the immune body is formed in the tissues of the splenomedullary system, which are, of course, the seat of the formation of the blood-phagocytes. And whenever it is being formed in quantity the bone-marrow exhibits evidence of markedly increased activity, as shown by Muir and others.

Moreover, Bulloch found for hæmolysin that the curve of immune body present in the blood follows the curve of daily variation of a particular variety of leucocytes.

Whether it is formed exclusively by leucocytes, as Metchnikoff believes, or is produced by other cells as well—the view maintained especially by von Dungern—is not perhaps at present quite determined. There is, however, no evidence obtainable of any marked activity in other tissues when it is being formed. Nor is there any reason why an anti-body formed by other cells should hold the very high affinity for complement—that is to say, for the ferment of the phagocytes which is exhibited by the immune body, since evidence is altogether wanting of any close relationship between the intrinsic ferment of the phagocytes and the side-chains of body cells in general.

We see, then, on the whole, that the destruction of

bacteria or other foreign cells within a living animal is brought about by the interaction of two substances produced by phagocytes—namely, a preparatory substance or 'preparer'—immune body—and a digestive ferment which destroys the foreign particles, but which can only act when the 'preparer' has already played its part. In animals which are immune or immunized this process is accomplished in the bodies of the phagocytes, which rapidly ingest the living particles; but where the animal is more susceptible destruction of the phagocytes themselves sets free these substances into the plasma, and leads to extracellular attack on the infective agent.

There still remains one phenomenon associated with the reaction of immunity which is of great importance—I mean the phenomenon of agglutination.

Charrin and Roger found in 1889, in the course of their experiments with the *Bacillus pyocyaneus*, that this bacterium, when grown in its specific immune serum, showed the remarkable peculiarity that it collected into clumps, and was deposited at the bottom of the culture-tube. This observation was confirmed by Metchnikoff for certain other micro-organisms. He showed, however, that it does not occur with all bacteria. Accordingly, it could not form a necessary part of the immunity reaction in all cases; and Issaeff found that it does not entail any impairment of the vitality or virulence of the bacteria which are thus agglomerated.

Bordet was the first to show that not only do bacteria which are grown in their specific serum thus agglomerate, but also fresh bacteria introduced into serum give the same reaction. This phenomenon is now usually spoken of as agglutination. And Pfeiffer found a similar process to occur in the destruction of cholera vibriones within the peritoneal cavities of guinea-pigs. Then came the discovery made by Herbert Durham in Gruber's laboratory in Vienna, and worked upon by Gruber, Durham himself, and Grünbaum, that in recovery from typhoid infection the blood acquires agglutinating action on the *Bacillus typhosus*. It happened that the application of Durham's reaction to the serum diagnosis of typhoid in man was published first in Paris by Professor Widal. The credit of the discovery is, however, due to Durham and Gruber, and the reaction ought to bear their names.

As the result of their investigation of agglutination, Gruber and Durham came to the conclusion in 1896 that in agglutinative immune sera there are present neither substances which destroy bacteria, nor such as stimulate the body cells to carry out bacteriolytic action, but that the action of the agglutinins, or substances which cause agglutination, is to induce a swelling up and alteration of the bacterial envelope, which is thus rendered permeable by the bacteriolytic substances. Upon this view agglutination is a necessary antecedent of bacteriolysis with the agglutinable micro-organisms—such, for example,

as the bacilli of typhoid fever and of glanders, the *Bacillus pyocyaneus*, the *Bacillus coli*, and the cholera vibriones.

On the other hand, Malvoz endeavoured to throw doubt upon the origin of the agglutinins, and questioned whether they arose from the reaction of the animal at all. Thus, he found that an agglomeration of bacteria could be induced by the action of certain chemical substances, such as formalin, corrosive sublimate, saffranin, vesuvin, fuchsin, acetic and lactic acids, and other reagents. Subsequently he showed also that culture media in which the bacteria have grown contain similar agglutinating substances. He therefore held that the agglutinins of blood have simply been derived from the injected cultures, and are not anti-bodies formed within the animal during the process of immunization.

This view of Malvoz is untenable on the following grounds : The agglutinins are discharged freely in the secretions of the animal concerned (Nicolle), and yet the agglutinating action of the blood may be retained for years after the animal has been immunized. Moreover, just as in the case of other anti-bodies, an animal may be frequently and very freely bled without a permanent reduction of the agglutinating action of its serum. From these results it follows that agglutinin must be produced within and by the animal itself. This I was able to show conclusively in the following experiment :

Of two rabbits among a number employed in

certain observations, the one had received on seven successive days a certain intraperitoneal injection of living typhoid culture, while the other had received the same infecting doses, and at the same time on each occasion 5 c.c. of highly agglutinative anti-typhoid serum. Now, it is evident that if the view of Malvoz were correct, and the agglutinins were derived exclusively from the bacterial cultures introduced, the serum of the animal which had received both culture and agglutinating serum should have become more highly agglutinative than the serum of the other animal, which had been treated with the cultures only. As a matter of fact, the serum which it yielded was only about one-half as agglutinative in its action as the other. It follows, therefore, that the agglutinins are formed by a reaction of the animal, and consequently that the animal which was in part protected by the immune serum given reacted less and formed much less agglutinin than did the unprotected animal.

Agglutinins are, therefore, anti-bodies, and Deutsch concludes from his experiments that they are formed within the tissues of the lung. Deutsch's results have been supported by an Italian worker named Moreschi. Ruffer, however, has lately found a close relation between the daily leucocytic count and the acquirement of agglutinative action during the process of immunization, and he concludes that the agglutinins are formed by leucocytes.

The view of Gruber and Durham that agglutina-

tion is an essential antecedent of bacteriolysis for the particular bacteria concerned was strongly opposed by Pfeiffer, Metchnikoff, and others ; and Pfeiffer and Kolle showed that in the cholera peritonitis of guinea-pigs protection can be carried out without the occurrence of agglutination. Similarly, Bordet found that both agglutinative action and protection could occur each in the total absence of the other. And these results have been confirmed by various workers.

But Durham has produced considerable evidence of the existence of a very close relation between the phenomena of agglutination and protection. Thus, he showed that an increase in the protective action of a serum is accompanied by corresponding increase in its agglutinating power, and that complete agglutinating power, complete protection, and complete bacteriolytic action are associated. Deutsch further found that the agglutinins and protective substances develop simultaneously, both appearing, both reaching a maximum, and both, again, gradually diminishing in quantity in the same number of days from the injection of bacterial cultures.

Again, I found in the examination of a number of antityphoid sera against a number of varieties of the *Bacillus typhosus* that the agglutinins are, like other anti-bodies, not only specific for the bacterium in question, but peculiarly ' special,' as Durham termed it, for the particular variety of that bacterium which gave rise to their formation ; that the protective

action of a given serum for any given variety of the *Bacillus typhosus* was in proportion to its agglutinating power for that variety; and that the agglutinability of any given variety varied inversely as its virulence.

Hence the two processes of agglutination and protection follow clearly parallel though not superposable directions. I say not superposable, because in the gradual loss of an acquired immunity some degree of protective action may remain at a time when the agglutinating power has disappeared.

The agglutinable substance of bacteria which agglutinate resides apparently in the bacterial envelope, and is diffusible. It certainly diffuses out of the bacteria into the culture media in which they are grown, for media out of which the bacteria have been filtered will, on the addition of agglutinating serum, exhibit changes comparable to agglutination. That it resides in the bacterial envelope was proved by Kraus; and Harrison found that it can be digested and removed by the action of the pyocyaneus ferment leaving the bacteria non-agglutinable. That the reaction of agglutination is independent of the life of the bacteria follows from the observation that dead bacteria both cause a production of agglutinins after their injection in the living animal, and are themselves equally agglutinable with their living representatives.

The nature of the relation which exists between the agglutinative process and protection is quite

unknown. But I suggest to you that it may possibly assist phagocytosis, and that, just as the chemical reaction of bacteriolysis is aided and initiated by the action of the immune body, so the preliminary physical ingestion by the phagocyte may perhaps be assisted for the bacteria concerned by the occurrence of agglutination, which brings the bacteria to rest, and collects them into larger or smaller masses, besides producing changes in their envelope.

This is *hypothesis*, but if it were established it would supply an explanation of the fact that the agglutinative and protective action of an immune serum are not coincident though they run parallel. For the protective action is made up of two constituents—namely, the bactericidal and the antitoxic action of the serum—while phagocytosis only deals with one of these, the former. And hence the agglutinative process would have no particular relation to the antitoxic, but might be quite coincident in its development with bacteriolytic action.

It follows, then, from all that we have learned of the processes occurring in infection, that the reaction of the animal body to bacterial invasion is developed along two lines, the first directed to the destruction of the invading micro-organisms, the second to a neutralization of their products. The latter, which we broadly term the antitoxic action, concerns all dead bacterial substances whatever which can be taken up by body cells, and leads to the formation of the anti-bodies, which include the antitoxins proper,

agglutinins, coagulins, the immune bodies, and the like. These anti-bodies are liberated side-chains or receptors of those cells which are respectively susceptible to the bacterial products, and the immune body consists of such side-chains derived from phagocytes.

The antitoxins neutralize the bacterial toxins, and thus prevent intoxication of the animal concerned, and the bacteria are themselves digested by the phagocytic ferments. The action of these ferments is made possible by a preliminary union of the immune body with the bacteria concerned.

On the destruction of the phagocytes their ferments are set free into the plasma, and can there perform the function of bacteriolysis ; but in immune or immunized animals bacteriolysis occurs within the bodies of the phagocytes after the ingestion of the micro-organisms.

Similar facts are true for micro-organisms other than bacteria, and for other foreign cells.

Successful resistance to infection, therefore, means the possession or formation of specific anti-bodies in sufficient quantity, and the supply of the essential lysogenetic ferment by a proliferation of the cells which form the phagocytes. Failure of either of these processes entails a fatal termination of the infection.

Next time I shall show you what specific treatment is available for man, and then commence the pathology of fever.

LECTURE X

We have seen that a susceptible animal acquires immunity against a given infection during and by recovery from the disease concerned, and that immunity can be conferred upon it either by the injection of an immune serum or by the method of inoculation. The latter process leads to an active durable immunity, whereas the former gives an immunity of only temporary duration, which is entirely passive in its character.

The production of passive immunity by the injection of immune serum, whether as a prophylactic agent or in the treatment of the actual disease, has this great drawback—that the development of active acquired immunity is thereby checked. This happens in the following manner :

The immune body needed and the anti-bodies of the bacterial toxins are supplied in the injected serum. The individual concerned has, therefore, only to provide bacteriolytic ferment ; and since the bacterial products are ' neutralized ' by the specific bodies in the immune serum, they cannot cause a

formation of such bodies by the side-chains of the infected individual. Hence, no facility in the formation of immune body and of antitoxins is acquired, and accordingly the individual remains susceptible. This represents an extreme case where sufficient immune serum is injected to *entirely* neutralize the bacterial products, but similar considerations show that any and every injection of the serum must, in so far, oppose the development of the immunity reaction and lessen the immunity acquired.

On this account it is advisable to avoid the exhibition of excessive doses of such sera, and to employ the minimum amount required to insure the recovery of the patient.

The production of immunity by bacterial vaccines is a production of acquired immunity of active character by the reaction of the individual concerned to mild infection with the specific agent of the disease in question. It is an imitation of the way of nature, and is a truly scientific method of protection. That natural processes continually work along this line is demonstrated by the following facts :

In times of epidemic it is found among persons similarly exposed to the infection that, for every case prostrated by a severe attack, many may have some slight indisposition, and many more exhibit no objective evidence of reaction. Now, it cannot be that all these latter have escaped infection where all are equally exposed, and hence we may conclude

that in these individuals the natural resistance is at such a level that the repeated entrance, in small quantity, of the infective agent leads to a gradual development of immunity without the production of a marked and visible reaction.

Thus, probably, must be explained a number of the slight febricula, sore throats, and passing diarrhœas which present themselves during an epidemic of infective illness, as well as the immunity of those who work continuously in fever hospitals, and the remarkable resistance of pathologists to post-mortem room infections.

The widespread prevalence of the natural method of protection is further evidenced by the diminution of susceptibility in general with increasing age, till after thirty or thirty-five many of the specific infections are quite unusual. The process is exemplified in the parallel, frequent observation of antirennin in the blood of horses, of anti-cholera protective bodies in the blood, and cholera vibriones in the *solid* stools in healthy men during a cholera epidemic (Sobernheim), and of diphtheria antitoxin in the blood of uninoculated horses, and of healthy men who have never suffered from diphtheria (Wassermann). Moreover, such occurrence of anti-bodies in the blood without previous attack of the disease concerned is much more frequently to be observed in adolescents and adults than in young children (Wassermann), thus pointing clearly to their origin from the reaction to repeated small infection.

It thus appears most clearly that the inoculation method imitates the way of nature, and, like the latter, it affords a durable immunity.

The pioneer discoveries of Jenner laid the foundations for the scientific use of this procedure. It is unnecessary here to enter the discussion of the causal agent and relations of variola. That its virus is identical with that of cow-pox which is used for vaccination is rendered highly probable by the work of Klein, of Copeman, and of Hime, and many others. Moreover, many of the strains of vaccine lymph now used have been derived originally from variola. The inoculation, therefore, is specific.

In rabies, a considerable measure of success has followed the distinguished work of Pasteur; and Wright's inoculation against typhoid fever is of undoubted value. The anti-choleraic vaccines used by Haffkine had not a great success. And all the evidence points clearly to the fact that, while an attenuated virus must of necessity be first employed in man, we cannot hope to gain complete protection until by later treatment with more active forms a full resistance to the bacterium of normal virulence has been attained.

The method of inoculation has, however, no value where an infectoin has already gained maturity, though by its more direct immediate entrance it may be able to induce immunity during the incubation period of the natural disease where this is long enough, as in variola. We therefore need a thera-

peutic agent, and this we find in the specific sera. In the use of these we seek to give assistance and to facilitate recovery from disease by a transference of anti-bodies to the affected individual, leaving him dependent only on his own phagocytic ferment to destroy the invading micro-organisms with the assistance of the immune body injected. Toxic bacterial products will be neutralized by the anti-toxic bodies of the serum. And Madsen has shown that even toxin which has already attached itself to cells can be removed from them and rendered harmless if a sufficient mass of the free antitoxin be injected.

In diphtheria the results from antitoxin treatment have been more than excellent. In tetanus also numerous cures have been recorded. In severe cases the serum should be injected intracranially, where it can act at once, and in considerable concentration on the toxin which has already reached the nervous centres.

A number of other sera have been tried with les success, such as the anti-sera for cholera, typhoid, plague, tubercle, rabies, and the streptococcic and pneumococcic infections. But in these cases where there is bacterial invasion of an extensive nature, as well as an intoxication with bacterial toxins, the results bear no comparison with those obtained from antitoxic sera in the intoxications. Some, however, are not without a value, and quite good results have been obtained with antistreptococcic sera and with

the serum against plague prepared by Lustig and Galleotti in Florence.

The specific serum treatment of disease will undoubtedly achieve more definite success when due account is taken of the necessity for polyvalency—that is to say, when as many and as widely different varieties of the specific micro-organism as possible are used in the immunization of the animal which is to yield protective serum. The researches of Marmorek on streptococci, the work of Herbert Durham, and an examination which I made of the conditions affecting the protective power of antityphoid sera show, among many other observations, that the protective action of a serum against a particular variety of a given bacterium depends on the degree to which the serum has been rendered 'special' for that variety of the bacterium in question—that is to say, upon the use of that variety in the immunization of the animal which yields the serum.

If you desire to put a muzzle on your dog, you obviously choose a muzzle that will fit—one that is 'special' for your particular dog. That muzzle will probably fit with fair success a large proportion of other dogs of the same breed, and may be applicable more or less to a considerable number of dogs of other breeds in which the head is somewhat similar in size and conformation. But your sheep-dog's muzzle would not be very serviceable for a terrier, and would be quite inapplicable to a mastiff or Newfoundland. And hence, if you required to muzzle

all varieties of dogs, you would provide yourselves with all the varieties of muzzles necessary. And certainly you would not say that muzzles were a failure because a particular example failed to fit a particular dog for which it was not made.

But in the therapeutic use of immune sera the mistake is sometimes made of expecting a particular monovalent serum—a particular muzzle, not only to suffice for all varieties of dogs, but even for the foxes, wolves, and prairie dogs as well. This error is, fortunately, though somewhat slowly, disappearing.

There is another factor also which requires consideration by clinicians—that is, the destruction of bacteria by the phagocytic ferments.

If you were anxious to get rid of dogs entirely because they bite, it would not be enough to muzzle them and turn them loose, because that leaves them capable of producing other dogs which bite ; and if you found that they produced new vicious dogs more rapidly than you could make new muzzles, it would naturally occur to you to kill the dogs.

Now, bacteria multiply at an enormous pace. They must be muzzled, as we have called it, with the antibodies, since they cannot be killed until the immune body is attached to them, but they *must* then be killed by phagocytic ferment, or they will multiply beyond all chance of muzzling, and the unmuzzled individuals will work destruction.

This is what happens when there is deficiency of complement. Accordingly, it follows that *a due*

supply of complement is as essential as specific serum. Unfortunately, we have no means at present of supplying phagocytic ferment from without. It follows, therefore, that it is essential to secure leucocytosis in infected animals. This can be done in a variety of ways, such as I mentioned in a previous lecture.

It has been thoroughly established in the case of animals that the experimental production of a proliferation and increase of the phagocytes can bring about recovery where death is otherwise inevitable. It rests with the physician to apply these facts to man.

One other fact of prime importance in the serum treatment of disease has been discovered recently —the fact that an *excess* of immune serum can work serious and even fatal injury. This is a matter of considerable moment.

Neisser and Wechsberg found that on injecting animals with too much serum they died as certainly as if too little immune serum had been given in the specific treatment of infections. This, on investigation, proved to be the result of a deficiency of complement occasioned by the excess of immune serum, as can be proved by experiments on bacteriolysis *in vitro*. The result appears to be brought about as follows : The affinity of immune body for complement is *not* increased when the former is united to bacteria ; it may perhaps even be diminished. Accordingly, on the injection of a marked excess of

immune serum, the complement is seized in greater or less amount by the free immune body which remains, and less, or even none, can be secured by the immune body which has attached itself to the bacteria. Hence, the bacteria are not destroyed, owing to deficiency of complement.

I was engaged in working on the question of the complement when Neisser's paper appeared, and have been able to confirm these observations. They afford a further argument in favour of the routine production of artificial leucocyte proliferation in association with the use of anti-bacterial sera. Under such circumstances the danger will be greatly minimized, especially as the clinical tendency is usually to give too little rather than too much of the specific anti-substances.

In the administration of an antitoxin also excess must be avoided, since I have found that the effect of giving large quantities of antitoxin which are not employed in neutralizing toxin is to arouse the formation of an anti-antitoxin, and this body can prevent the protective action of the antitoxin in a subsequent infection.

From all these facts it follows that, though specific sera have a most valuable protective action, yet the inoculation method alone is truly preventive, and confers active immunity against the infective agents ; and thus we see that the great work and works of Edward Jenner, more than a century ago, laid bare the very root of the whole question of protection

from the specific infections, and that the means for its production, found by him for small-pox, was then, and is to-day, the only safe and certain method of defence against the invasion of the body by bacteria in natural disease.

The General Pathology of Fever

Fever is a process characterized by increase of body temperature and disorder of nutrition, and is due to the entrance into the circulating fluids of certain morbid products which are usually of bacterial origin.

Since the introduction of the clinical thermometer into medical practice—a comparatively recent event—the term 'fever' has come to be often used as though it were synonymous with one of its most prominent and constant symptoms—namely, pyrexia.

Such a use is both inaccurate and misleading, for many fevers are, or may be, apyrexial during some portion or at certain periods of their course. And, on the other hand, pyrexia may be present without fever, as in the case of the so-called cerebral puncture, in various head injuries, in insolation, and after the administration of certain drugs. The presence of pyrexia, therefore, is not in itself sufficient for the diagnosis of fever, nor does its absence at the time of observation exclude that condition. It is an easily recognised phenomenon, and hence convenient as a clinical guide ; but its importance is in general very

much less than that of the other event which I have mentioned—namely, the disorder of nutrition which invariably occurs in fever.

The older views of fever regarded it as a state of overaction. That theory is interesting only from the historical standpoint. It was supported by no evidence except the observed pyrexia, which was attributed to an overproduction of heat, the observed increase of the heart's action, and a supposed increase of tension in the whole vascular system. It was, moreover, fundamentally at fault in looking upon fever as a *state*, instead of as a *process* marked by a definite succession of stages.

As Sir John Burdon Sanderson has pointed out, Johannes Müller was the first to recognise it as a reactive process. He compared it to a reflex action, and supposed it to be initiated through a stimulation of the spinal cord by afferent 'organic nerves.'

Vaso-constrictor nerves had already been discovered by Claude Bernard, and about this time Weber discovered the inhibitory action of the vagus on the heart. Then followed the discovery of Schiff of the existence of vaso-dilator mechanisms. And thus arose the conception of the vascular system as controlled by nervous centres by means of two antagonistic sets of efferent nerve-fibres.

From the idea of the controlling of organic processes by a double innervation from the central nervous system, the one stimulating in its action, the other inhibitory, thus introduced in physiology,

Virchow developed his celebrated view of fever which regarded it as a neurosis—the outcome of a failure of the control normally exercised by the central nervous system not only on the vascular system, but, as he suggested, on all the organic processes of the body. This theory of a loss of control over the circulation and metabolism by the so-called 'moderating centres' absolutely reversed the teaching previously accepted of an overactivity, and exhibited the events of fever as the outcome of a paralysis of all the controlling centres. It appeared to receive support from the observations of Traube (1855) two years later that the excretion of nitrogen increases during fever. This could be attributed to the paralysis of the trophic nerves normally controlling katabolic action.

Traube himself, however, regarded the increased breaking down of proteids as being secondary to the circulatory disturbance. He held that the fever-producing agent acted on the vaso-constrictor nerves, causing contraction of the peripheral arterioles, and hence diminished flow of blood to the surface, diminished temperature of the skin, and diminished loss of heat, with the result that the internal temperature rose rapidly. To the increasing difference between the internal and the surface temperature he attributed the rigor of accession. He taught that normally the *discharge* of heat at the surface was *regulated in accordance with* the heat-production of the body. The principal event in fever was a disordering of

the regulative heat-discharge in the direction of diminished loss, so that an undue amount of heat was retained in the body, and the temperature became increased. All the other events were secondary to this.

In opposition to Traube, it was shown by Liebermeister that, even if the temperature of the surroundings be raised to such a height that no heat can leave the body, and surface loss becomes impossible, yet the temperature of a healthy individual does not rise nearly so quickly as in the initial stage of many fevers. The theory of Traube therefore could not be maintained, and Liebermeister came to the conclusion that in fever, as in health, the temperature is regulated by the *adaptation of production to discharge*, but that in fever the normal or standard to which it is regulated is several degrees higher than in health. By this he meant that the temperature, instead of tending to a normal of, say, 37·5° C. (98·5° F.), as in the condition of health, tended towards a mean of 40° C. (104° F.), or whatever it might be in different cases. And certain evidence seemed to support this view. Thus, the temperature of a healthy individual can be increased or depressed by placing him in a bath, and gradually warming or cooling the water.

If the body temperature be by this means increased as much as one-fifth of a degree C. (about one-third of a degree F.) above the normal, the subject perspires; if it be lowered below the normal by the

same amount, he shivers. The same observations are found to hold for a fever patient whose body temperature is, say, 40° C. (104° F.). If his temperature be lowered by cooling him in a bath to 38·9° C., he shivers; while if it be raised to 40·2° C., he perspires. The explanation of this is that it is the change of temperature, and not the temperature itself, which causes the reactive shivering or sweating. If the alteration be produced extremely gradually, as in the method of tepid sponging in enteric fever, the rectal temperature can be reduced by a whole degree or more of Centigrade (2° F.) without resultant shivering taking place.

Liebermeister, however, went further than was warranted by his experiments when he concluded that, because arrest of surface loss of heat in a healthy individual does not cause such a rapid rise of temperature as occurs at the onset of many fevers, an arrest of surface loss is inadequate to produce pyrexia, and that therefore the nervous control which suffers diminution in fever is one normally exercised by means of regulated heat-production.

Traube's theory, on the other hand, attributing everything to vaso-motor action, regarded the control as one consisting in a nervous regulation of the surface loss of heat.

The view of Liebermeister found support in the experiments of Finkler, carried out in the laboratory of the physiologist Pflüger, on the respiratory ex-

change of fevered animals, and was endorsed by Cohnheim in his well-known lectures. That of Traube gained adherence from the results obtained by Senator and Leyden, both on animals and in the course of clinical investigation also.

The phenomena of fever, which we must presently consider, may be conveniently grouped under four headings—viz., the disturbance of temperature, alterations in the pulse and circulation, nervous phenomena, and, lastly, the disorder of metabolism, including the respiratory exchange.

The process of fever itself is divisible into three stages or periods—namely, the period of onset, or the *accession*, the *fastigium*, or period of continuance, and the stage of *defervescence*. The accession may be abrupt or gradual. When it is gradual the temperature curve usually exhibits a daily remission corresponding to the normal morning fall of temperature in health. The fastigium may be long, or of such short duration as to be almost imperceptible ; and the defervescence may occur rapidly, the temperature falling by crisis, or may be more prolonged, and show a gradual fall of temperature by lysis.

As regards temperature, the fevers are divided into various classes according as the pyrexia is *continuous*, *remittent*—that is, varying more than about 1° C. (2° F.) in the twenty-four hours ; *intermittent*—that is, falling to or below the line of normal temperature in the daily remission ; or *irregular*, a term which sufficiently explains itself.

The *continued fevers* have all the stages long. There is a gradual onset—as, for example, in typhoid fever, where in a typical accession the temperature rises about 1° C. (2° F.) each evening, falling about $\frac{1}{3}$° C. ($\frac{2}{3}$° F.) in the morning, until the fastigium is reached. During the fastigium the pyrexia continues, but with a daily remission, and an evening rise of $\frac{1}{3}$° C. ($\frac{2}{3}$° F.), as in the normal temperature of health, until the defervescence, which frequently presents first a remittent, then an intermittent type of pyrexia, and often ends with a few days of a subnormal temperature before the normal is again attained.

In *relapsing fever* the pyrexia is broken by intermissions. These, as we now know, correspond to the periods during which the spirochæte is absent from the blood. Its reappearance leads to a new accession of pyrexia on the day following this event, and the relapse may be repeated several times.

A similar condition is to be seen in true relapses of enteric fever, of which, again, there may be more than one. The cause of the relapse in the case of the former of these diseases is, of course, the reappearance in the circulation of the causal agent the spirillum of Obermeyer. Of the latter a very ingenious and probable explanation has recently been suggested by Herbert Durham. This is as follows: An ordinary attack of typhoid fever is probably due to infection by a number of different varieties of the *Bacillus typhosus*. One or more of these varieties

may be only feebly represented, and perhaps multiply slowly in the infected animal. These will accordingly give rise to very slight production of their special anti-substances, though anti-substances for the other and more numerously represented varieties are formed in quantity and convalescence begins. If, now, from any change in the conditions in the body one of the feebly-represented forms takes on an active growth, there will not be sufficient of its special anti-bodies present to arrest it; hence a relapse occurs until these special anti-bodies have been formed. The same events might be repeated with another variety after the termination of the first relapse. This theory would explain the occasional occurrence of several relapses, and the fact that they are rarely fatal. It is, however, pure hypothesis.

An *intermittent fever* is one in which a rapid accession is followed by a very short fastigium and rapid defervescence, after which there is a period of apyrexia to which succeeds a new accession, fastigium, and defervescence as before, and so on. These are the periodic fevers of which the tertian ague is a good example.

Hectic fever presents irregular pyrexia with a tendency to normal or subnormal morning temperatures.

The term *aseptic fever* is employed in contradistinction to the fevers of infective origin.

LECTURE XI

THE phenomena of fever which require consideration may be conveniently grouped, as I said, under the following headings : (1) The alterations in the pulse and circulation ; (2) nervous phenomena ; (3) the disorder of metabolism and respiratory exchange ; and (4) the disturbance of temperature.

As regards the *pulse and circulation*, we must distinguish first between the changes which are attributable to the fever itself and those which are merely secondary to pyrexia.

The increase in the pulse-rate which occurs is—in the first case, at any rate—simply due to the increase in temperature of the blood. Even in an isolated frog's heart a definite ratio may be observed, as shown by Lauder Brunton, between the temperature at which the surroundings and the fluid perfused (if perfusion be employed) are maintained, and the rate of the heart-beat, the rate increasing with increase of temperature within the usual limits. And Liebermeister showed that in man there is an increase of about fourteen beats per minute for each

degree Centigrade—that is, eight beats for each degree Fahrenheit—of increased temperature. This phenomenon is particularly well illustrated in the early stages of many cases of enteric fever.

Increase in the pulse-rate beyond this physiological ratio must be attributed to the injurious action of the cause of fever, either directly on the cardiac muscle, where it gives rise to the albuminoid degeneration so often seen in cases which have died of febrile illnesses, or indirectly through its action on the cardiac centre in the floor of the fourth ventricle.

Although the rate of the heart-beat increases, the blood-pressure is usually diminished in a case of fever. But this does not occur invariably nor to the same degree in all the fevers ; indeed, in certain fevers the blood-pressure may be raised. *A sthenic* fever is physiologically one in which the blood-pressure keeps high, *asthenic* fevers those in which it suffers diminution.

The fall of pressure is to be ascribed to a relaxation of the peripheral arterioles. In sthenic fevers with a rapid pulse and very vigorous systole the arterial relaxation may be counterbalanced, or nearly so, by the increased heart's action, the pressure remaining high, or the general arterial relaxation may itself be absent ; while, on the other hand, when the arterial relaxation is very marked, or where the cardiac muscle becomes enfeebled by the action of the febrile agent, the fall of pressure is progressively

more marked as the systole diminishes in vigour. Between these two extremes, marked fall of pressure from peripheral relaxation, associated with a good flow of blood and a good systole, leads to the phenomenon of dicrotism of the pulse, which is so commonly to be observed in the earlier stages of enteric fever.

The most convenient method for measuring blood-pressure in a fever patient is by means of Mosso's finger plethysmograph, which consists of an upright limb communicating laterally with two chambers, one of which holds the patient's finger, while the other is so arranged that graduated pressure can be applied to the fluid with which the apparatus is filled. The column of fluid in the upright limb oscillates synchronously with the systolic increase and diastolic decrease in the volume of the finger. Pressure is now applied through the second chamber until this oscillation is just abolished. The pressure required to produce this effect gives the measure of the blood-pressure in the finger.

Many of the ill-effects of fever are in part attributable to the lowering of the blood-pressure. This gives rise to a lessened flow of blood from slowing of the general circulation, and thence leads to a diminution of nutrition, the effects of which are often markedly in evidence—for example, in the kidneys.

As regards the vaso-motor changes, there is usually associated with the onset of a fever a marked contraction of the cutaneous arterioles. This is most

pronounced where the accession is rapid and is accompanied by a chill or definite rigor. It is, in fact, the cause of the feeling of cold or of the rigor itself.

Traube, who, as we have seen, regarded the pyrexia of fever as entirely due to a diminished loss of heat, laid a great stress upon this spasm of the cutaneous vessels, which he believed persisted steadily until the period of defervescence. This, however, is not the case. After the termination of the cold stage there is, on the whole, a condition of cutaneous vaso-dilatation, though this is variable, and varies in any given area from time to time. Thus, at any given moment the vessels in a particular cutaneous area may be found constricted, while those in other parts remain dilated ; and in any given part the vessels may be found dilated at one time, but constricted at a subsequent examination. But, on the whole, the condition throughout is one of cutaneous vaso-dilatation.

Further, the reaction of the vesesls of the skin to stimulation or mechanical interference is remarkably slowed. Thus, for example, if an area be blanched by pressure, the return of colour takes place much more slowly than in health. This is—at any rate, partly—due to the diminished rate of flow already mentioned.

The defervescence is accompanied by a marked and universal dilatation of the cutaneous arterioles, with restoration of secretory activity in the skin and

other evidences of an increased rate of blood-flow, which is probably to be associated with a restoration of control over the peripheral arterioles of the splanchnic area.

We have, then, as the result of the entrance into the circulation of a febrile agent, first a brief contraction of the cutaneous vessels, then dilatation and diminshed flow, and finally, in the period of defervescence, a gradual restoration of the circulation to normal. In this connection it is interesting to remember that in the case of inflammation, which is the local reaction to the local introduction of closely similar substances, the local succession of vascular changes runs, as we saw, a very similar course.

The *nervous phenomena* of fever are to be attributed in part to the actual increase in temperature of the blood and the altered conditions of the circulation, and in part to the direct action of the cause of fever on the nervous tissues themselves. As they concern the higher centres they are chiefly headache, hyperæsthesia of the special senses, apathy, and sleeplessness in milder cases; loss of muscular power, general depression, delirium, and all the symptoms of an intoxication in the severer forms.

As regards so-called 'organic centres'—that is to say, those centres whose reflex action is less definitely associated with consciousness than is that of the higher centres, which for convenience we call psychic centres—the interference with the normal develop-

ment of the heat-regulating reflex is the most prominent and the most important symptom. This we shall deal with fully when we come to the discussion of pyrexia. The respiratory centre is also affected by the febrile process, more especially at the onset, when the respiration is considerably increased both in frequency and volume.

This is in part resultant from the muscular activity which asserts itself during the cold stage, and leads to an actual increase in the absorption of oxygen ; in part it is the effect of increased internal temperature, for the experiments of Fick and Goldstein showed that a heat-dyspnœa is readily produced by heating the blood in the carotid arteries of animals. The cardiac centre may probably be similarly influenced, for there are certain fevers in which the pulse-rate rises rapidly out of all proportion to the rise of temperature, and before any evidence exists of a direct injurious action of the febrile process on the heart muscle—as, for example, in the case of scarlatina. Here the increase is possibly to be ascribed to interference with the normal inhibition exercised by the cardiac centre through the vagus nerve.

The *metabolic phenomena* of fever are seen in the dystrophia—that is, the diminution of assimilative power—and the disturbance of the excretory processes, which are evidenced by the condition of the urine. This is diminished in quantity often to about one-third of its normal volume ; there is an increase in the nitrogen elimination, not only relatively to

the quantity of urine passed, but absolutely, and an alteration in the salts.

There is an accumulation of water in the body during fever. However much is taken by the mouth, less than the normal is invariably discharged. An increased loss of water by the skin occurs, but this is never anything like enough to compensate for its decreased excretion by the kidney. The water thus stored up is discharged later in the epicritical stage following the defervescence.

The diminution in the urinary excretion is due, as was shown by Heidenhain, to the diminished pressure and the resultant diminution of the blood-flow through the kidney. It has also been attributed to the fact that all glandular activity is lessened by fever. But against this explanation is the observation already mentioned that the secretion of urea is actually increased.

This increase in urea discharge was first discovered by Traube in 1855. It has been confirmed by Parkes and Ringer and many others. The amount may be as much as from 30 to 50 per cent. greater than in a healthy person on the same diet and under similar conditions.

In health the nitrogenous excretion is almost all derived from the nitrogen of the food ingested in the preceding twenty-four hours, as proved especially by the very exact experiments of Rubner. The excess of nitrogen eliminated in fever can only arise from tissue disintegration.

The daily loss of sodium and potassium salts in health is approximately equal, but in fever the excretion of sodium may be diminished to as little as one-sixth the normal amount. This fact was first discovered in pneumonia, and we now know that not only is the normal loss of sodium diminished, but that considerable additional amounts of sodium given by the mouth in the form of common salt may be retained. The excretion of potassium, on the other hand, increases, as also that of the phosphates.

Here, again, we have evidence of the tissue waste which is proceeding, for cells contain an excess of the potassium salts over the sodium compounds and phosphorus in the form of nucleinic acid and in other combinations. Acetone, another product of disintegration of cells, is also often present in the urine of fever patients, just as in other conditions of rapid cell-degeneration—such, for example, as cancerous cachexia, diabetes, and, as shown by Zuntz, during starvation in the healthy subject. The excretion of kreatin, which, as you know, is probably a product of the muscular metabolism, is also subject to a considerable increase in fever.

We must now pass on from this broad general view to a more detailed examination of the disturbance of metabolism and the pyrexia of the febrile process, and shall consider first the variation from the normal as concerns metabolism.

We have seen that in acute fevers the respiratory

movements are increased in frequency and depth, and this implies an increased oxygen tension and a diminution of the carbonic acid tension in the blood, supposing the rate and volume of the circulation to remain the same; but with the fall of the blood-pressure in fever the blood-flow becomes slowed, a condition naturally tending to increase the venosity of the blood by increasing the time of the circulation, and therefore the intervals during which any given volume of the blood is absent from the lung capillaries. Some part of the increase in the respiratory movements, therefore, may be dyspnœic, and due to an excess of carbon dioxide in the circulating blood. It certainly is so in fevers which deteriorate the functional activity of the lung tissue, though even here the greater part of the increase is to be attributed to the other causes which we have already mentioned—namely, the action of the superheated blood and of the fever-producing agent on the nervous centre. That this is so is evidenced by the rapid fall in respiration rate with the crisis of pneumonia, although, of course, no sudden change in the condition of the lung itself occurs.

But whether the blood be slightly more arterial than normal, as in the early stage of increased respiration and before the fall of blood-pressure and the slowing of the circulation has begun, or slightly less arterial than normal, cannot materially affect the respiratory exchange, since, as you know, the respiration of the tissues is intrinsic, and is not im-

mediately dependent on the blood condition. It is the rate of tissue metabolism itself, and the requirements of the various tissues which determine how much oxygen is taken up from the blood, and how much carbonic acid gas is formed. Accordingly, it is the actual respiration of the tissues which requires to be determined in investigating fever.

Now, Liebermeister found in his experiments that in the initial stages of fever the respiratory exchange may be as much as twice or thrice as great as normal. But Senator, in investigating the same subject, came to the conclusion that the increase in the discharge of water and carbon dioxide by respiration was never greater than could be accounted for by the increased activity of the respiratory movements. Leyden, however, repeating the experiments some years later, found in all cases accompanying the rise of temperature an increased discharge of carbon dioxide of such amount and duration as could not possibly be explained by the increased respiratory movements alone. And his results were supported by the experiments of Finkler, working under the great physiologist Pflüger.

A brief increase in the elimination of carbonic acid could be accounted for by increased activity of respiration leading to a more rapid discharge of the carbonic acid already accumulated in the blood and tissues, but a considerable and continued increase must imply increased production of the gas in question by increased metabolism.

After the invention by Professor Zuntz of a much more accurate and convenient apparatus for determining respiratory exchange in man than had previously been available for the purpose, and the exact investigation made by himself and Lehmann on the exchange of gases in the two fasting men Cetti and Breithaupt, the subject of the exchange in fever was again taken up by Kraus and also by Loewy. The general results which they obtained may be summarized as follows: (1) There is usually increase of the intake of oxygen and of the elimination of carbon dioxide with or without increase of the respiratory movements. But this only occurs while the temperature is rising during the accession, and is associated with the shivering and increase of muscular tone which present themselves during this stage. (2) The respiratory quotient—that is, the ratio $\frac{CO_2 \text{ discharged}}{O_2 \text{ taken in}}$ — is in many cases unaltered, but it may be diminished. Such diminution, however, is not a pathological event, since it is present equally in healthy persons kept on fever diet and under the same general conditions.

On the whole, therefore, the respiratory exchange is unaltered in fever. Such variations as may be noted occur only in the early stage, and are secondary to an increased metabolism of the muscles, and do not constitute an essential or invariable character of the febrile process. Accordingly, there is no increased consumption of fat in fever, since this we

know would show itself in an alteration of the respiratory quotient.

Following the discovery of Traube of the increased elimination of urea in fever came a series of investigations on the discharge of nitrogen both in man and fevered animals by Ringer, Naunyn, Senator, and many others. Huppert had early shown that on the whole the nitrogenous excretion varies with the temperature, and Ringer found that the increased discharge commences even *before* the rise of temperature at the onset of the febrile process.

The discharge of nitrogen in fever is equal to or often even greater than that which occurs in health, and is frequently more than double what it would be in a healthy person on the same diet and under the same conditions as the fever patient. It is, therefore, clear that tissue proteid is being broken down in fever ; and this is evidenced again, as we have seen, by the increased potassium, kreatin, and phosphates of the urine, and in the appearance of acetonuria. What is the cause of this increase of the metabolism of the tissue proteids ?

There are several possibilities before us. It might be due (*a*) to a direct action of the cause of fever on the tissue cells producing an increased lability of tissue ; or (*b*) to the action of the same agent on a trophic nervous centre, either in the direction of stimulation or of a paralysis of normal trophic inhibition ; or, again, (*c*) to the action of the increased temperature in accelerating metabolic change ; or,

lastly, (*d*) to the dystrophia associated with the fever, which, by preventing normal assimilation, forces the animal body to carry on organic processes at the expense of its own tissue substances.

Now, to examine the causation of a result in which several variable factors may take part, the proper course is to determine the result of varying each factor separately. We thus determine what part, if any, of the general result depends on any one particular factor.

Proceeding in this way, we must examine first the condition of inanition which most closely resembles in its physiology the dystrophia of fever. Here, as regards the human subject, very exact results have been presented by the observations of Zuntz and Lehmann on the fasting men already mentioned. In animals the very accurate experiments of May on rabbits, published in 1894, furnish the most reliable data available.

Taking an animal in a condition of inanition—that is to say, in fasting—it is found that after the first few days—in rabbits by the third day—the daily loss of nitrogen and of carbon becomes very nearly constant. This point corresponds to the period when the food last taken and the reserve of carbohydrate in the form of glycogen have become used up. The animal has now to live on its own body tissues. Hence, from its daily loss of nitrogen, we can determine the amount of tissue-proteid waste, since fifteen parts of nitrogen correspond, as we

know, to about a hundred parts of proteid matter. Having thus calculated the amount of proteid broken down, we determine next the amount of carbon it contained, and, subtracting this from the total carbon eliminated, obtain the quantity of carbon which has been derived from fat, and thus the amount of fat used by the animal.

In this way May found that in eight rabbits which he employed for the experiment the daily elimination of nitrogen was about 0·055 per cent. of the body-weight. When, however, a condition of fever was induced in the animals in addition to the inanition, the loss of nitrogen increased, and amounted, for example, to 0·066 per cent. of the total body-weight. But the consumption of fat was found to be unchanged—a result confirming the conclusion which we have already reached from the consideration of the respiratory exchange. These results are well illustrated by a table from one of the analyses prepared by May, which is as follows :

Condition of Rabbit.	Daily Loss of Nitrogen.	Proteid Equivalent.	Carbon in the Proteid.	Total Loss of Carbon.	Carbon lost in Fat used.	Fat used.
	Grms.	Grms.	Grms.	Grms.	Grms.	Grms.
Inanition -	2·1	14·0	7·4	15·0	17·6	10·0
Inanition *plus* fever - -	2·7	18·0	9·7	17·3	7·6	10·0

Proteid waste increased nearly 30 *per cent. by fever; fat used not increased in amount.*

It follows that the nearest approach to the metabolic conditions which obtain in fever is to be found in the condition seen in inanition, the only difference being that in the former an increased amount of tissue proteid is used. Dystrophia, therefore, as we must conclude, is the prime factor in the metabolic disturbances of fever. Only the excess of proteid waste in fever over the tissue-proteid waste of inanition can be ascribed to causes other than the nutritive disturbance. And this excess may amount, as we have seen, to something like a 30 per cent. increase on the nitrogenous metabolism of inanition.

What is the cause of this increase in fever? It might be accounted for in part by the pyrexia. All chemical processes go on more actively at a high temperature than at a lower, and we should therefore expect more active tissue change when the body temperature is raised than in a state of inanition, which is usually associated with subnormal temperatures. Moreover, exact experiments on hibernating animals, and especially those carried out by Dr. Pembrey, have proved that the diminution of metabolism in hibernation occurs in consequence of the lowering of the animal's temperature. High temperature alone, however, cannot account for the excess of the nitrogenous metabolism in fever over that of inanition, since, as we shall see in the discussion of pyrexia, there is probably a nervous regulation tending to diminish metabolism and thus lessen the heat-production of a normal animal should

the conditions tend to cause a rise of body temperature which is insufficiently controlled by thermolysis.

We are therefore driven to ascribe the excess of proteid waste in fevered animals to the direct influence of the cause of fever. And this position is confirmed by the observation of Ringer that the increased excretion of urea begins *before* the temperature rises at the onset of the febrile process—that it is greatest at an early period in the fastigium—that is to say, when the reserve of carbohydrate in the body is used up, and the activity of the febrile agent has presumably reached its height—but that it declines towards the end of this stage and through the defervescence when the action of the causal agent is again subsiding. The proteid disintegration is, however, apparently of the same nature as that of inanition, and its end products, including acetone, are identical with those observed in an afebrile wasting illness, and in the experiments on fasting men already mentioned. Moreover, May has shown that as much as 25 per cent. of the nitrogenous elimination in fever may be saved by giving carbohydrate in the immediately assimilable form of glucose—a fact which has not as yet received the clinical recognition it deserves.

Now, just as there was found in inanition the most useful guide to the condition of nutrition in fever, and one which made it possible to examine the condition of dystrophia with or without an associated febrile process, so the experiments of Kraus and

Loewy with tuberculin both in the human subject and in animals exhibited the metabolic changes of febrile pyrexia apart from those associated with dystrophia. These observations made it clear that increased proteid waste accompanies the action of a febrile agent. The injection of tuberculin in tuberculous individuals gives rise to fever without important alteration in the digestive and assimilative functions. It none the less occasions an increased excretion of urea. And hence it follows that the excess of proteid waste in fever over the proteid-tissue waste of inanition is due directly to the action of the cause of fever.

Whether the febrile agent acts immediately upon the tissues or only mediately through the nervous system cannot perhaps be definitely answered in the present state of knowledge. But while, as we shall see, there is—as yet, at any rate—no *proof* of the existence of a central nervous mechanism for heat-production, nor of the existence of a system of trophic nerves by which that mechanism could control the tissues, there is, on the other hand, abundant proof in the phenomena observed in local inflammations that morbid substances which gain a local entrance can produce tissue disintegration by a direct action on the cells concerned. Such substances, moreover, are akin to those which bring about the febrile process.

During the defervescence the nitrogenous waste diminishes, but following it there freqeuntly occurs

an epicritical increase, as it is called, in the elimination of urea in the urine. This is to be ascribed to the increased assimilation which occurs, and is the ordinary physiological result of increased diet, for, as you know from the experiments of Voit and others, if an animal be in a condition of nitrogenous equilibrium or below this level, an increase in its consumption of proteid food invariably leads in the first case to an increased destruction of proteid in the body and an increased excretion of urea greater than corresponds to the increase of proteid assimilated.

We have seen that an animal in fever has an increased excretion of urea over the excretion by a normal animal on the same diet; this means increased production of heat from proteid metabolism, and this implies greater facilities for increase of body temperature or pyrexia. All this, however, is insufficient to explain the rise of temperature, for in the normal animal an increased supply of heat is counterbalanced by an increased loss under the action of a nervous regulation. This regulation we must now consider.

The process of heat-production is spoken of as thermogenesis, that of heat-discharge as thermolysis, while the regulation by the central nervous system of these two opposing factors to maintain a constant and a stable body temperature is called thermotaxis.

The *stability* of the body temperature in health is quite as marked and definite as its *constancy*; and the importance of this character was especially

emphasized by MacAlister in his Goulstonian Lectures upon fever. Man is not only homoiothermic, but also thermostatic. Not only does the temperature in health tend to maintain a constant level or normal, but it also tends to rapidly regain this normal level if it be temporarily diverted either up or down by outside agencies; and it is only with considerable difficulty that it is thus diverted. The temperature of fever, on the other hand, is not only not constant, but it is also remarkably unstable. Very slight changes in the external conditions produce considerable variations, and the return from such a variation is not only slow, but often also very incomplete.

It is, of course, familiar to you how easily a fall of temperature can be produced by tepid sponging in continued fevers, and how comparatively slowly it regains its former level subsequently; and, on the other hand, what very slight disturbances may cause a rise in temperature of one or two degrees. Accordingly, the view of Liebermeister that in fever the temperature is merely adjusted to a new 'normal' is untenable; for adjustment or regulation means stability as well as uniformity, while stability is conspicuously absent from the temperature of fever, even in those cases where the pyrexia of the fastigium usually maintains a fairly constant level.

Such uniformity of temperature as occurs in fever is therefore not dependent on an adjustment of the regulative mechanism to a new level, comparable to

the readjustment of a thermostat by a slight alteration of its regulator—a mystical change, as Cohnheim put it in his criticism, from the human regulation to the regulative level of a bird. Liebermeister's view would make the process comparable to the tuning of an instrument to a higher key, where all the relations of the different parts remain unchanged, and the mechanism quite unaltered in its accuracy, only the general level of its action being raised; whereas in fever the elevation of the general level is only secondary, and is the outcome of a condition of disorder in the mutual relationship of the different factors which take part in the production of the body heat. Whatever uniformity may be observed in the temperature of the fastigium of continued fevers is rather to be correlated with the fact observed by Wood, of Philadelphia, that the *production* of heat during this period of the febrile process is fairly constant, and is not a markedly fluctuating quantity.

The regulation of the production, distribution, and discharge of body heat so as to maintain a uniform body temperature is characteristic of the higher Vertebrata, which are accordingly spoken of after Bergmann as homoiothermic animals, in contradistinction to the poikilothermic animals, whose temperature is variable, and varies with the temperature of their surroundings. This does not mean that the so-called cold-blooded animals have a temperature identical with that of their surroundings. Their own production of heat in the course of their meta-

bolism prevents exact coincidence with the external temperature. What is implied is that in these animals the regulation is rudimentary, or at any rate imperfect, so that increase of the external temperature induces increase of their metabolism, and a decrease of temperature a diminution in its activity, as shown by Pembrey and by Vernon. The relations are well seen in the following table, which I have taken from Landois and Stirling :

Frog in Water.		Frog in Air.	
Temperature of Water.	Temperature of Frog's Stomach.	Temperature of Air.	Temperature of Frog's Stomach.
41·0° C.	38·0° C.	40·4° C.	31·7° C.
30·0° C.	29·6° C.	27·4° C.	19·7° C.
20·6° C.	20·7° C.	16·4° C.	14·6° C.
5·9° C.	8·0° C.	6·2° C.	7·6° C.
2·8° C.	5·3° C.	5·9° C.	8·6° C.

Homoiothermic animals, on the other hand, are able to diminish their production when the external temperature rises to such an extent as to seriously check the surface loss of heat, and to increase it when external cold leads to excessive loss of heat, sufficiently to maintain an almost constant level under all ordinary variations of their environment. And moderate changes of external temperature do not affect their rate of heat-production at all, being entirely dealt with by the regulated loss of heat.

The hibernating animals form an intermediate class, maintaining in their waking periods a uniform and stable temperature, but during the winter sleep reacting like cold-blooded animals to variations in external temperature.

Temperature regulation to a constant level is thus peculiar to the higher animals—that is to say, it is of late development in evolution. It is also of late development ontologically in the individual. Thus, as was shown by Pembrey and Gordon, the embryo chick reacts as a poikilothermic animal to variations of external temperature, the chicken only gradually acquiring homoiothermic characters within the last few days before it leaves the shell. And probably the human infant is at birth and for some period afterwards quite incompletely capable of homoiothermic regulation of its body temperature.

This regulation is controlled by the nervous system, and we may here recall in this connection the established observation of the late development of the functional activity of the higher nervous centres, and the late acquirement of their medulla by the cortical fibres and the sensory tracts, which probably contain the efferent conducting-paths for heat and cold sensations. For, as we shall see, the regulation concerns the higher centres, and is to some extent under the control of individual volition—that is to say, the reflex is in part one of the so-called psychical reflexes.

LECTURE XII

At the end of the last lecture we were speaking of the regulation of the body temperature in its relation to the pyrexia of fever. Such regulation is dependent primarily on the existence of an adequate supply of heat from heat-producing processes. Into these processes we must therefore now examine briefly.

The subject of animal heat was first investigated by Lavoisier, who came to the conclusion that heat-production was carried on by means of the combustion of carbon in the lungs. His view, however, soon became untenable, and was abandoned with the discovery that the oxygen taken up is not combined with carbon in the lungs, but passes on into the blood. This observation led to Liebig's theory that the oxidation processes occur in the blood-stream. We cannot enter here in detail into the physiology of the respiratory exchange, but we now know that Liebig also was in error as regards the destination of the oxygen inspired, and that the processes of oxidation, like all other metabolic

processes, are carried on both in and by the cells themselves which form the body tissues, and not within the circulating fluids. Hence, heat-production is a function of the cellular metabolism. Heat is, in fact, the only constant form in which the energy of the body is expended, and all other forms of energy tend to transform themselves into this form, in terms of which they all may be conveniently expressed.

The great discovery of the principle of the Conservation of Energy (according to which all energy arises out of previous energy, and none is ever lost) by Joule in England and Meyer in Germany led the latter sixty years ago to the conclusion that the output of energy by the animal body must correspond exactly to the energy taken in in food. And this conclusion gained wide acceptation, and constantly received support from the experiments of physiologists ; but it remained for Rubner to obtain a proof of mathematical precision and completeness. This observer, by a long series of experiments, from which all sources of possible error were carefully eliminated, was able finally to show that the output of energy in the twenty-four hours expressed in calories of heat exactly coincided with the heat value of the food consumed less the heat value of the excrete products.

It has been further proved that the chief source of heat-production is the muscular metabolism. This is established by the following facts : The ratio of

the work done by the whole body to the heat produced is about one to four; the ratio of the work done by a muscle to the heat which it produces is also about one to four. But all the work of the body is done by muscles; hence they produce also practically all the heat. This is the meaning of the normal muscle tonus, which represents continuous heat-productions.

A small proportion of heat is also produced by glandular activity, and, on the authority of Mosso, by the central nervous system.

We now perceive the meaning of the shivering or rigor associated with the onset of acute fevers, and of the increased tone of the muscles at this period even in cases where there is no rigor. It is the immediate cause of increased heat-production, and is associated with the resultant rapid rise of body temperature.

Thermogenesis, therefore, is a function chiefly of the muscular metabolism. What is the relation of the central nervous system to this process, and how is the regulation of the process carried on?

Liebermeister showed that if an individual be placed in a bath at body temperature, so that no heat can be lost except by respiration, yet the body temperature does not rise—at any rate, at first. It follows, therefore, that the normal heat-production can be diminished by the nervous regulation.

Then Pflüger showed (about 1880) that if the body temperature be slightly lowered by exposure to cold,

there is an increase in the respiratory exchange, evidencing an increased heat-production. But if the experiment be done on animals, employing equal artificial respiration first on a normal animal and then after the muscles have been paralyzed by an injection of curare, it is found that in the latter case there is a fall of temperature on exposure of the animal to cold, showing that the power to react to such exposure is dependent on the muscular metabolism of the normal animal.

Some ten years later the subject was again investigated by Zuntz, a former pupil of Professor Pflüger. Zuntz showed both on himself and others that the reaction to cold is partly conscious, and is controllable by the will ; that is to say, that if a man shivers under the influence of cold his heat-production is thereby increased, and if he shudders the increase is very considerable ; but if by an effort of the will he restrains the shivering (and this is possible), there is then no increase of the heat-production under the influence of external cold.

The increased heat-production, therefore, is the result of a subconscious psychical reflex, comparable to the usual reflex which leads to closure of the eyes on the sudden approach of foreign bodies ; it is a more or less instinctive reaction, but is in no sense a true reflex process.

Thus, then, we see that heat-production *can* be controlled in both directions by the nervous system, either to lessen or to increase the existing rate of out-

put. And MacAlister came to the conclusion that such a regulation was in normal and continuous action. This supposition, however, as pointed out by Burdon Sanderson, is by no means necessary. In the warm-blooded animals, the supply of heat is always in excess, whether external conditions be such as tend to lower the body temperature or not. Whatever these may be, the body temperature would tend to rise at any moment if the surface loss should cease. If the available supply of heat were not thus in excess of the requirement, there could not be a regulation at all. You cannot regulate a tap to allow a flow of water of, say, a cubic foot a minute if the supply in the pipe can fall below this quantity. And the experiments of Zuntz showed clearly that even though the tendency to shiver on exposure to cold be fully inhibited by an effort of the will, so that there is no increase in the heat-production, yet the body temperature maintains its normal level, owing to the natural excess supply of heat.

It is accordingly not necessary to suppose, as some have done, the existence of a thermogenetic centre in constant action, nor is such constant action *a priori* probable. Heat regulation is a development of evolution in the higher animals ; and the results of evolution tend to be such as act to the advantage of the animal concerned. This could not with propriety be said of a regulation which necessitated a change of muscular activity with every change of the external temperature conditions, quite irrespective of

the existence or otherwise of a demand for muscular activity in the form of work.

Conditions which call for a direct diminution of the thermogenesis are only of rare occurrence in natural surroundings; and the increase of thermogenesis associated with shivering is, as we have already seen, of psychical origin. It is not essential to the maintenance of the body temperature in ordinary circumstances, and it is due not to a lowering of the body temperature, but to the sensation of cold resulting from a diminution of the surface temperature of the skin. The same is true of shivering and rigors in fever. The old and often-repeated statement that the fevered patient shivers *although his skin is hot* is absolutely without any vestige of foundation. Exact investigations by the thermo-electric method have proved that in these cases the *skin temperature is considerably reduced*, and that, during the period of accession, while the body temperature is rising that of the skin is undergoing marked and definite diminution. The rigor, therefore, is the consequence of sensory impulses ascending from the cold skin surface, and is exactly comparable to the shivering in the experiments of Zuntz of which I told you, and which is purely psychical in origin.

The increased heat-production of fever as a whole is therefore not the result of the action of a thermogenetic centre, nor of the paralysis of a thermo-inhibitory mechanism; it must be the direct result

of a katalytic action of the febrile agent on the tissues, and of the increased katabolism due to heightened temperature.

Distribution of Heat.—The distribution of the body heat is effected chiefly by the circulation. The temperature of a muscle even outside the body may be raised as much as 0·5° to 0·8° C. (1° to 1·5° F.) by throwing it into a condition of tetanus; accordingly, the blood flowing from active muscles is perceptibly warmer than that which reaches them. By the constant circulation of the blood through all the tissues the temperature of the different parts tends to be equalized, and heat produced locally is rapidly distributed throughout the body.

Without a circulation the existence of the larger animals would be quite impossible. The heat produced would then only be carried to the surface slowly by direct conduction, and this would mean that while the surface temperature tended to the level of that of the surrounding objects, the heat as one proceeded inwards would steadily increase, until a temperature was reached at which the life of cells would be impossible. A condition comparable to this is sometimes seen in the rapid rise of the internal temperature in fever cases after death, when circulation ceases, while the heat-producing processes are still in active operation. The importance of the circulation in maintaining a relatively uniform temperature throughout the body is therefore fundamental; it is sometimes too little recognised.

Now, we have seen that in the course of fevers the circulation is considerably slowed; and this must necessarily retard the distribution of heat. Hence there will be a greater difference than normal between the temperature of the internal parts and that of the body surface, the former being raised out of proportion to the surface temperature. But an increased temperature means increased katabolism. Thus, it follows that the disturbance of the rate of blood-flow tends of itself to increased heat-production, and to an increase in the loss of nitrogen, apart from any special katalytic action of the febrile agent.

The actual amount of increase in the heat-production in the course of fever is a variable quantity. In the experiments of May, already mentioned, it was found to be about 10 per cent. greater than that produced in inanition. Thus, in the experiment already quoted the animal in inanition showed a daily waste of 14 grammes of proteid and 10 grammes of fat, while in a condition of inanition with fever added the figures were for proteid 18 grammes, and fat 10 grammes, as before. Reducing these to their heat values, we have as follows :

	Inanition.	Inanition plus Fever.
Proteid - -	54·3 calories	69·0 calories
Fat - - -	92·0 ,,	92·0 ,,
Total - -	146·3 ,,	161·0 ,,

giving an increase of about 15 calories on a total of about 146, which is approximately 10 per cent. Nebelthau found an increase never exceeding 10 per cent., and frequently a good deal less than this amount.

Heat Discharge.—The discovery by Claude Bernard in 1852 of the existence of vaso-constrictor nerves, and then by Schiff a little later of the vaso-dilators, evidencing as they did the regulation of the circulation, and especially of the cutaneous circulation by a nervous centre, paved the way for Traube's view of fever as a disorder of the process of heat-discharge, and led to what is spoken of as the *retention* theory. This explained the pyrexia as the outcome of a diminished surface loss of heat—that is to say, an abnormal retention of heat within the body. The diminished loss was attributed to vaso-motor spasm causing constriction of the cutaneous vessels. This Traube believed continued throughout the fastigium of the fever.

Liebermeister, on the other hand, maintained, as we have seen, that the pyrexia was due to the increase of heat-production by the animal. This position is, however, quite untenable. Violent muscular exertion will give rise to an increase of heat-production as great, and frequently much greater than occurs in fever, even up to as much as double or treble the normal ; the effect of feeding on a fasting animal is precisely similar, yet no pyrexia results, because the normal regulation leads to a proportionate increase of the heat-discharge.

It is this regulation and the regulating mechanism which are at fault in fever. The existence of a regulation is, as we have seen, only made possible by the fact that the heat-producing processes tend to exceed the requirements of the organism; and hence it is that a disturbance of the regulation leads to pyrexia, and not to a diminished temperature.

Only on the failure of the heat-producing activities as death approaches does pyrexia give place to collapse and subnormal temperature where these occur. Conversely, whenever the body temperature rises, regulation is at fault. This is the crucial fact which must be firmly and clearly grasped to obtain a true conception of the pyrexia of fever. It is not that heat-production is increased, though this occurs; nor that the discharge is diminished below the normal, for this is not the case during the fastigium; but that the two opposing mechanisms are no longer balanced, which gives rise to the development of pyrexia. The regulation is disordered, so that the discharge is not co-ordinated to the heat-production; not *enough* heat is given off in fever.

Discharge of heat occurs by conduction, radiation, and evaporation from the surface of the body. A proportion, probably less than one-fifth of the whole, according to MacAlister, is also lost in the respired air which has been heated in the naso-pharynx. This latter portion is under no direct control; it

varies with the temperature of the air breathed—colder air requiring more heat to raise it to the normal temperature—and with the rate and amplitude of respiration. In animals which do not sweat—as, for example, dogs—it is a most important factor in the thermolytic process, but in man it plays a comparatively unimportant part.

The surface loss of heat is governed firstly by the vaso-motor mechanism, since the rate of heat loss from the surface is dependent on the state of dilatation or constriction of the cutaneous vessels, and the rate of flow within them. It is governed also by the so-called sudo-motor or hidrotic nerves, the nerves which regulate the secretory activity of sweat-glands. These nerves, which have been investigated more especially by Langley, were discovered by Luchsinger. They take their origin from the same region of the central nervous system as the vaso-motor nerves, follow a similar course, and have a very similar distribution. But that they are entirely independent of the latter system is shown by the occurrence at times of sweating associated with constriction of the cutaneous vessels—the so-called cold sweats—and by the fact that stimulation of certain nerves—for example, of the peripheral end of the divided sciatic of a cat—may produce vaso-constriction and sweating of the pad of the foot at the same time.

In the process of the conversion of water into aqueous vapour, a large amount of heat becomes

latent or is absorbed, and hence a considerable portion of the surface loss of heat from the body is got rid of in the evaporation of the sudatory secretion. This is the means by which the body temperature maintains its normal level in the presence of great external heat where loss by radiation and conduction have become impossible—as, for example, in the hotter chambers of a Turkish bath. And this explains why great external heat is much more difficult to tolerate in a moist atmosphere where evaporation is limited—as, for example, in certain parts of India—than in a drier climate.

In conditions of health, whenever circumstances tend to cause a rise of body temperature above the normal, these two nerve systems, the vaso-motor and the sudatory nerves, exert a prompt and an efficient regulating action, and by increasing the discharge of heat at the body surface prevent disturbance of the normal temperature. This action fails in fever. In many fevers the skin remains throughout remarkably dry, owing to a cessation or great diminution of its secretory activities. In some, however, as in rheumatic fever, there may be considerable perspiration going on. The feeling of heat imparted to the hand by the skin of fever patients is in great part attributable to its abnormal dryness, which improves conduction, for what is estimated by the hand is not the actual surface temperature, but the conduction rate of the part with which it is in contact.

The cutaneous circulation is disordered in a similar manner. In the accession of fevers which begin with definite chills or rigors, there is undoubtedly a spasm of the cutaneous vessels ; this is well seen in ague. The rigor, as we have already seen, is the result of sensory impulses of cold ascending from the cold anæmic skin. It may at times be reinduced, especially in the early part of the fastigium, by an exposure of the surface of the body, which leads to a rapid cooling of the skin. The arterial spasm, however, does not persist, as Traube thought, but yields in the fastigium to a condition of variable and varying dilatation of the vessels with diminished rate of blood-flow. With the establishment of defervescence, and especially marked when this occurs by crisis, there appears a re-establishment of sudatory activity with copious perspiration, and a marked dilatation of the cutaneous vessels with a rapidly increasing flow of blood to the surface—that is to say, a restoration of the thermolytic process to its normal capability.

The characteristic feature of the fastigium is the great variability of the cutaneous vascular conditions, so that even rough measurements show differences in temperature between the different parts of the skin surface at one and the same time, and between the same part tested at different times, such as are quite unknown in normal health.

The paresis of the vaso-motor system which occurs in fever is further evidenced by the fact that the

vessels do not react to stimuli so readily as in the normal animal. So long ago as 1870 Heidenhain showed that in fever reflex stimulation of the vaso-motor centre does not, as in health, give rise to an increase in the cutaneous circulation, but rather the reverse; there is no vaso-dilatation. And in continued fevers one can readily demonstrate the fact that the reaction of the vessels is very sluggish by drawing the finger firmly along the skin. The line thus pressed upon becomes pale, and the pallor lasts for several minutes, fading quite gradually, and spreading slightly at the edges in the meanwhile.

The condition of the cutaneous vessels in the course of fevers has been investigated accurately by Maragliano with the plethysmograph, and by the thermo-electric method by Geigel. Geigel used a pair of junctions of German-silver and iron, one pair being applied to the skin of the patient, and the other kept in a vessel of oil at constant temperature. The variations of the skin temperature were indicated by the amount and direction of the current produced. This method gives the actual skin temperature; all thermometric measurements are entirely unreliable for this purpose; they are affected by the underlying tissues, and give a record of the temperature an indeterminate distance underneath the skin.

The observations carried out by Geigel proved the following facts: During a rigor the skin temperature sinks very considerably, so that the difference

between the surface and internal temperatures increases rapidly. In the fastigium the surface temperature is only very little greater than in health, but it is much more variable ; it is not uniform in the same part at different times, nor identical in different parts at the same time. The commencement of the defervescence is signalized by a rise of the skin temperature, due to the now increasing circulation through it.

Similar results were obtained by Maragliano with the plethysmograph applied to limbs. The accession of an attack is marked by definite diminution of the volume of the limb, the result of vascular constriction ; while increased volume due to increased circulation precedes the occurrence of the crisis, and appears some time before the critical sweating commences. And there may be a gradual and steady increase in volume throughout the latter part of the fastigium. During the fastigium there is, on the whole, a condition of moderate vasodilatation.

Although, as we have seen, the regulation of temperature is disordered in fever, so that not enough heat is lost to balance the increase of heat-production, yet the thermolytic mechanisms are far from being entirely paralyzed. The loss of heat is actually increased in fever, and frequently the increase is very great. It may amount to as much as 50 per cent. above the normal rate of heat-discharge, according to Richter. This is the meaning of the

continuous though variable condition of vaso-dilatation during the fastigium, a condition which contrasts most strikingly with the persistent vaso-constriction seen in cerebral pyrexia, of which I shall speak directly. Were it not so the increased heat-production would of course result in a continued rise of temperature, terminated only by the patient's death.

The thermolytic mechanism, therefore, is not paralyzed, but only weakened in its action and control. It may be stimulated to renewed activity by certain powerful drugs usually referred to as antipyretics. These were discovered by Filehne some twenty years ago, and he himself investigated the properties of the first two which were obtained —kairin and antipyrin. Their action is, as Burdon Sanderson puts it, translating the expression of Filehne, to open all the sluices for the escape of heat from the surface.

Experimenting with such drugs, Geigel has shown that the diminution of the internal temperature which results from their administration is preceded and accompanied by an increase of the skin temperature. And Maragliano found with the plethysmograph that in similar circumstances a dilatation of the peripheral arteries accompanies the fall of temperature, and that, as the effect of the dose administered passes off, the reappearance of pyrexia is initiated by a diminution in the volume of the limb. Richter, again, using the method of calorimetry, found that

the loss of heat increases under the influence of the drugs in question some 25 per cent. above the previous rate of loss in fever, and about 75 per cent. above the normal rate of heat-discharge in health. These three independent observations, therefore, show alike that the action of these drugs is to increase the rate of thermolysis, and this occurs by stimulation of the vaso-dilator centre in the central nervous system.

The experiments also serve to show most clearly, as Burdon Sanderson distinctly pointed out, that the mechanism which regulates the *loss* of heat at the body surface is capable of giving rise to alterations of the body temperature as great as any which occur in fever. And hence it follows that there is no evidence to be obtained—from this direction, at any rate—of the existence of a thermogenetic centre whose function is to exercise a *continuous* control on heat-production, and whose activity is disordered by the action of the febrile agent.

Since pyrexia is not due essentially to a diminution of thermolysis, nor necessarily results from increase of the thermogenesis, but is the outcome of disturbance of the regulating mechanisms which normally adjust and balance these two processes to secure an even normal temperature, it follows that pyrexia will occur not only in fever, but also under every other condition which similarly disturbs the regulating centres. This is well seen in certain cerebral injuries. Its meaning was most thoroughly discussed by Hale

White in his article on 'The Theory of a Heat Centre from the Clinical Point of View,' in the *Guy's Hospital Reports* for 1884.

The influence of the nervous system over body temperature was first investigated by the great physiologist Claude Bernard, who found that after division of the cervical cord an animal becomes incapable of normal maintenance of its body temperature. The observation, however, does not afford any evidence on the question of the existence of so-called calorific nerves, since the result is capable of explanation as due to the complete paralysis of the muscles and of the vaso-constrictor channels of control, leading, on the one hand, to diminished heat-supply from diminution of the muscular metabolism, and, on the other, to an increased loss from the dilated vessels of the skin.

It was, however, observed by Wood, in 1880, that injuries inflicted on the brain in the neighbourhood of the great basal ganglia were followed by considerable rise of temperature. This was confirmed by Aronsohn and Sachs, who showed that the supposedly existing thermic centre was situated in the corpus striatum and the optic thalamus, as had been claimed by Wood. Still later Hale White showed in a whole series of experiments that the centre in question is limited entirely to the former of these ganglia, and lies especially in its anterior end. Lesions confined to the optic thalamus alone did not produce pyrexia at all. The area in question corresponds to the so-

called nodus cursorius of Nothnagel. Wood showed by the calorimeter that in these cases there is an increase of the heat-production. And in his Croonian Lectures for 1897 Hale White recorded two clinical cases in which a unilateral paralysis was associated with unilateral pyrexia on the paralyzed side, accompanied by unilateral increase of sweat on the same side, and increased surface temperature, as estimated by the flat coil of a mercurial 'skin thermometer'; while there was no visible appreciable difference in the vascular conditions on the two sides of the body.

Such observations have been taken to show that cerebral pyrexia is the result of a disturbance of a nervous centre whose normal function is the regulation of the heat-production. MacAlister, in his Goulstonian Lectures in 1887, had also summed up in favour of an independent regulation constantly controlling thermogenesis, and incidentally put forward the conclusion that the heat-forming processes in muscle are altogether independent of its motor functions.

The question is a very complicated one, and one which it is hardly possible to answer definitely in the present state of knowledge. But the following considerations are of great importance, in a sense adverse to the conclusions of MacAlister :

Firstly, in cerebral pyrexia there is throughout a marked constriction of the superficial vessels ; these are in such conditions so incapable of responding

normally to a rise of body temperature that if the rabbit used for the experiments be placed in a hot chamber at 37° C. it rapidly becomes hyperpyrexial, and yet its ears remain quite pale from the persistent vascular constriction present—that is to say, its surface loss of heat is markedly reduced by vascular spasm. Similarly, by reducing surface loss of heat in healthy animals by keeping them in a chamber at 37° C. their temperature may be brought up to fever heat and there maintained. And hence pyrexia could be accounted for by diminution of the thermolysis. Further, the increased heat-production of cerebral pyrexia is not so great but that it might be explained as the *result*, and *not* the *cause*, of the raised body temperature, since increase of the temperature alone leads of itself, as we have previously stated, to increased katabolism—that is, to increase of the heat-production.

Secondly, we have seen that if the thermolytic mechanism is in order it is capable of dealing with very great increases of the thermogenesis, as great or greater than occurs in cerebral pyrexia, without permitting any rise of body temperature.

Thirdly, as Gottlieb found, in cerebral pyrexia the action of such drugs as antipyrin, though it increases the discharge of nitrogen—that is to say, leads to increased katabolism—yet brings down the temperature to normal by giving rise to an increase of surface loss by means of vascular dilatation precisely as it does in fever cases. From which it follows that, even

when the heat-production is above the normal, a normal temperature can be maintained so long as the thermolysis is not impaired.

The increased sweating on the hotter side in Hale White's cases by no means proved that there was no diminished loss of heat upon that side, but only that the lesion of the regulating centre was so placed as not to have involved the sudatory mechanism. This being uninjured, an increase of sweat formation would naturally accompany the unilateral pyrexia, which it would not abolish, since sweating alone is insufficient to discharge the amount of heat to be got rid of if a normal temperature is to be maintained. This latter statement is completely proved by the phenomena of rheumatic fever.

The point at issue can only be decided satisfactorily by the use of the plethysmograph upon such cases in order to determine the exact condition of the peripheral circulation, and by the application of the thermo-electric method of determining the surface temperature. The mercurial skin thermometer, as MacAlister has pointed out, does not by any means give a true reading of the surface temperature, but records that of the parts some little distance in below the skin, where obviously the temperature is over normal in such cases.

On the whole question Burdon Sanderson sums up the evidence adversely to the theory that there exists a special thermogenetic centre which is constantly in action. But whatever be the view which

we accept upon this question, it is essential to clearly recognise that such pyrexia as occurs in certain cases of head injury is not fever. It has no stages such as characterize a fever, but the temperature rises gradually to reach its height and then gradually again subsides. There is no rigor, and the vascular conditions are not those of fever, in which throughout the course of the fastigium the vessels show a moderate dilatation. It is not preceded nor accompanied by a nutritional disturbance; and, most important of all, its cause is not the same, but is entirely different from the cause of fever.

The question of the etiology of fever is still an open one in its minuter details, but certain valuable evidence is forthcoming on this subject. It had already been found that septic material or the products of acute inflammations were capable, when introduced into the subcutaneous cellular tissue or the circulating blood, of giving rise to fever in the inoculated animal. And with the development of bacteriology and the discovery of the relation of bacteria to infective processes the view arose that the pyretogenetic or fever-causing property of such substances was dependent on the presence in them of bacteria. Burdon Sanderson, however, was able so long ago as 1875 to prepare from putrefying animal matter bacteria-free substances which none the less were capable of giving rise to fever. To the material thus obtained he gave the name of pyrogen. It was prepared by destroying all bacteria and pre-

cipitating at the same time most of the proteid matter of the tissues used by means of alcohol; the fluid was then filtered off, and the filtrate evaporated to dryness to remove the alcohol, and redissolved in water. Its property of causing fever was removed by filtering it through porcelain. From the results he came to the conclusion that the substance causing fever might be a body analogous to the enzymes. A little later Edelberg discovered that fibrin ferment can similarly give rise to fever on injection; and it was subsequently found that all commercial enzymes will produce the like result.

Kühne, however, was able to determine that the absolutely pure enzymes which he prepared have no such action. This he accordingly concluded must be due to the proteid disintegration products present in such enzymes as ordinarily prepared. He further showed that albumoses derived from various sources, and notably the deutero-albumose which he obtained from samples of tuberculin, possess a similar action. And Krehl has found a fever-causing albumose in cultures of the *Bacillus coli communis;* while Matthes has obtained a like result with albumoses formed in ordinary digestion. Rouques, moreover, showed that similar bodies can be extracted from fresh animal tissues, and hence that normal cells contain materials capable of giving rise to fever-causing substances. And all the evidence submitted goes to show that these are either albumoses,

or, at any rate, so intimately associated with the albumoses as to be precipitated with them from solution. Their action in the living body is to cause a disorder of metabolism associated with disturbance of nutrition, and to produce derangement of the thermotactic centre in the brain, causing impairment of the thermolytic mechanism.

Fever, then, is not, as the old writers thought, a state of overaction of the normal functions, but is a process characterized, as Virchow claimed, by partial loss of power—an interference with the normal processes.

The pyrexia is not the effect of increased heat-production, as was taught by Liebermeister, although the heat-production is in fact increased; nor is it due to a diminished loss of heat, as Traube held, for the heat-loss is not diminished, but is actually increased. It is the result of a disorder of the regulating mechanism by which these processes of thermogenesis and thermolysis are normally adjusted. And this disorder of the thermic regulation is both preceded and accompanied by a disturbance of the nutritive exchanges similar in kind to that which is observed in inanition though greater in degree. Further, although a special heat-production centre may perhaps exist, no evidence in this direction is to be obtained from a consideration of the events of fever nor of the phenomena of pyrexia in general.

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