THE BOWMAN LECTURE ON THE PRESENT POSITION OF OUR KNOWLEDGE OF INFLAMMATION.

WITH ESPECIAL REFERENCE TO INFLAMMATION
OF THE EYE.

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United Kingdom.*

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[ABSTRACT.]

AFTER expressing the veneration which, in common with the whole scientific world, he felt for Sir William Bowman, and the great sorrow caused by his death a few months ago, the lecturer said:—In earlier times the opinion prevailed, that all foreign substances that entered the tissues of the body must necessarily give rise to inflammation. This belief became untenable by the knowledge derived from the antiseptic treatment of wounds; and also from experiments conducted upon the lower animals. For it was shown that chemically inert substances introduced aseptically into the body could remain there indefinitely without causing any inflammation in the clinical sense of the word; nowhere can the truth of this theory be demonstrated more easily or more plainly than on the eye. If we introduce through a small wound, made with due antiseptic precautions, a suitable piece of gold or glass into the anterior chamber of a rabbit's chamber, no inflammation is called forth. It is true, however, that changes are caused by the presence of even such inert bodies; certain degenerations and proliferations occur in the tissues of the eye, especially in the retina, which are scarcely apparent, and absolutely different from those following an infection of the wound. Indeed many maintained that though inflammation in general could be occasioned by the action of chemical irritation, the production of pus was peculiar to certain micro-organisms.

It was proved, however, by experiments that not only the products of such organisms, but also pure chemical substances, possessed the same capability of calling forth purulent inflammation. Among the pus-producing chemical substances quicksilver stands in the first rank. A single drop rendered absolutely sterile by heat, antiseptically introduced into the anterior chamber of the eye of the animal, always gives rise to a circumscribed collection of pus in its immediate neighbourhood, which in the course of time can even lead to purulent infiltration and softening of the inner layers of the cornea. But purulent inflammation set up by the action of chemical substances has not the same power of extension as that due to the action of microbes. In chemical substances only the limited quantity which has been introduced into the body comes into action; and the anatomical structure of the affected part very often restricts its extension. Thus the inflammation caused in the eye by chemical agents remains more or less limited to the affected area.

As far as we know at present metallic copper is the commonest chemical substance which produces suppuration in the eye. Should a fragment of copper rest either on the iris or inner surface of the ciliary body, suppuration will certainly be produced, but a similar fragment in the lens is completely enveloped by a thick coating of albumen, which effectually prevents it from exercising its irritating chemical action, and no pus is produced.

If we introduce copper filings into the anterior chamber of a rabbit's eye, each fragment is completely enveloped by pus; after some time, however, the inflammation subsides and the pus is gradually absorbed, and with it the copper also. So that after some months complete healing may result. Aseptic suppuration from the presence of particles of copper also occurs in the human eye, as may be proved by the careful examination of exudation removed from the eye and of enucleated eyeballs. In cases of injury by explosions of percussion caps, if the symptoms seem to point to an aseptic injury, the attempt to extract the fragment from the vitreous can be

justified although there be pus around the foreign body. If the extraction of the foreign body has been successful, we make culture preparations with the exudation around the chip; if these cultures prove the absence of micro-organisms, we are justified in continuing conservative treatment. But should the culture experiments show the presence of micro-organisms we should immediately proceed to remove the eye, on account of the great danger of sympathetic inflammation.

Although some chemical substances can call forth purulent inflammation this power is not possessed by all which have a powerful irritating action. Croton oil and cantharides, for instance, cause, under ordinary circumstances and by aseptic introduction, no pus, but a more fibrinous exudation with necrosis of tissue, though their action on the vessels is much stronger than that of quicksilver and copper, and other chemicals which cause pus. Nevertheless by a special method of application some such substances, notably croton oil, can cause suppuration visible to the naked eye, if its action be weakened and limited to a certain spot. Other substances, as arsenic, have, in comparison with their strong necrotic action, only a slight power of provoking inflammation, and therefore belong to a separate class. The cause of the difference in the mode of action of the various substances is not yet understood, and is not explained by their known chemical affinities.

All powerful substances capable of exciting inflammation are, in a concentrated form, poison to protoplasm. They cause necrosis; and, in a less concentrated form, they cause those changes in the vessels and their contents upon which the occurrence of inflammation depends. Another important circumstance to be noted is the relative solubility of these substances. Severe inflammation is not to be expected from the easily soluble, but, on the contrary, from the slowly soluble foreign bodies. Very irritating substances which are easily soluble will, in concentrated solutions, rather destroy the organ than produce inflammation. In weaker solution they will be too quickly absorbed to produce any visible effect. Slowly soluble bodies, on the contrary, will, it is true, act upon the tissues only in weak solutions; but this action is a continuous one, and is confined within the limits where the vital powers of the tissue elements, which are necessary for inflammation, are still preserved, whereas a too powerful agency does not lead to inflammation, but to necrosis.

A decoction of a pure cultivation of staphylococcus aureus in distilled water, in which the micro-organisms have been completely killed by heat, still produces an intense purulent inflammation when injected into the anterior chamber. The inflammation is so severe that in one or two days softening and perforation at the sclero-corneal margin may take place. By appropriate filtration the organisms may be removed from the decoction of the cultivated microbes. In this way, as well as by treating the microbes with alcohol, it is possible to obtain extracts which, though completely free from organisms, prove to be in the highest degree active. I have also several times succeeded in obtaining from the alcoholic extract a crystallised substance of very irritating action, which perhaps represents the active principle of this micro-organism.

If in keratitis caused by inoculation of micro-organisms the microbe has developed in the centre of the cornea, so as to occupy a certain area still remote from the corneal margin, the effect in the area directly attacked will consist only of retrogressive changes in the cells, resulting in necrosis and exfoliation of the anterior epithelium; loss of the endothelium covering the posterior surface and decay of the stellate cells of the cornea; vesicular degeneration of the protoplasm; and loss of the staining property of the nuclei. At first, if the action of the microbe is sufficiently intense, neither migration of leucocytes nor proliferation of the cornea-cells takes place. Growth of the fixed corneal cells does not commence till later, and does not contribute at all to the formation of pus cells. But at some distance from the neurotic area there appears a zone of dense infiltration of pus corpuscles, which affects more or less the entire thickness of the cornea. The fibrinous nature of this fluid leads to an interstitial deposit of fibrin within the cornea near to the scleral margin.

The pus corpuscles which form the ring-like infiltration of the cornea are white blood corpuscles which have migrated

from the vessels at the corneal margin and have made their way towards the microbic area, without, however, quite reaching it.

The process of the migration of the white blood corpuscles observed under the microscope on the living animal has furnished the true explanation of the appearance of the pus cells, which was otherwise incomprehensible.

It would lead me too far afield here to set out all the proofs establishing the origin of the pus cells from the leucocytes. I will mention only two experiments performed on the cornea, as they appear to present no ground for doubt.

The first experiment depends upon the fact that the leucocytes eagerly take up fine particles of foreign substances, for example, cinnabar, and can thereby be readily recognised in any place to which they may wander. The experiment is most easily conducted on frogs. If we provoke a purulent keratitis in a frog after a large number of white corpuscles have taken up the cinnabar injected into the blood, a great many of the pigmented corpuscles will be included in the collection of pus cells in the cornea, whilst the remaining part of the cornea shows no trace of free particles of cinnabar. The latter circumstance shows that no free cinnabar has reached the corneal tissue, and also that all the cinnabar which has entered the cornea has been carried there by the leucocytes, and that the cinnabar-holding cells have really wandered to the cornea. Since the pus cells not holding cinnabar do not differ in any respect from the others, and as not all the cells in the blood take up the pigment, we can be certain that all the pus cells in the cornea are migrated cells.

Another experiment is founded upon the already mentioned observation that the purulent infiltration of the cornea takes place at a certain distance round the microbic area. Thus pus cells migrating from the corneal margin meet with a resistance on the part of the microbic area to their further advance.

Those who support the view that the pus cells are produced by proliferations of the corneal corpuscles must explain this appearance by supposing that the corneal corpuscles in the neighbourhood of the microbic area perish, while at some distance from the same they are stimulated to proliferation. Which of the two views is correct can easily be shown by inoculating the microbes in two or more separate places between the centre and margin of the cornea. If the microbic colonies thus produced be small and wide enough apart from each other, then if the proliferation theory be correct, each colony must be surrounded by a circular zone of purulent infiltration beginning in the middle of the cornea where the action of the different colonies would be concentrated. But if the purulent infiltration of the cornea depends upon marginal emigration, then the infiltration will commence first in the neighbourhood of the corneal margin, and the separate zones of infiltration perhaps never form, because the pus cells find a great resistance to their advancement in the spaces between the single colonies. The facts completely confirm the latter theory, for separate infiltration rings are not found, but only one common zone of infiltration near the corneal margin surrounding all the separate colonies.

But the vessels at the corneal margins are not the only ones which experience the influence of the diffusing poison. It is especially upon the vessels of the iris and ciliary body that the toxic substance acts. On this depends the formation of hypopyon, which appears at a time when the development of the microbes is entirely limited to the cornea and far from the region of the anterior chamber. Accordingly the microscopical and bacteriological examination of the hypopyon shows, at any rate at first, a complete absence of micro-organisms.

The occurrence of necrosis within the microbic area and in its immediate neighbourhood, and of inflammation at a distance, is to be explained by the supposition that at this distance the injurious substances are not sufficiently concentrated to cause death, but only to produce those changes in the vessels and their contents on which inflammation depends. The dilatation of the small veins and capillaries in inflammation may be regarded as the result of a toxic paralysis of the cells of the vessel walls, causing loss of their tone, and an inability to resist the pressure of the blood. Upon the widening and greater permeability of the vessels, together with the slackened circulation, depends also the increase of the transudation of the plasma, which regularly occurs in inflammation. The emigration of the leucocytes, on the contrary, is not to be regarded as a purely passive process. They are not simply pressed through the spaces in the vessel walls, but pass through by means of their amoeboid movements, after first lining the inner surface of the vessel wall. Concentration of the injurious substance causes a paralysis of the cells, and its dilution exercises a stimulating action, causing the cells to direct their movements towards the point of the great concentration. Under any other supposition it is impossible to understand why the cells press forward so densely in the neighbourhood of the microbes; and how they manage to overcome such obstacles to their movements as present themselves. This theory is confirmed by direct observation.

Influences of the same kind as we have assumed in the movements of the leucocytes are active also in many other cells of very different character, as well in animals as in plants.

The botanists have given to this process the name chemotaxis. Very similar to the chemotaxis of leucocytes is that observed in one-celled organisms, as in certain bacteria, whose movements in a fluid are excited through appropriate food substances, so that they are allured in great numbers to the food material; whilst other substances, and even too strong a concentration of the food material, have a repelling action.

As to the mode in which the accumulation of the leucocytes can be of benefit to the damaged tissues, we must first mention their ability to take up into their substance, and remove, all finely divided foreign bodies. By this means they are able to free the organism from all intruding substances. The liver is the chief deposit of these cells laden with foreign bodies, which are there disintegrated, or in other ways rendered harmless.

Recent investigations have shown that the power of the body to kill micro-organisms, or to render them harmless, is not the property of the leucocytes alone; the blood and other tissues or fluids possess this power in a still higher degree.

It is true that in the blood the leucocytes are numerous, but in the normal tissues they are far too scarce to take up in a short time any considerable quantity of matter. This we see when we inject finely powdered cinnabar into the anterior chamber of the eye of an animal. Introduce a considerable quantity of this pigment, and you will find that only a slight hyperæmia, but a very profuse migration of leucocytes into the chamber, takes place, and that the cinnabar is taken up by the leucocytes, which soon will wander into the neighbouring tissues, especially into the iris and ciliary body. It is plain, therefore, that cinnabar, which has always been regarded as a completely insoluble and chemically inert substance, exercises a certain action upon the vessels which is doubtless of a chemical nature. From this and other experiments, the conclusion must be drawn that insolubility in the strictest sense of the word does not here exist, but only a great difficulty of solution. If we introduce the cinnabar at the bottom of a little tube into the anterior chamber, it causes a migration of pus cells into the lumen of the tube similar to that produced by quicksilver, only in smaller quantity, affording certain proof that its action depends upon the solution of a minute quantity of the substance. A smaller but still positive action is seen when the glass tube contains one of the nobler metals, as gold or platinum, in a finely powdered state. I have been unable as yet to find any single substance which, when introduced into the anterior chamber, proved itself to be absolutely inert, not even excepting those substances which are considered by chemists to be completely insoluble, for example, sulphate of baryta, crystallised silicic acid, and pure carbon. Especially striking is the proportionately strong action produced by the introduction of chemically pure carbon carefully obtained from graphite.

There is still another property of the leucocytes to which I would draw attention, namely, the power to soften and finally to throw off organic substances, especially dead portions of the body. This softening is to be attributed to the action of a ferment which must be produced by the leucocytes and not by the micro-organisms. Although certain positive results have been obtained, this tissue-softening ferment has not yet been isolated. It is, however, possible to demonstrate that leucocytes alone, in the entire absence of micro-organisms, have the power of softening and dissolving the tissues. The processes in the tissues and organs of the body which are caused by the action of foreign substances are, as we have seen, most numerous and complicated; and especially so because all these various processes occur and act in unison. They vary in their nature and degree with the influence of the external injury, all the processes having the character in common of being directed towards the attainment of a definite object. Thus, inflammation is to be looked upon as a conflict which the organism maintains against the injurious influences from without.

It is evident that our treatment of inflammation will be influenced by our recently acquired knowledge; for we shall deal with these processes in an entirely different spirit if we no longer consider them to be injurious in themselves, but rather the unavoidable consequences of the damages from without, which damages they ever aim to remove. Then shall we understand that our therapeutical efforts should be chiefly directed against the causes of inflammation, and that they should not combat, but, on the contrary, aid this *vis medicatrix Naturæ*.

Dr. E. HOFFMANN, Professor of Forensic Medicine in the University of Vienna, has been elected Dean of the Medical Faculty for the academic year, 1892-93.

Dr. RHIGAS NIKOLAIDES has been appointed Professor of Anatomy, and Dr. Anastasios Damberges, Professor of Pharmaceutical Chemistry in the University of Athens. Both these gentlemen, like the majority of the colleagues in the Athens Faculty, received their medical education in Germany.