THE CROONIAN LECTURES
ON
THE PROGRESS OF DISCOVERY RELATING TO THE ORIGIN AND NATURE OF INFECTIOUS DISEASES.

Delivered before the Royal College of Physicians of London.

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LECTURE II.

Production of Inflammation by Chemical Irritants; Councilman's Experiments; Scheuerlen's Experiments.—Production of Inflammation by the Chemical Products of Microphytes.—Leucocytes and the Chemical Noxæ produced by Phlogogenic Microphytes; Chimiotaxis.—Metschnikoff's Theory of Phagocytosis.—Its Application to the Pathology of Erysipelas.—Is Inclusion in a Leucocyte an Invariable Antecedent of the Death of the Microphyte?—Effect of Leucocytes on the Multiplication of Microphytes.—Destiny of Microphytes in Susceptible and Insusceptible Animals.—Views of Hess and Bouchard.—"Aggravation" and "Attenuation."

IN the discussion of the etiology of inflammation in the last lecture I understood the word inflammation to be the name for the changes which occur in a living tissue in consequence of an injury, and the general result was that in all those instances in which suppuration occurred, under ordinary conditions, the efficient cause of the morbid process was a morbific microphyte—it being understood that there are several species of microphyte which can more or less replace each other as pus-producing agents.

Up to the time which immediately preceded the discovery of these microphytes the principle was accepted in pathology that an inflammation might be produced either by a mechanical, by a chemical, or by a thermal injury, that is, that it might result from violence, from the action of an irritant, or from exposure to heat or cold; but, long before these specific characters were recognised, experiments, such as those of Professor Kocher, of Berne (of which I gave an account in my lecture in 1882), in which he found it possible to subject the most vulnerable tissues, such as the marrow of bone, to mechanical injuries of the most violent kind, provided only that microphytes were excluded, as well as the experience which was year by year accumulating in the practice of antiseptic surgery, had made it clear that at all events mechanical injuries were incapable of giving rise to suppuration of themselves, but the question whether the proximate cause of an inflammation may be purely chemical was, up to a very recent period, undetermined. The previously-accepted belief—according to which suppuration could be produced by any chemical irritant of sufficient intensity—was discredited by the insufficiency of the evidence afforded that in all the instances investigated microphytes were rigidly excluded. Consequently the dictum commonly attributed to Weigert—"no suppuration without bacteria"—became generally accepted.

My aim must be just now to restore the old doctrine in so far as to show that, leaving out of consideration those wholly exceptional instances in which inflammation is produced by exposure to heat and cold (and which have not yet been investigated in their relation to microphytic influence), its proximate cause is always chemical. To justify this proposition I must show, first, that inflammation, that is suppuration, can be produced by chemical agents in the absence of microphytes, and, secondly, that when it is produced by microphytes the action is chemical.

For the establishment of the second point I shall have to refer to a series of observations, extending over about eight years, made by a number of highly competent bacteriologists. The methods of experiment by which the proof has been finally attained are various, but of them all the essential feature is to introduce sterilised irritant liquids either subcutaneously or into serous cavities, using precautions to preclude the entrance with them of microphytes. Experiments of this kind were made as early as 1881, but it was not until after that time that the perfect means of sterilisation and the improved *technique* of infection experiments which Dr. Koch had created had come into general use. One of the first of the more exact investigations of the subject which this technical advance rendered possible was that of Dr. Councilman,[1] at the suggestion, I believe, of the late Professor Cohnheim. It consists, first, in charging capillary tubes with the liquid to be experimented on, closing the ends hermetically, and then, after sterilising the tube and its contents, introducing it under the skin, and closing the wound antiseptically. After it has remained *in situ* for several days it is broken between the fingers, so as to discharge its contents subcutaneously. This method is not open to any objection as regards risk of contamination, provided that it is properly carried out. It may, however, be alleged that inasmuch as even a glass tube becomes encapsulated—that is, becomes surrounded by cicatricial tissue which is known to be relatively liable to inflammation—the experiment does not afford a true criterion of the susceptibility of perfectly normal tissue to the chemical agent which it is desired to test.

This consideration led Dr. Scheuerlen,[2] then a student, who worked at the subject later, to improve on the Cohnheim method by substituting fusiform for cylindrical tubes, and to introduce the tube under the skin, say over the sacrum, to shove it up to the neck and let it rest. Then, having ascertained that it produces no disturbance, move it to a new position, and at once break both points. By this method the contained liquid very slowly finds its way into the subcutaneous tissue. Similar tubes may be used for introducing liquids into the peritoneum, in which case it is desirable to attach them to the wound by a long sterilised silk thread. In all cases the skin must be washed with alcohol, and disinfected with 1 per cent. corrosive, and then covered with a layer of collodion.[3]

In all these experiments it must be understood not only that the materials used are sterilised, and that they are introduced with the most rigid antiseptic precautions, but that the pus obtained or produced is tested by cultivation, and that dry cover-glass preparations are subjected to microscopical scrutiny. In every instance, provided that the experiment has been properly performed, the inflammatory exudation liquid is sterile.[4]

The conclusion to be derived from these facts scarcely needs stating. It is not true, as we once inclined to think possible, that suppuration can only be brought about with the concurrence of microphytes. On the other hand, experiments show that the readiness with which pus is formed depends on conditions which belong to the animal rather than to the noxa. For while in the dog a sterile abscess can be produced with ease with such different agents as mercury and turpentine, it is much more difficult to obtain this result in a rodent.

The other point I have undertaken to prove is equally important. It is not only true that inflammation can be produced without the co-operation of microphytes, but that when these organisms are directly concerned in its production, their mode of action and its proximate cause are still chemical. We have already seen that the two effects which the cluster coccus exercises on its surroundings are, first, destruction of the vitality of the elements which come immediately within its influence; and, secondly, the evoking of exudation and emigration of leucocytes from the capillary blood-vessels in the neighbourhood

[1] Councilman, Zur Ætiologie der Eiterung, *Virchow's Archiv*, vol. xcii.
[2] Scheuerlen, Weitere Untersuchungen ueber die Enstehung der Eiterung, *Langenbeck's Archiv*, vol. xxxvi.
[3] The chemical substances experimented on, either by this or by other methods, have been extremely various. I can refer only to the most important, such as, among inorganic substances, mercury, nitrate of silver, and ammonia; among organic, turpentine and croton. Mercury produces suppuration in the dog, not in the rabbit. In the former, if it is injected hypodermically, each drop becomes the centre of a minute abscess. Silver nitrate in 5 per cent. solution produces suppuration in the dog with great certainty, but not in rodents. Ammonia fails to produce pus in any animal. It is either absorbed or kills the tissue with which it comes into relation. Of organic substances, the body which has been most experimented on is turpentine. In the carnivora it produces abscess with great certainty. The action of croton is similar but inferior.
[4] J. Steinhaus: *Die Ætiologie der acuten Eiterung*, Leipzig, 1889, pp. 152-170

—effects which can only be explained on the supposition that these microphytes, so long as they continue to vegetate and multiply, give off products which are sufficiently diffusible to impregnate the tissue, but not sufficiently so as to be easily absorbed. The experimental proof that this is so lies in the observation that, not only in the case of staphylococcus but in that of many other micrococci, the symptoms which result from the presence of the microphytes themselves in the living organism can also be produced by the soluble chemical products of their vegetation. So long ago as 1878 M. Pasteur[5] showed that cultures of the *microbe générateur du pus* which had been sterilised were as capable of producing abscess as living cultures, and that the resulting pus was sterile; but it was not until a few years ago (1887) that Grawitz[6] made similar experiments with pure cultures of pyogenic microphytes, particularly with the ordinary staphylococcus. Since then various other experimenters have investigated the subject in relation to this and other pus-producing microphytes, with the general result that in carnivora sterile abscesses can be produced with the same certainty by the injection or introduction of devitalised cultures of staphylococcus, as by turpentine or mercury.

PART II. BEHAVIOUR OF LEUCOCYTES IN RELATION TO PHLOGOGENIC MICROPHYTES AND THE CHEMICAL NOXÆ PRODUCED BY THEM.

When a capillary tube containing a bubble of mercury is introduced underneath the skin of a rabbit, and the ends broken, almost the only sign of reaction is that leucocytes creep in at the ends. The behaviour of leucocytes in this and other similar cases has for the last twenty-five years attracted the attention of pathologists, and has repeatedly suggested the idea that the movements of these "wandering cells" are guided by something like discrimination. Of late the theory that leucocytes are endowed with special powers for the protection of the organism against the invasion of contagious microphytes, and that they first swallow and then digest them, has been so energetically advanced by its author, and supported by arguments and seeming proofs of so convincing a character, that it has exercised a very marked influence.

But before we enter on the examination of the experiments on which this theory was founded, I am desirous to draw your attention to another aspect in which the part which leucocytes play in the process of inflammation and their function as phagocytes may be considered. It was several years ago observed by the distinguished plant physiologist, Professor Pfeffer, with reference to a variety of motile unicellular structures, that the power which they enjoy of locomotion in water, and particularly their power of apparently guiding their own movements, may be accounted for on the principle that in executing them they are allured towards any substance in the media in which they live, provided that it is not too remote; and that the attracting object contains some soluble constituent which is, so to speak, agreeable to the attracted organism, with which its immediate neighbourhood is impregnated. To this attraction, which seems to imply the existence in the simplest organisms of a rudimentary sense of taste, Pfeffer has given the name chimiotaxis, denoting thereby that however incomprehensible the movement may be, there is yet a definite relation between it and the chemical substances by which it is enticed, or, putting it otherwise, between the vital movement and the chemical action which determines it.

Now as regards leucocytes, we have long—I might even say all along—recognised that although their power of amoeboid movement may explain their power of incorporating objects with which they come into contact, and may even help us to understand their ability to squeeze themselves through very narrow openings in the walls of the blood vessels, it does not serve to account for their tendency to emigrate.[7] A few years

ago it was suggested by Dr. Lebert that the migration of leucocytes might be regarded in the same light as the migration of antherozoids and zoospores had been regarded by Pfeffer, that is, the escape of the colourless corpuscles might be due to the existence in the tissues of chemical substances attractive to them. The suggestion has since led to a number of experimental investigations of which those of Buchner in Germany, of Massart and Bordet in Belgium, are perhaps the most important.

The method employed is similar to that which I have just described in its application to the determination of the phlogogenic properties of various chemical substance. In its simplest form it consists in charging a capillary tube with the liquid of which the "chimiotactic" property is to be tested, closing one end and then introducing it into the lymphatic cavity of a frog, the result being that if the material is chimiotactic, leucocytes swarm round the open end of the tube and crowd into the liquid it contains. It might, however, be objected that these phenomena are merely the indications of a process of inflammation, consequent on the presence of a foreign body in the lymph sac. It is, however, easy to give such a form to the experiment as to exclude this interpretation. The plan which I have myself adopted is to seal two capillaries together, and to charge the one with the liquid to be tested, as, for example, with sterilised culture of staphylococcus, the other with an indifferent fluid such as the fresh bile of the frog. The contrast between the one and the other affords the required evidence that in "going for" bacterial product the leucocytes are actuated by their own free choice. But, in admitting this, we must guard against the supposition that in the exercise of this choice the leucocytes are impelled by a "protective" motive, for Buchner has conclusively shown that although the constituents of certain microphytes are specially attractive to them, they are scarcely less partial to products of similar nature derived from the tissues of the higher plants.

The facts of chimiotaxis may serve to explain how it is that leucocytes, like vultures, gather together wheresoever the carcass is, but they do not afford any support to the theory of Metschnikoff that they are actuated by an almost conscious discrimination between what is advantageous and what is detrimental to the organism as a whole.

The Phagocytic Theory.

In the examination of that theory which I propose to begin to-day we shall see, while we are now able to understand better than was before possible, that as Sir John Simon taught thirty years ago, there is an antagonism between inflammation and contagion, between leucocytes and viruses of all kinds, there is no reason for attributing this to the maintenance of a mysterious relation between the leucocyte and the organism with which it is no longer in structural continuity.

Metschnikoff's theory was first developed in 1884. It was founded on a theoretical conception derived from the science of morphology—namely, that the familiar process by which a leucocyte takes into its own body any small solid particle which happens to be suspended in the liquid medium in which it lives is an attribute which it derives by inheritance from the remote progenitors of the animal of whose body it forms a part;[3] that is, eventually from amoeba and less remotely from coelenterates, the mesodermal cells of which enjoy this faculty of incorporation in a high degree. That in these animals intracellular incorporation performs an important part in digestion and in the absorption of effete structures there is no reason to doubt, nor is there any doubt that not only leucocytes but other fixed cells of mesodermal origin exist in the bodies of vertebrates and are capable of incorporating. The fact has been familiar to every student of medicine for twenty years, and known to physiologists much longer; but it remained for a morphologist to point out to us that we saw and perceived not, that the intracellular incorporation is in reality a protective mechanism, and that the cells which exercise this function are endowed with the power not only of distinguishing between what is advantageous and what is pernicious, but of appreciating all the fine distinctions of ills to which flesh is heir. All such cells Metschnikoff calls "phagocytes," and speaks of them as of two kinds, "microphages" and "macrophages"—words which, it is to be hoped, will not find their way into the English dictionary. Under the former term he includes what for the last twenty years we have commonly called "leucocytes;" under the second a variety of histological elements, most of them old friends, among which are included connective tissue corpuscles, the large pulp cells of

[5] L. Pasteur: De l'extension de la théorie à l'étiologie de quelques maladies communes, *Bulletins de l'Acad. de Méd.*, November 4th, 1880, p. 435.
[6] Grawitz u. de Bary: Ueber die Ursachen der subcutanen Entzündung u. Eiterung, *Virch. Arch.*, vol. 108, p. 67.
[7] In describing the phenomenon for the first time in 1870, I admitted myself wholly unable to state why "in an inflamed part leucocytes should separate from the blood and tend towards the internal surface of the veins and capillaries." Metschnikoff, writing in 1883, makes this a reason for regarding Cohnheim's doctrine of inflammation as unsatisfactory.

[8] Metschnikoff, Untersuchungen ueber die intercelluläre Verdauung bei wirbellosen Thieren. *Arb. aus dem zool. Institut zu Wien*, vol. v, p. 141.

the spleen, and the large cells with vesicular nuclei which, in the mammalian liver, surround the capillaries--all of these have single vesicular nuclei—and finally the so-called epithelioid and giant cells of tubercle.[9]

It cannot, I think, be doubted that one reason why this theory has attracted so much attention is that its author, himself a morphologist, has clothed it in a language of science which is now in vogue. When the human or animal body is invaded by a morbific microphyte, he imagines a "struggle for existence" to occur between phagocyte and microbe. In this struggle it "adapts" itself to its "environment." According to Metschnikoff,[10] this adaptation is not only acquired by those leucocytes which have actually taken part in the fray, but is handed down to their posterity, and so their protective function is explained. One of the earliest subjects of observation was erysipelas, a disease well adapted to his purpose, as one of which the microphytic origin had been very definitely ascertained. But before I give an account of these researches I must remind you of one or two preliminary facts relating to the pathological anatomy of erysipelas.

Twenty years ago we knew, from the researches of Volkmann and Steudener, that in skin which is being invaded by the spreading inflammation the change consists in intense vascular injection of the superficial layer of the corium and corpuscular infiltration of the cellular tissue, following the course of the blood vessels and interfascicular spaces; and that the raised border which one feels with the finger in passing over the line of extension from the healthy to the inflamed area was due to exudation of liquid containing leucocytes, which in process of time were disintegrated and absorbed; but it was evident that changes must take place in the skin antecedent to the corpuscular infiltration, [11] and that, if such changes existed, they would be found, not in the inflamed skin, but in the skin about to be inflamed, not in the swollen line of extension, but beyond it. Guided by this consideration, Lukomsky, a young pathologist who worked under Professor v. Recklinghausen, was able to show by such methods as we then had at our disposal that the first stage in the erysipelatous process is not either exudation or emigration, but the choking of the lymphatic channels of the corium with micrococci. As to the nature of these micrococci, all that we then knew was that they were in chaplets, not in clusters. I had the opportunity of observing this in several cases at St. Thomas's Hospital, and particularly in one in which it was perfectly easy to obtain exudation liquid containing chains by tapping with a perforated needle the very edge of the spreading redness. No sooner had Koch introduced the present methods of discriminating microphytes than he, and at the same time Fehleisen, proved that the organism which Lukomsky had seen to occupy the lymphatic capillaries in the zone of apparently healthy skin was a specific organism. Pure cultivations were made by Fehleisen in 1881, and used for experiments on animals, which gave positive and unequivocal results.

Here, then, was a case eminently suited for illustrating the antagonism between leucocytes and microphytes. What are the details of the contest? Koch and Fehleisen both were able to show that in a spreading erysipelas cocci are to be found only at, or rather beyond, the visible edge of extension, where the skin is apparently as yet unchanged; and that at the swollen edge, where the vessels of the papillary layer begin to be injected, and leucocytes abound in the lymphatic spaces, the cocci are less abundant, and those that there are can no longer be stained. That they disappear, and that their disappearance is coincident with the appearance on the scene of innumerable emigrants, is not disputed, but how this happens is open to question.

Metschnikoff[12] observed first, that wherever the process goes on normally many leucocytes are charged with streptococci, although there are also many free from them: but that in parts which were "going wrong" incorporation was almost absent, and that the reason why the struggle for existence between leucocyte and microphyte terminated in favour of the latter was, to put it plainly, that there was not enough inflammation. Throughout, according to this view, the want of reaction is the sign, if not the source, of danger. The unfavourable condition in a wound which makes it likely to be the starting point of an erysipelatous inflammation is that it is not suppurating freely, and the unfavourable condition in an erysipelas already begun is that there is not enough corpuscular infiltration.

We have, therefore, here unquestionable antagonism between inflammatory reaction (that is, abundant exudation and emigration), and the manifestation of infective virulence, nor can it be questioned that the facts afford evidence of the beneficial influence of intracellular incorporation, in so far as they show that in general the issue is most favourable when the process is most active, and that we have in them a fresh proof of the power which the living body possesses of defending itself against the invasion of disease-producing microphytes. What they do not show is that this protective function is dependent on incorporation by leucocytes. All disease-producing microphytes die, some rapidly, others more gradually, when they are surrounded by the living tissues of man or the higher animals. All are sentenced to death. The question is—is death always preceded by imprisonment? This is a question which cannot be determined by merely watching processes from the side. It can only be determined by experimental methods, in the application of which no one has shown more resource and ingenuity than Metschnikoff himself.[13]

One of Metschnikoff's first experiments consisted in introducing under the skin of an insusceptible animal, the frog, a bit of liver or spleen of a rabbit affected with splenic fever. The bit, when examined a couple of days later, was coated with gelatinous exudation, full of leucocytes. These leucocytes were charged with bacilli, which he observed to be in various stages of degeneration.[14]

If the experiment was done at the ordinary temperature the frog was none the worse, but if it was exposed at the time and subsequently to a temperature of 38°, the leucocytes, paralysed by so high a temperature, failed in their office, the bacilli got the better, and the frog inevitably died. A much more exact observation of the same kind consisted in introducing under the skin of the same animal a membranous tube made of the lining of the common large grass which grows on the banks of rivers (phragmites) containing spores of bacillus anthracis. Soon the little tube filled with lymph, but contained no leucocytes, for to them the membrane is impermeable. A similar experiment was made with another tube, of which the ends were left open, so that leucocytes could enter. In a day or two both tubes were examined. The contents of the closed tube swarmed with virulent bacilli. In the open tube the spores had been so effectually disposed of by the leucocytes that the contents could be inoculated to susceptible animals without effect.

The proof by direct observation that a leucocyte may contain living bacilli, or, in other words, that incorporated bacilli are not necessarily defunct either as regards viability or virulence, is obtained by a most ingenious method. A "hanging preparation" of exudation, containing incorporated bacilli, was examined on the warm stage.[15] This done, a drop of nutritive bouillon previously placed on the under surface of the cover glass close to the drop of exudation, was brought into confluence with it. The addition of the bouillon to the exudation killed the cell, but afforded to the bacilli the required nutriment. In the course of an hour, during which the cell was watched under the microscope, the bacilli, by lengthening into filaments, had given unequivocal evidence that they were alive. But it might still be questioned whether they retained their virulence. To settle this, a cell which had been so observed was dexterously transported from the drop to another drop in which it grew to a felt work of fibres, and this was removed, eight hours after, into a flask of bouillon. Next morning this culture, the product of the bacilli contained in a single leucocyte, was used on a mouse,

[9] The introduction into Metschnikoff's theory of elements of such different kinds is a complication. As, however, the colourless corpuscles of the blood take chief part in the process of inflammation, it is to them that the prophylaxis of the body against the invasion of microphytes is chiefly assigned.
[10] Metschnikoff, Ueber eine Sprosspilzkrankheit der Daphnien, Virch. Arch., vol. xcvii.
[11] See the author's paper on Erysipelas in "Recent Researches on the Pathology of the Infective Processes" in Reports of the Medical Officer of the Privy Council, etc., N. S., iii, 1874, p. 19.
[12] Metschnikoff, "Ueber den Kampf der Zellen gegen die Erysipelkokken," Virch. Arch., cvii, p. 209.

[13] There are three ways in which the question can be approached, namely (1) by ascertaining in what way the multiplication of microphytes within the animal body is affected by the intervention or exclusion of leucocytes; (2) by the direct observation of the changes which incorporated microphytes undergo when watched under the microscope; and (3) by comparing susceptible with insusceptible animals as regards the way in which they deal with morbific microphytes when introduced into their bodies, it being understood that, as regards the last question a distinction must be made between animals in which insusceptibility is acquired with those in which it is congenital, or, as more often expressed, natural.
[14] Sur la Lutte de l'Organisme contre l'Invasion des Microbes, Ann. de l'Inst. Pasteur, vol. i, p. 325, 1887.
[15] Metschnikoff, Etudes sur l'Immunité, Ann. de l'Inst. Pasteur, vol. iv, p. 65.

a guinea-pig and two rabbits. So much for direct observation. I think we must admit that it is possible for a live bacillus to be incorporated.

Let me now describe Metschnikoff's method for comparing the process of incorporation in a susceptible animal with that observed when susceptibility has been annulled or diminished by previous infection. Insusceptibility to the well known disease of pigs, called in France *rouget*, is acquired by inoculation with mitigated cultivations, in the same way as in the case of anthrax. Rabbits, of which the "immunity" as it is called, had been tested by inoculation with virulent material, and found to be infection proof, were used by Metschnikoff for the purpose of comparison with normal rabbits, as regards the behaviour of their leucocytes.

The method used consisted in introducing under the skin a contrivance familiar to all pathological students as a Ziegler's chamber,[16] but differing from it in being made up of four cover glasses arranged in pile, and cemented together at their edges, so as to leave the intervening spaces accessible. If this system of plates has been dipped in a virulent culture of *rouget*, the spaces between the cover slips are found, when removed for examination two hours and a half after insertion, to be crowded with leucocytes, in which a very considerable number of bacilli are incorporated, whether the rabbit has been protected by inoculation or not. But subsequently, says Metschnikoff, the difference between the behaviour of the leucocytes in the two cases becomes more and more marked; so that, for example, two days after insertion, the leucocytes in the trap taken from the unprotected rabbit contain normal bacilli, whereas those yielded by the protected rabbit are all in a state of degeneration. He admits that there were also degenerated bacilli which were not incorporated, but thinks that these had probably escaped from leucocytes destroyed in preparation.

Similarly, Metschnikoff finds that in animals naturally insusceptible, the immunity is due to the endowments of their leucocytes. Thus in the white rat, to which anthrax can be communicated with great difficulty, the introduction of active virus gives rise to a local inflammatory reaction; whereas, in other rats, it fails to do so. On "phagocytic" principles, inflammatory reaction is prophylactic. It is the colourless corpuscles of the blood, therefore, which, by virtue of the part they take in ordinary inflammatory reaction, form the first line of defence against the invasion of microbes. If this is broken through, a second line—admitted by Metschnikoff to be in general an ineffectual one—is constituted by the tissue cells of the liver and spleen.

Such are some of the most important and convincing proofs which M. Metschnikoff offers in support of his theory. As the theory itself has been received, on the whole, with little favour by pathologists, it is the more necessary to refer to the arguments of the few writers who have given it a more or less qualified assent. In my last lecture I referred to the work done by one professed adherent of the doctrine of phagocytosis, Dr. Hess.[17]

Hess scarcely went more than half way with Metschnikoff. He anticipated him in the use of glass chambers introduced under the skin as a means of comparing the local reaction which is occasioned by the introduction of bacillus anthracis in an insusceptible animal such as the rabbit with that which is to be observed in an insusceptible (the dog). He found that whereas there was scarcely any suppurative reaction in the rabbit, the virulent material which had been introduced was invested by a zone of leucocytes, in which many bacilli were incorporated. As these were surrounded by an outer zone of leucocytes free from bacilli, the focus of infection was secluded and effectually protected from the influence of the surrounding tissue. Again, when he observed that the bacilli of splenic fever introduced into the circulating blood of the frog were incorporated by the colourless corpuscles, that after several days they disappeared and were then to be found in the spleen, the advantage or use of this incorporation seemed to be little more than mechanical.

In France one of the strongest and most influential supporters of the doctrine of phagocytosis is Professor Bouchard.[18] But he, like Hess, is eclectic, and chiefly emphasises the fact that the existence of inflammatory reaction, that is, exudation and emigration of leucocytes at the seat of infection, is a condition unfavourable to its spread. In the exposition of the subject which he gave in the general sitting of the Berlin Congress he took the process of inflammation as his point of departure, defining it, in accordance with the definition which I submitted to you ten years ago, as the reaction of living tissue to injury, that reaction consisting in the accumulation of mesodermic cells "qui affluent vers le foyer du mal et le circonscrivent," and further on he designates this as a " pathological act provoked by a local irrita-

[16] Metschnikoff: Études sur l'Immunité, *Ann. de l'Inst. Pasteur*, vol. iii, p. 289.
[17] Dr. C. Hess: Untersuchungen zur Phagocytenlehre, *Virch. Arch.*, vol. cix, p. 355.
[18] See M. Bouchard's Address at the Berlin Congress in vol. i, p. 49 of the *Verhandlungen*.

tion of the part." Admitting, as Hess does, that virulent microphytes, when introduced into the circulating blood of non-susceptible animals, are incorporated by the colourless corpuscles, M. Bouchard agrees with Metschnikoff in thinking that they may be devitalised or attenuated, but this he attributes, not to the mechanical action of incorporation, but to an " état microbicide " or " bactéricide " which is common to the fluids and solids of the living body. As to what is meant here by the bactericidal state and how it is brought about, Bouchard has made observations of great importance, to which we shall have to recur later; for the moment it is sufficient to indicate that to him, although he is regarded as a champion of Metschnikoffism, the function of leucocytes is merely mechanical—the dissemination of contagious particles is prevented partly by the crowding round them of leucocytes in great numbers, partly by incorporation, but not by virtue of any power of digestion, or by any chemical action whatever which is peculiar to amœboid cells.

I have referred to Hess and Bouchard not as opponents but as supporters of the doctrine of phagocytosis, and we have seen that that support is a very partial and qualified one. I am indeed unable to find that any pathologist of repute accepts what I think must be regarded as M. Metschnikoff's fundamental propositions, namely, (1) that the devitalisation of microphytes is a special and exclusive privilege of phagocytes—understanding by the term both leucocytes and certain connective or epithelioid cells in which incorporation is observed to take place; and (2) that leucocytes are capable of discriminating between contagious particles of different kinds, and that they exercise this power of choice for the good of the organism of which they form part.

I must defer the examination of these propositions in order that I may ask your attention to another observation of Metschnikoff's, the consideration of which belongs more immediately to our present subject. He finds that if a comparison is made between a virulent contagium and a cultivation of the same kind which has been deprived of its pathogenic action by any of the processes of attenuation or mitigation, by the method which I described in the beginning of this lecture, the mitigated virus festers but produces no ulterior consequences, the unmitigated evokes no local inflammatory reaction, but kills the subject of experiment. Metschnikoff's explanation is the teleological one—that it is for the good of the organism. But if the purpose of festering is, as he maintains, defensive, why does it happen when there is no danger, and fail when to fail is fatal? It is, I think, much more probable that local reaction and liability to infection are linked together, not by causal relations to each other but as products of the same antecedent conditions —that is, that the reason why a virus of great intensity does not fester is that it is intense; in other words, that the same agent which in smaller concentrations excites exudation and emigration paralyses these processes when in greater intensity.

If it is true that a physiological link such as I have indicated exists between the tendency to local reaction and proneness to infection, we should expect that any cause or agent capable of paralysing local reaction—that is, of inhibiting the inflammatory process—would, so long as it operated, aggravate the intensity and promote the spread in the infected organism of a contagium. Guided by considerations which, although otherwise expressed, are in substance the same as those which I have now submitted to you, M. Bouchard and his able collaborators in Paris have thrown much light on this difficult subject. The purpose of their investigations has been, first, to ascertain whether agents of the kind suggested exist, and secondly, whether they possess the aggravating power assigned to them—using the word " aggravating " as opposed to " attenuating." Whether, in short, under their influence a mitigated virus acts as if it were virulent or the immunity of an individual is diminished or annulled.

Do agents exist by which inflammatory action can be arrested at will? To obtain an answer to this question we must go back with M. Bouchard to the starting point of their inquiry. Among the most interesting of the specific pathogenic microphytes which have been worked out during the last few years is the bacillus pyocyaneus, the bacillus of blue pus. This organism is, in the first place, remarkable as the

source of the colour from which the pus derives its name, which is communicated readily to any of the cultivating media in which the bacillus grows. It is no less remarkable for the definite character of the symptoms which it produces when injected into the circulating blood of a living animal. A few drops of the pure cultivation produce pyrexia followed by collapse, purging, and death, with, as is seen on dissection, intense enteritis. In addition to this, all that is necessary for us to have before us just now is that the blue pus bacillus is not only virulent but toxic, that is, that although when introduced in minimal quantity into a vein it kills by multiplication in the organism, after the manner of a contagium, almost all the symptoms of its action can be produced by the injection of the products of its vegetation outside of the body, that is, of a sterilised culture. Now it is this product which M. Charrin found in 1888 to possess the required power of inhibiting the inflammatory process. In the rabbit, as we have seen, cultures of this microphyte when injected *intra venas* produce rapid death, preceded by fever and collapse. If it is injected subcutaneously it does the same thing, producing no local symptoms. In the guinea-pig, which is much less susceptible, it produces local inflammation at the seat of puncture, but no signs of general infection; but, says M. Charrin, if the insusceptible guinea-pig is "prepared" by infusion of some of the product of the very same bacillus it is thereby, so to speak, converted into a rabbit for the nonce; local reaction disappears, constitutional infection takes its place.

What is the meaning of all this? What M. Bouchard says about it is, that the action relates to the inflammatory process as a whole, that is, that it is not a paralysis of amœboid cells, as has been supposed, but an action on the whole machinery of living tissues, on vasomotor nerves as well as blood vessels; and accordingly he places the chemical action of microphytic products with the action of such general depressants as cold, exhaustion, or even mere restraint of bodily movement, each of which has been shown to favour infection by diminishing local reaction. For by experiments which appear to me to be of surpassing interest, he shows that the same culture which, when introduced under the skin of the relatively insusceptible animal in a Cohnheim's tube, produced general infection without local reaction if the animal were immobilised, produced local reaction (that is, suppuration without infection) if it were left at liberty.

What explanation can be given of all this but one, namely, that in each instance the same cause which weakens local reaction weakens at the same time and in a similar degree the power which the organism as a whole possesses of defending itself against infection? In what this power of defence consists I will endeavour to set forth in the next lecture, in so far as present knowledge is adequate. In the meantime, let us avoid attaching any other meaning to the unquestionable fact of phagocytosis, excepting first that the emigration of leucocytes is an essential part of the process of inflammation, and that there is an antagonism between this process and the process of general infection.

OBSERVATIONS ON THE EFFECT OF THE INJECTION OF TUBERCULIN ON THE PULSE.

Read in the Section of Therapeutics at the Annual Meeting of the British Medical Association held in Bournemouth, July, 1891.

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THERE is a striking contrast between the present state of public and professional opinion on the subject of Koch's treatment and that which prevailed during the later months of last year. The period which has elapsed has been fruitful in experience, and the clinical study of the action of tuberculin has yielded valuable results. In addition it has undoubtedly had the effect of greatly modifying the views originally advanced by Koch and his immediate followers.

The conclusions at which I have arrived may be briefly stated as follows:—

1. That tuberculin is a vastly more potent remedy than originally believed; and that it is a complex substance, certainly containing, in addition to its remedial element, several of a highly toxic character.

2. That it certainly does not act therapeutically as Koch supposed, but that it seems to act principally as a direct and potent stimulant to the nutrition general and local, that is, especially the pulmonary tissues themselves.

3. That the vital phenomena included under the term reaction have been erroneously regarded as advantageous and the measure of the beneficial effect of the remedy.

I was much impressed by the extreme distress and prostration exhibited by the patients in the Berlin hospitals during and subsequent to the reactions. I felt that they could not be beneficial, and my subsequent experience has confirmed it. I was at the time even inclined to attribute them to the toxic elements contained in the tuberculin rather than to the large doses of the tuberculin itself. I always found that if excessive reactions were induced the patients lost weight, and the physical signs were exaggerated, and that on the other hand improvement invariably commenced when a dose was reached which did not raise the temperature much above normal.

One remarkable fact should be noted in connection with the tuberculin treatment. It is this that Koch's second discovery has materially affected the pathogenic position of his first. The tubercle bacillus is not itself directly influenced by the tuberculin. In fact the true position of the bacillus can only be realised when tuberculosis is regarded as an essentially parasitic disease. Tuberculin, and indeed all other remedies hitherto employed in the treatment of tuberculosis, are directed to increase the local and general health of the patient, so that the renewed vitality of the pulmonary tissues render them inimical to the parasites and prevented their multiplication and extension. I have had under observation a gentleman in his 76th year who had been professionally condemned to early death from tuberculosis, but who had since married and had healthy children, and who is in fairly good general health, yet he has bacilli in his expectoration. Tuberculin seems, I repeat, to have a specific effect in stimulating the local and general nutrition. It is the only remedy which undoubtedly has an elective affinity for the tuberculous tissue and which certainly has a potent effect upon it.

There is to be observed a continuous improvement in many of the cases in the condition of the circulation as compared with that before inoculation, in large part no doubt due to the improved state of health, as evidenced by increase of weight under the treatment, but also no doubt to the tolerance established by repeated inoculations of largely increased doses of tuberculin. It was only by such close study of the clinical phenomena observed during the employment of a remedy so potent and so novel, in a disease so conditioned by disturbing elements, that it could be used with safety, its efficacy noted, and its effects—therapeutic and otherwise—correctly estimated.

I believe the time has come when more moderate and judicious views will prevail as to the position of tuberculin as a remedy in tuberculosis. I still hold that, although far from fulfilling the absurdly unscientific expectations with which tuberculin was at first regarded both by the public and the profession—and by the former, it must be admitted, not unreasonably—this remedy has already begun again to receive the attention it deserves. I have no doubt that it will gradually and steadily assume its true place in the treatment of tuberculosis. If the researches, on which it is understood Professor Koch is engaged, with a view to eliminate some of those toxic elements which have been for some time suspected to be present in tuberculin, and which the recently published experiments of Dr. William Hunter have sufficiently demonstrated to exist, result in giving us the innocuous active therapeutic principles contained in tuberculin, the treatment of tuberculous disease will present an encouraging future.

The full and varied expression of opinion, and the numerous details of experience of the tuberculin treatment which the discussions at Bournemouth have evoked, are a striking proof of the utility of the annual meetings of the Association; they afforded an opportunity for those personal explanations which cannot be so satisfactorily given in the columns of the