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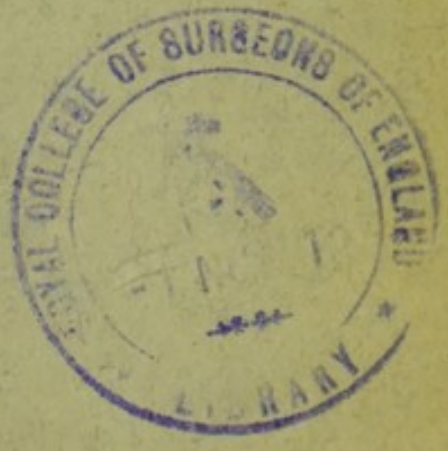

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METCHNIKOFF ON THE COMPARATIVE PATHOLOGY OF INFLAMMATION.*

By JOHN LINDSAY STEVEN, M.D.

Since the appearance of Virchow's *Cellular Pathology*, and the publication of Cohnheim's classical researches on the inflammatory process, no more important or remarkable work on inflammation has been given to the world than Metchnikoff's *Lectures on the Comparative Pathology of Inflammation*. Whether we have regard to the clear records of carefully observed natural phenomena, or to the cogent inductive reasoning by which the author seeks to establish the theories which he propounds, we are forced to the conclusion that this book is one of the most suggestive, and in some respects most revolutionary, that has been written on inflammation in recent times. It is hardly to be expected that all the opinions advanced by M. Metchnikoff will be accepted without question, for should this occur all previous teaching with regard to the pathology of inflammation must be departed from. In its ultimate essence his theory of inflammation differs from all others with which we are acquainted; and this being so, the author must, of course, be prepared to submit to the most searching criticism and scrutiny of his opinions before he can expect them to be accepted either in whole or in part. That M. Metchnikoff's work deserves the most attentive consideration of all scientific physicians, and that it is likely to receive such, is the highest praise we can bestow upon it. The views propounded do not originate in a mere desire for novelty or in a craving for notoriety, but they have sprung from an exhaustive and conscientious investigation of biological

* *Leçons sur la Pathologie Comparée de l'Inflammation, Faites à l'Institut Pasteur en Avril et Mai, 1891*, par Élie Metchnikoff, Chef de Service à l'Institut Pasteur. Paris: G. Masson. 1892.

phenomena in so far as they are calculated to throw light upon this most interesting and complicated pathological process.

Towards the end of the first lecture M. Metchnikoff strikes the keynote of the whole book when he says that, instead of placing the phenomena of inflammation in two categories fundamentally distinct (degeneration and regeneration—injury and repair), we must endeavour to regard all of them as presenting "une réaction salutaire contre une cause nuisible quelconque." This proposition is led up to by one of the most masterly and concise *résumés* of the older and current theories of inflammatory action, associated with a suggestive indication of their relationships to the doctrine of evolution, the processes of fermentation, and the cell theory, that we have ever read. He also shows us that comparative pathology, by taking cognisance of the phenomena observed in the lower invertebrates, may supply information which experimental research in the vertebrates is unable to supply on account of the presence in these of disturbing elements. Indeed, the only factor of the inflammatory process which, in experimentation as hitherto conducted, it has been possible to eliminate, is that of elevation of temperature, for the reason that the frog is a cold blooded animal and "incapable de produire de la chaleur en quantité appréciable." In order still further to eliminate complications invertebrate animals must be employed in the study of inflammation, and in this way only can we ever hope to be able to answer the following questions:—Can the factors (traumatism, infection) which provoke inflammatory phenomena in the higher animals produce something analogous in the inferior vertebrates, as the amphioxus, or in the invertebrates? Is the presence of a circulatory system indispensable to the production of inflammation, or can it also be produced in animals which have no blood-vessels? What is the part played by the nervous system? In order to the production of inflammation, is it necessary that an animal should possess a series of differentiated organs, or is it sufficient that it should be composed of an accumulation of non-differentiated corpuscles? Can anything analogous to inflammation be found in the vegetable kingdom? Do unicellular organisms present inflammatory phenomena? These are the problems which M. Metchnikoff has set himself to solve; and we cannot read the succeeding lectures, in which he supplies us with his material for arriving at a solution to them, without being struck with amazement at the vast new field for enquiry and analogy which he has opened up.

Starting with the general principle that, as regards their

surroundings, the most salient characteristics, both of plant and animal organisms, are those which adapt them either for aggression or for defence, and showing that active aggression is easily transformed into infection, and that defence, from this point of view, is equivalent to the salutary reaction of the organism against infection, the author, from the second to the seventh lecture inclusive, clearly and concisely describes all the phenomena observed by himself or others in the invertebrates and lower vertebrates which have any bearing upon the explanation of the inflammatory process. As regards unicellular organisms, we are told how amœbæ and infusorians react to traumatism or infection. It will be something new to many medical men to know that amœbæ are liable to epidemics of infectious diseases, occasioned by other minute organisms attacking them (*microsphæra*). It is with something akin to astonishment that we read of the effects produced upon bacteria when taken into the bodies of amœbæ (they absorb vesuvine there, although it has no effect on them outside), and are told that these results are produced by the digestive action of the amœba called forth in self-defence. The parasites also protect themselves by the production of substances, which are defensive for themselves, but fatal to the host. In the case of the paramœcium, we find that organisms capable of thriving vigorously in the nucleus are digested and rejected in the protoplasm of the organism itself.

Passing to the polycellular organisms, the phenomena observed in those large protoplasmic masses, to which the term "plasmode" is applied, are, first of all, described in detail. It is shown that the currents observed in this undifferentiated living mass may flow towards, or be directed away from external agents, according as they are beneficial to, or destructive of, the vitality of the protoplasm. The effects of traumatic, physical, and chemical irritation are considered in detail; and the significance of the property of "chimiotaxie" (positive, if the plasmode is attracted, negative, if it is repelled by the external agent), so well illustrated in these "masses protoplasmiques, les plus grandes qui existent dans la nature," is indicated, especially as regards the important bearing it has as explaining the behaviour of corpuscles in the higher animals during the inflammatory process. It has been shown that the chemiotaxy of these inferior beings obeys Weber's law for the sensitive perceptions of mankind; and it would also seem that they can become acclimatised to their surroundings. The production of cicatrices in plants, as the result of traumatism, and the bearing

of this upon Virchow's theory of inflammation, as a nutritive and formative hyperplasia of the inflamed tissues, are discussed. The author cannot admit that it lends any great support to Virchow's opinion, because no account is taken of the phenomena even more characteristic of inflammation which are exhibited by organisms intermediate between plants and the higher animals. We scarcely think, however, that this is sufficient reason for rejecting the analogy, and it seems as if here, and perhaps in one or two other places, there was, we had almost said wilful blindness to the force of arguments which might be advanced in support of a theory of inflammation different to that upheld by the author. Plants are protected from the onslaughts of bacteria by the thick resistant cell membranes; but, on the other hand, they are specially liable to be invaded by moulds, which possess a great power of growth, and secrete a diastase which dissolves the cellulose membrane of the plant. If the mould obtains entrance it absorbs the cell contents without hindrance, and the cells invaded perish; or, if they survive, undergo hypertrophy, often giving rise to the formation of special tumours or galls, and, sometimes, even to a hypertrophy of the whole organism. As in the cure of wounds, infections in plants are accompanied by regenerative phenomena, due to the abundant multiplication of corpuscles not directly attacked, without presenting processes comparable to the essential conditions of inflammation. To arrive at these, it is necessary to examine the conditions met with in the animal kingdom. In thus drawing a hard and fast distinction between proliferative or regenerative phenomena and the "actes essentials de l'inflammation," the author is promulgating an opinion which is not unlikely to call forth a good deal of adverse criticism—criticism which we would be inclined somewhat strongly to support.

Having called attention to the circumstance that we do not know "le mode par lequel les animaux polycellulaires, ou Métazoaires, sont dérivés des Protozoaires," and that we must fill up the gap by theories based on embryological observations, and having indicated the object of his own theory on this subject, to which he has given the name of *phagocytella* (the stage phagocytella easily being transformed into the stage gastrula), M. Metchnikoff then gives an account of his experiments on sponges. He points out the different rôles played by the contractile and sensitive cells of the ectoderm, the flagellated epithelial cells of the entoderm, and the mobile amœboid corpuscles (phagocytes) of the mesoderm, in the protection of

the organism from noxious external agencies. The flagellated cells of the entoderm are also endowed with the powers of phagocytes as they englobe small granules carried to them by the currents of water passing into the sponge; but the chief power in this way is located in the mesodermic cells. The contractile cells of the ectoderm have also power of preventing, to a certain extent, the passage of noxious matters by closing the superficial pores.

In similar detail, and with undiminished interest, the phenomena bearing on the inflammatory process in the higher members of the invertebrate groups, such as the cœlenterates, worms, molluscs, &c., are described. In the case of those species supplied with a vascular system, it is shown that the blood-vessels take no part in the reactionary process (phagocytosis), which M. Metchnikoff believes to be the essential element in inflammatory action. As we ascend higher in the scale of animal existence, it is interesting to note how the phagocytes become specialised and located in different parts of the economy. In the case of worms it is shown that the mesodermic phagocytes are represented by the cells suspended in the perivisceral liquid or by the endothelial cells of the peritoneum; and in this case the strife between the parasite and the phagocytes goes on while the blood-vessels, developed to a high degree in the annelida, remain completely inactive, presenting neither visible changes of volume nor secretion of the reddish coloured plasma. Among the invertebrates we find leucocytes with phagocytic properties, presenting different characters—some granular, some hyaline—all possessing a large oval non-lobulated nucleus. In invertebrate animals whose vascular system is not entirely shut off from the general body-cavity of the organisms, we do not find polynuclear leucocytes. In such (arthropodes and molluscs) inflammatory reaction may be induced, and abundant leucocyte accumulation, accompanied by giant cell formation, take place, without any question of diapedesis, for the simple reason that the vascular system is not completely closed, and is in communication with the body cavity.

Observations of inflammatory affections in several of the lowest vertebrates and their embryos are recorded, and it is shown that it is possible for these to be excited without the intervention of the vascular system. Having described these observations in great detail, the author gives a comprehensive recapitulation of the whole series of phenomena detailed in the first seven lectures. It is pointed out that in the vegetable kingdom, although there may be lesions (primary necrosis and

regeneration), yet there is no inflammation. Inflammation appears only in the animal kingdom, commencing in those organisms endowed with a mesoderm.

The eighth lecture gives a detailed description of the different varieties of leucocytes. Of these there are mainly four varieties—(1) the small lymphatic corpuscles (*lymphocytes*), formed by the lymphatic glands, containing one nucleus surrounded by a thin layer of protoplasm; (2) mononuclear leucocytes (*leucocytes mononucléaires*), having a single oval or round nucleus, and having a certain resemblance to certain fixed elements of the connective tissue; (3) Ehrlich's eosinophile corpuscles (*leucocytes éosinophiles*), containing often a lobulated and variously shaped nucleus, and staining best with acid aniline colours; (4) multinucleated corpuscles (*leucocytes polynucléaires*), a name which is quite justifiable, although, in reality, they possess only a single nucleus, often having the appearance of a clover leaf or a raspberry, the different lobes being united by thin filaments. The first two varieties of leucocytes merge the one into the other; the fourth variety is often denominated *leucocyte neutrophile*, because it is only possible to stain both the nucleus and the protoplasm by a mixture of acid and basic aniline colours. As regards their origin, these corpuscles develop in the lymphatic glands, the spleen, bone-marrow, and the blood, the last named being the tissue in which the ordinary polynuclear corpuscles chiefly originate. All the varieties are amœboid, but the lymphocytes and the eosinophile corpuscles have no power of phagocytosis, a property which specially characterises the mononuclear and neutrophile (polynuclear) corpuscles. Certain organisms (streptococcus of erysipelas, the gonococcus) are never taken up by mononuclear corpuscles, whilst they are easily englobed by the polynuclear. On the contrary, the leprosy bacillus is never taken up by polynuclear corpuscles, although it is readily devoured by the mononuclear. This difference in the reaction of the two classes of leucocytes is attributed to "chimiotaxie." A number of observations and researches, illustrating the chemiotactic and digestive properties of leucocytes are given in great detail. Although the author holds it to be a fact that leucocytes can digest microbes, he admits that at present we do not know the agent by which this is accomplished, whether it is a digestive diastase, or something else; and he states that because in the higher animals the peptic and tryptic ferments do not destroy microbes, we have no right to assume that there are not in them other ferments possessed of a batericidal action.

With regard to the multiplication of leucocytes, M. Metchnikoff shows that, although polynuclear corpuscles most often divide directly, they are still capable of reproduction by the method of Karyokinesis. This has been demonstrated by Flemming in the leucocytes of the salamander, and by M. Spronck in the leucocytes of the blood of the rabbit. By means of observations on the fin of the tadpole, artificially inflamed, the author has convinced himself that in these animals polynuclear leucocytes can transform themselves by fusion of the nuclei into the mononuclear variety, and, indeed, become veritable fixed cells of the connective tissue. On these grounds, then, he holds that the opinion accepted by the Berlin Congress of 1890, that "leucocytes (*i.e.*, emigrated corpuscles), can play no active part in the new formation of tissue," is no longer to be sustained. It is not the new view of Ziegler, but his old one of 1875-76 that is correct. In support of this statement he adduces the fact observed by himself and his pupils, that in rabbits inoculated with tubercle, epithelioid and giant cells are formed in the interior of the vessels at the expense of the mononuclear leucocytes.

In summing up his remarks on leucocytes, he shows that the two classes of corpuscles which play the principal part in inflammation are the "leucocytes mononucléaires and les neutrophiles;" these are the elements endowed with "une sensibilité chimiotactique et physiotactique," capable of amœboid movements, and able to englobe and digest foreign bodies, notably living microbes. In amphibians, at least, polynuclear leucocytes can transform themselves into mononuclear corpuscles and become fixed cells of the connective tissue. In vertebrates in general mononuclear leucocytes can be transformed into epithelioid and giant cells. And all that has been said on the subject of leucocytes applies with equal force to the different varieties of migratory corpuscles.

The part played by the endothelium of the blood-vessels is discussed in detail. It is shown that they are contractile, and that this property has much to do with the stomata that are formed in the process of diapedesis. It is also asserted that the endothelial cells under certain morbid conditions can quit the vessel wall in virtue of their amœboid movement, and form a kind of adventitious membrane in the interior of the vessel. These cells are also capable of taking up foreign granules and microbes. It is admitted that the connective tissue elements play some part in the inflammatory process, chiefly in production of cicatricial tissue. The "plasma-cells" of the connective tissue are leucocytes which have become

immobile, to resume their migratory character under the stimulus of inflammation; and the "mast-zellen" of Ehrlich, abundant in inflammatory products, are regarded as a kind of scavenger for clearing away the detritus of other elements. Emigration of leucocytes is regarded as determined by the chemiotactic state of the corpuscles induced by the poisonous microbic agency employed rather than by any condition of the vessel wall or circulating blood. The axial and peripheral arrangement of the blood corpuscles is not regarded as in any respect due to mechanical causes, and it is asserted that Cohnheim had overlooked the influence of the nervous system in the causation of inflammatory hyperæmia and diapedesis. It seems to us that in this part of his work the author is more dependent upon the observations of other authors than upon his own, and that consequently his opinions are not so valuable. "Toutes ces expériences démontrant une certaine influence du systéme nerveux sur l'inflammation, mais prouvent en même temps que cette influence ne sert qu'à accélérer ou à ralentir la marche du phénomène pathologique." No one has ever doubted it, and we imagine that there is little risk of its influence being overestimated.

In the author's view the sensibility of the leucocytes plays the most preponderating part in inflammatory maladies, although this does not mean that in the vertebrates endothelial sensibility, nervous influences, and other functions may not also take part in the process.

In acute inflammation, according to M. Metchnikoff we have a vascular dilation, an active state of the vascular endothelium, and an exudation with diapedesis, three phenomena which result in an afflux of phagocytes towards the inflamed area. Do we have the same phenomena occurring in chronic inflammations, in which the principal rôle has hitherto been attributed to local changes in the tissues without any notable concurrence of sanguineous and vascular elements? In the consideration of this question he studies in detail the processes involved in the formation of a miliary tubercle as a type of chronic inflammatory change. He rejects entirely the generally accepted view of Baumgarten that the tubercle is the product of a proliferation of fixed local elements, due to the presence of the tubercle bacillus. According to this view leucocytes and phagocytic corpuscles play only a secondary part in the formation of tubercle. After describing in detail the development of artificially induced tuberculosis in the liver of a rabbit, he formulates his own view of the origin of tubercle as follows:—"*Le tubercule est composé d'une réunion de phago-*

cytes d'origine mésodermique, qui affluent vers les endroits où se trouvent les bacilles, et les englobent." The phagocytes which take part in the formation of a tubercle are of the mononuclear character; polynuclear phagocytes take up the bacilli very easily, but soon perish, and with their contained microbe become the prey of the different varieties of mononuclear phagocytes, denominated macrophages. He regards the calcification of tubercle as the result of an active secretion on the part of the giant cell, not as a degenerative process; and, in support of this details his studies of the effects of inoculation of the gerbille (Meriones Shawi), a rodent of Algeria which is very resistant to tubercle, and defends itself in this way. He has to admit, however, that frequently the tubercular phagocytes themselves perish and become caseous. This theory of the action of the giant cell in the tubercular process is directly opposed to that supported by Koch and Weigert, who regard the tubercular giant cell as presenting a state of partial necrosis. We confess that, although desiring to retain meantime a perfectly open mind on the subject, we have a strong sympathy with the latter view.

With regard to serous inflammations, it is pointed out that generally the serous exudation contains very few phagocytes, in this respect differing from the ordinary varieties of acute and chronic inflammatory processes. Some varieties of serous inflammation are due to the fact that there is a "sensibilité négative" of the leucocytes, which prevents their passing out along with the fluid through the inflamed vessel walls. The exuded fluid in these cases, however, contains a considerable number of microbes which multiply without hindrance. In another class of cases (*e.g.*, diphtheria) serous exudations take place in areas more or less distant from the nests of microbes, and in these exudations there are no microbes. The question then arises as to the object of the serous exudation, some regarding the process as a means of ridding the organism of its enemies, and the serum as possessing a bactericidal power. As is well known, M. Metchnikoff strongly objects to this view, and in the present volume he details a number of experiments in support of his opinions. Phagocytes and phagocytes alone are the agents provided in the organism for the destruction of pathogenic organisms. All the same, the fact of serous inflammation has evidently given him some difficulty—a difficulty which he scarcely fairly meets by saying that at present we are only incompletely acquainted with the phenomena of serous inflammations, and that from whatever point of view we regard serous inflammation, "elle se présente toujours comme un

phénomène d'un ordre beaucoup moins important que l'inflammation par excellence, c'est-à-dire celle qui est accompagnée d'une accumulation des phagocytes dans le foyer enflammé." From the point of view of comparative pathology, he also regards serous inflammation as genealogically of much more recent date than inflammation *par excellence*, which is accompanied by a " réaction leucocytaire."

In the twelfth lecture the theories of Virchow and Cohnheim are criticised in detail. The nutritive attraction theory of Virchow is summarily dismissed as untenable. More consideration is shown to the injured vessel wall theory of Cohnheim, and many facts, experimental and natural, are adduced to demonstrate that it also must be rejected. He insists upon the different effects resulting from inflammatory causes introduced into the blood stream, and applied outside of the vascular system. In arguing thus, however, he applies the term inflammation in a manner that Cohnheim, and probably also the majority of living pathologists, would not accept. It is certainly something quite new to think of an intravascular inflammation. To quote the phenomena of recurrent fever in this regard, seems to be arguing in a way that Cohnheim would never have recognised. What we ordinarily understand by recurrent fever, and the poisoning of the blood that takes place in consequence of the presence there of the organisms, is something very different from inflammation as ordinarily understood by the morbid anatomist and the clinician. If we accept M. Metchnikoff's views of inflammation as indicated in this passage of his work, then we must start afresh and include in our definition of the process phenomena that have never been so included before. The *primum movens* of inflammation is a digestive reaction of the protoplasm against a noxious agent according to him. Cases of intravascular inflammation without diapedesis (" hemitis "), as illustrated by recurrent fever and the formation of intravascular tubercles have, so far as we know, never before been included in what we ordinarily understand by inflammation. But M. Metchnikoff makes out a tenable case in favour of his opinion, and whether we accept it or not, we are not surprised when he defines inflammation as follows:—"Inflammation in its entirety should then be regarded as a phagocyte reaction of the organism against irritant agents, a reaction which is sometimes accomplished by mobile phagocytes alone, occasionally with the concurrence of vascular phagocytes or that of the nervous system." Inflammation, then, is not a process for the regeneration of tissue, nor a provision for the absorption of, and consequent riddance of the

organism from, dead and useless material, but it is a battle against noxious agencies—particularly virulent microbes. While we are not prepared to accept entirely the views of M. Metchnikoff, we willingly grant that he has stated a clear case, and has laid before the medical profession and the scientific world generally, facts and arguments which demand the most careful examination and consideration. In pursuing his studies of abnormal conditions among the invertebrates, he has opened up an immense new field of research, and for this men of all opinions owe him hearty thanks. While admitting all this, we have the feeling that the work is, on the whole, one sided—the author has limited himself too much to one aspect of his subject, although he prepares us for this in his preface, by pointing out that several aspects of the inflammatory process have been designedly omitted. Phagocytosis is, on the whole, too much in evidence—we get tired of it—we wish some other aspects of this great morbid process of inflammation could be treated of with the same lucidity and power. We feel disappointed that this could not be done, and we finish our careful study of the work with the conviction that although it is a great work, and likely to be a lasting work, it is the work of a biologist pure and simple, and could not possibly be that of a practical physician or pathologist.

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