The Goulstonian Lectures

ON

THEORIES OF IMMUNITY AND THEIR CLINICAL APPLICATION.

Delivered at the Royal College of Physicians, London.

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LECTURE I.

[AFTER some introductory remarks on the history of the subject of specificity, the lecturer said:]

Immunity may perhaps be defined simply as the power to resist infection. Metchnikoff thinks it at present impossible to give a more precise definition of immunity to infectious disease than "the complex of phenomena by which an organism can resist the attack of the specific pathogenic microbes," and the resistance (we may add) to their products.

The two chief theories of the present day are those promulgated and supported by Metchnikoff and Ehrlich respectively. Originally opposed to one another, like the humoral and iatrochemical theories of the Middle Ages, they are really only rays refracted at different angles from the same source of light, and will ultimately be made to fuse into one brilliant cellulo-humoral theory of immunity. Not that we can accuse the upholders of the modern humoral theory, as we could their predecessors of a period of bacterial supremacy, of neglecting the fundamental ideas of cellular pathology; it is merely a question of distribution.

While on the one hand Metchnikoff and his school believe that the white cells directly attack the invading bacteria, Ehrlich and his followers have laid more stress on the constituents of the body fluids. But even they regard a bacterial toxin as poisonous only in the form of a chemical combination with a cell constituent. If the cell does not possess this constituent the bacterial toxin is innocuous; the cell possesses a natural immunity. On the other hand, these cell constituents coursing in the blood are the protective bodies, and they have had their origin in the cells. As Behring tersely puts it, "That substance in the living body which, when situate in the cell, is a preliminary essential to the toxic process, becomes a curative agent when it enters the blood stream." To take a very gross illustration, suppose a ball of cotton wool to have wrapped up in it some small lumps of sodium carbonate and immersed in an acid fluid, there will be an evolution of gas in the ball, and it will be partly disintegrated. If the ball had previously secreted these lumps, the chemical reaction would have gone on outside.

CONGENITAL AND ACQUIRED IMMUNITY.

Immunity may be either congenital or acquired. When congenital, true infection for particular disease is impossible. Into the explanation of this phenomenon we shall inquire later. This form of immunity is always natural. Acquired immunity may be either active or passive. By active immunity we understand that acquired either by an attack of the disease, in which case it is natural, or by inoculation, when it is artificial. In both instances a process of what may fairly be termed infection occurs. Passive immunity is produced by the introduction into one organism of the products of active immunity in another. By the injection of the products of active immunity against diphtheria from the horse into the human subject, the latter becomes passively immunized against the disease. But infection itself is not of a single kind, and immunity will vary with the nature of the infection.

The action of some infective agents—for example, the tubercle bacillus and the leprosy bacillus—is largely mechanical; they produce fibroid and degenerative changes in the tissues which they attack. Others, when introduced into the body, do not multiply extensively, but, remaining at the site of inoculation, perform their malignant functions by secreting poisonous substances to enter the circulation. To this group belong diphtheria and tetanus. Yet others are capable of multiplying in the tissue as well as producing poisons, and so exert their influence in both ways.

A suitable soil is essential for many bacteria. Introduced beneath the skin the comma bacillus is comparatively soon destroyed; if put into the alimentary canal it produces cholera.

Cutaneous infection with *B. anthracis* produces severe illness; taken in the alimentary canal it is practically harmless. The tubercle bacillus by whatever route it may enter the body can settle, multiply, and produce its specific lesions. It must be remembered that the mere presence of a specific bacillus is not evidence either of infection or immunity of the organism in which it is found; the tubercle bacillus has been found in the sputum, the typhoid bacillus in the faeces, and the diphtheria bacillus in the throats of healthy persons. Both are relative terms; there is no certain infection or absolute immunity. Infection may then be due chiefly either to the micro-organism or its products. Corresponding to these two modes we can distinguish two classes of immunity, namely, a bactericidal and an antitoxic immunity. Again corresponding to these distinctions we find a variable duration of immunity—it may be only for months or it may be for years. It may be slight or nearly absolute, and finally it may be either individual or racial.

THEORIES OF IMMUNITY.

Metchnikoff was originally a zoologist who, as he himself tells us, has "strayed into the domain of chemical biology and of medical science," and his theory is essentially that of a zoologist. I should like to make it clear that I say this in no depreciatory sense. On the contrary: nobody, I hope, can be more alive to the interdependence of the several sciences and particular of the dependence of the science of medicine—I say advisedly the science, not the art, of medicine—on the sister sciences. It is rather with the object of directing attention to the way in which a theory based on the broad principles of cellular biology has been applied to the special problems of disease as contrasted with another theory which, starting from the comparatively narrow basis of disease, is finally found applicable and pertinent to many wide biological problems. The starting point of Metchnikoff's theory was the observation that the protozoa habitually ingest and digest bacteria, whether pathogenic or no—that the bacteria form for them an important aliment. On the other hand, the more highly developed organisms with a digestive tract are unable to digest bacteria, but when they enter the circulation, unless they are pathogenic, they disappear, and not by way of the kidneys unless the latter are injured.

The blood of the invertebrates contains but a single kind of amoeboid cell; in the vertebrates, especially warm-blooded vertebrates, there are two kinds, which Metchnikoff designates as macrophages and microphages respectively. They correspond to what the ordinary nomenclature calls large mononuclear leucocytes and the smaller polymorphonuclear white cells. On the introduction of any foreign matter, whether bacteria, metallic granules, or even sterile fluids into the organism, its leucocytes leave their normal habitat, and, passing through the vessel walls, go to the attack and often the annihilation of the intruder.

The macrophages, as befits their larger, slower, and more unwieldy character have, according to Metchnikoff, a preference for animal cells, for example, xanthocytes; for the bacteria of chronic disease, for example, tubercle and leprosy, and for the malarial and other analogous parasites. The microphages, on the other hand, show a preference for the micro-organisms causing acute disease. The phagocytic theory was in this crude condition in 1888, when Nuttall discovered the bactericidal action of serum, and it received further blows by Behring's discovery of antitoxins in 1891, and Pfeiffer's finding of the bacteriolysins in 1894. But Metchnikoff has managed with considerable ingenuity to adapt his theory to these new factors, and with much facility to abandon the purely mechanical explanation at first afforded by his theory.

The real starting point of Ehrlich's side-chain theory was his laborious investigation for the standardization of diphtheria toxin. Certain anomalous results occurred. The standardization of the various samples of toxin was done with a standard serum. To a quantity of this serum able to neutralize 100 lethal doses were added successive quantities of toxin until two limits were obtained; one in which so much toxin was added that the antitoxin was just neutralized and the other in which there was just so much excess of toxin as to produce death in the test animal in four days. Ehrlich found, first, that of various toxins a quantity less than 100 lethal doses often neutralized the standard quantity of antitoxin; and secondly, that the excess of toxin required to be added to the neutral mixture was more than one lethal dose. In order to explain this anomalous phenomenon, Ehrlich assumed, and finally proved, the existence of a modification

of the toxin, the "toxoid," which is nearly non-poisonous, but is, nevertheless, capable of uniting chemically with the antitoxin. The toxoids may again be subdivided into three groups, according to their affinity for the antitoxin, which may obviously be either greater (protoxoid), equal (syntoxoid), or less than (epitoxoid) that of the toxin. When the affinity is less than that of the toxin to the antitoxin, it is obvious that the epitoxoid will first be set free in the mixture, or until they are all set free no toxin will be free, so that the difference between a neutral antitoxin + toxin mixture (L_0) and one just killing (L_+) will be several lethal doses.

Ehrlich makes the following chemical comparison:—

that is, the difference between L_0 and L_+ is enormously increased by the presence of epitoxoid.

The modification from toxin into toxoid may be brought about in various ways, and is perhaps comparable to the allotropic change occurring in the case of phosphorus. When a toxin is kept, some alteration takes place, and its toxic power diminishes; it may apparently occur also by the action of high-frequency currents on toxin solutions. Since the toxoids are not only capable of producing immunity, but are also very much less poisonous, there may be some hope for the clinical treatment of diphtheria and tetanus within the solenoid by the conversion of toxin into toxoid within the living body.

Having shown that the union of toxin and antitoxin occurs in fixed ratios, more rapidly in concentrated solution and in the warm, etc., Ehrlich deduces the following conclusions:—

The capacity of the toxin to saturate the antidotes must depend upon a specific atomic group of the toxin molecule, which group must have a maximal specific relationship to a definite atomic group of the antitoxin molecule, the one fitting easily into the other, as a key into a lock; in the same manner as Emil Fischer has explained "the specific" action of ferment.

Various observations tend to verify the statement. Thus tetanotoxin affects primarily the cells of the central nervous system, and Wassermann showed that by previously mixing the toxin with an emulsion of brain substance, it was neutralized.

The affinity was specific; emulsion of other organs were devoid of action. It appears most reasonable to assume that such specific atomic groups of antitoxin pre-exist in small numbers, and that their saturation by the toxin affords a stimulus to the cells for their reproduction. As Ehrlich says:—

In the course of a typical process of immunization the cell become trained, so to speak, to produce the specific side-chains in large quantity. In such processes of regeneration, not compensation but hypercompensation is the rule, and with the enormous increases of the poison dose a point must be reached when there is such an excess of side-chains that he cell is surfeited, and casts them off as useless ballast into the blood. If on the one hand the presence of such receptive side-chains is a necessary condition for the occurrence of the toxic process, this circumstance also explains in the most simple way the production of the antidotes.*

The existence and formation of the toxoids he explains as follows:—

One must assume in the toxin molecule two independent atomic groups. One of these is haptophore, and brings about the union with the antitoxin or the antitoxic side-chains of the cells. The other atomic group is toxophore, namely, is the cause of the specific toxic action.

The toxophore group is unstable and easily decomposed, with its decomposition the toxin is converted into the toxoid. The union of the haptophore group with the cell side-chain enables the toxophore group to act on the cell through the bridge thus formed; when the side-chain is circulating in the blood, and becomes attached to the toxin molecule there is no cell on which it can exert its toxic action; it is neutralized.

Starting from this central point, it has been possible to explain a number of biological phenomena by similar reasoning and similar experiments, which in their turn confirm the correctness of the original theory. Pfeiffer's phenomenon gave the stimulus for this series of investigations. Already before Pfeiffer's observations the bactericidal power of normal serum and its property of dissolving xanthocytes of other species, together with the loss of this power on heating to 56°C ., had been observed and recorded. The increased bactericidal power of the serum of an animal immunized against cholera without any antitoxic power was

also known. Its bacteriolytic property was yet unknown. Pfeiffer found that either by the simultaneous intraperitoneal injection of a lethal dose of cholera vibrios, together with the serum of an immunized animal, or by the injection of cholera vibrios alone into the abdominal cavity of an immunized animal, the micro-organisms lost their motility, became spherical, and then underwent a granular degeneration, while the animal survived. (Pfeiffer's phenomenon.)

It was shown by Fraenkel and Sobernheim that this result obtained also if the immune serum had been previously heated to 56°C ., and its bactericidal power consequently destroyed. It follows that if the bactericidal substance plays any part in this reaction, it must be supplied from the blood of the animal subjected to the experiment. Bordet proved that two substances contributed to Pfeiffer's reaction by showing, first, that it occurred *in vitro*, and, secondly, that if the bactericidal property of the immune serum were destroyed by first heating it to 56°C ., the bacteriolytic action could be restored by the addition of a small quantity of normal serum. (It will be convenient to note here that a serum deprived of such a property by heating is called an inactivated serum, and when this property is restored a re-activated serum.) By similar experiments, using xanthocytes instead of bacteria for immunization, Bordet was able to show that the haemolytic power of the immune serum was destroyed by heating, and could be restored by the addition of normal serum, which, by itself, possessed no haemolytic properties.

In order to extend his theory of the formation of antitoxins to that of haemolysins Ehrlich made a long series of experiments. He recognized, of course, that Bordet was right in assuming the existence of two bodies for the production of the phenomenon, and that one body (mediator) (amboceptor) was present in quantity in the serum of immunized animals only, while the other (the complement) occurred in the serum of normal untreated animals.

He reasoned that if the mediator were formed in a similar way to antitoxin, then it ought to be saturated and neutralized by the addition of xanthocytes which would correspond to the toxin in a toxin-antitoxin mixture. This was proved to be so by taking the serum of a goat immunized against sheep's blood, heating the serum to 56°C . to destroy its haemolytic power (by destruction of the complement) and then adding to it sheep's xanthocytes.

After standing awhile they were again separated by centrifugalizing. If the amboceptor had united with xanthocytes, then on the addition of normal serum to the corpuscles haemolysis ought to occur. This was found to be the case. On the other hand, if the mediator had been removed from the immune serum, then on the addition of fresh normal serum and xanthocytes to it no haemolysis of the latter should occur. Nor did it. This proved, as Ehrlich says, "that the amboceptor possesses a specific haptophore group which binds it to the xanthocyte, as required by the side-chain theory."

On the other hand, if to normal goat's serum which contains the second body, the complement, there be added sheep's xanthocytes, then, if they were capable of binding the complement, on centrifugalizing off the xanthocytes and adding fresh xanthocytes and mediators to the removed supernatant serum, no haemolysis should occur. But it does, showing that the complement has not united with the xanthocytes. Moreover, if xanthocytes and immune serum be mixed as before but kept in the cold, no haemolysis occurs.

On centrifugalizing and treating the xanthocytes as just mentioned, one can prove that the amboceptor has united with the xanthocyte, but not the complement with the intermediary body. Since the interposition of the amboceptor is thus shown to be essential, Ehrlich concludes:—

That the amboceptor has two different haptophore groups; one having a great affinity to the corresponding haptophore group in the xanthocyte and a second haptophore group of less chemical energy which can attract more or less completely the complement present in the serum.

Since the action of the complement produces effects which, with Pfeiffer, we must regard as analogous to digestion, we shall probably not be far wrong in regarding the complement as possessed of the properties of a digestive ferment.

Taking a familiar illustration in which, however, the characters are really reversed, we may regard the pepsin in an artificial digestion mixture as the amboceptor and the acid as the complement. That is, the pepsin is the special factor like the amboceptor occurring only in the immune serum, while the acid which may, as we know, be either hydrochloric, or sulphuric, or oxalic, etc., corresponds to the complement to be found in a variety of serums.

* I use this word instead of the hybrid enormity "antibody."

The lock and key simile of E. Fischer affords perhaps the best analogy. The lock is the cell, the key is the amboceptor, and the hand which turns the key the complement. As a rule but one key (or at most a few similar ones, a small number compared with the total) will fit a given lock. But nearly any hand, it may be of a monkey or performing dog, can turn the key in the lock.

The same explanations hold good for the action of the agglutinins, namely, those substances in immune serums which cause agglutinations in the corresponding bacteria; for the action of the precipitins, namely, those substances in immune serums which cause precipitation when added to the fluids or solution of substances used for immunization. In the case of milk they have been called coagulins.

I shall return later to these particular substances. It will suffice here to point out that their occurrence led Ehrlich to expand his hypothesis and apply it to explain also the normal processes of food assimilation. The formation of antidotes to normal foodstuffs is quite analogous to the formation of antitoxins to toxins, so that the generation of antitoxins "is only a reproduction of a process in normal cell-life." Ehrlich believes that the proteid molecule of a food becomes attached to one group of the cell receptor, while the other group is already occupied by a ferment (the complement) molecule to make the foodstuff assimilable. In this respect the receptor is more-complicated than that for the toxin which has only one group; but is less complicated than that concerned with the formation of haemolysins, cytolsins, etc.

In the last instance separate groups are required for union with the broken-down bacteria or xanthocytes and for the complement circulating in the blood-stream.

This can be most easily explained by reference to the diagrams (modified from Ehrlich).

A PSYCHOPATHIC HOSPITAL FOR NEW YORK CITY.—A Bill has been introduced into the New York Legislature, at the instance of the State Commission in Lunacy, providing for the establishment of a psychopathic hospital in New York City. It is intended that the hospital shall serve as a place for the detention and expert examination of persons suspected of incipient insanity. The hospital would be conducted in connexion with the existing lunatic asylum on Ward's Island, and would probably be situated on the East River, opposite that institution. The Bill appropriates £60,000 for the establishment of the hospital, for which the city is to furnish the site. It will accommodate from 150 to 200 patients.

The Lettzmian Lectures

ON THE CONDITIONS WHICH MODIFY THE CHARACTERS OF INFLAMMATIONS OF THE SKIN, AND THEIR INFLUENCE ON TREATMENT.

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LECTURE III.—(Abstract). THE TREATMENT OF DERMATITIS.

INTERNAL TREATMENT.

THE internal treatment, as far as our knowledge permits, rests on the same foundation as that of visceral diseases—namely, an accurate diagnosis and full knowledge of the etiology, pathology, and prognosis of the disease in question. Owing to imperfections in the knowledge of these factors, empirical remedies had to be employed to fill up the gaps, and although glimpses of their *modus operandi* were being gradually gained, practical experience in their employment had to be relied upon in great measure. The lecturer did not discuss treatment so far as it depended on the general principles of medicine beyond insisting on the importance of clearing out the alimentary canal, and, by diet and intestinal disinfectants, endeavouring to prevent intestinal fermentations, the generation and absorption of toxins and ptomaines, on which, in his last lecture, he had laid so much stress, as important factors in the production of many inflammatory and other diseases of the skin. The administration of large quantities of feebly alkaline waters, such as was given at many of the spas, had also a flushing effect on the liver and kidneys, and was often an important aid in many inflammatory and urticarial diseases, especially in senile and the so-called gouty eczema.

ARSENIC.

While the long-established position of arsenic, and its widespread use by the mass of the profession for almost every cutaneous disease, and its undoubted merits for some diseases, entitled it to the first consideration, he thought most dermatologists would agree that it was often a most disappointing drug and that its place became more restricted as experience widened. Its action appeared to be partly direct on the epithelial cells and partly indirect through the peripheral vasomotor nerves. Its local action was shown by its effect on psoriasis patches actually present. It did not prevent others forming even in the neighbourhood, and in rapidly developing eruptions actually made it come out faster. Moreover, there was more pigmentation in the site of psoriasis treated by arsenic than after treatment by other means. He therefore deprecated arsenic being given for very long periods at a time in order to ward off fresh attacks, as it not only failed to do so, but was liable to produce effects of its own, which might not only be disfiguring, but even serious. These were the well-known pigmentation of a sepia colour, which in the early stage was recognizable from its sparing for some time the immediate neighbourhood of the hair follicles so that they appeared as white dots on a dark ground on the abdomen; eventually they also were invaded and a more uniform tint was observed. The other lesion was the thickening of the horny layer of the palms and soles which commenced round the sweat ducts and increased to small warty nodules which at this stage were distinctive, but ultimately the intervals were levelled up to a uniform horny plate covering the whole palmar surface and all the sole which touched the ground in standing. In a few cases epithelioma developed on this warty thickening. An instance of its occurrence thirty-eight years after the arsenic had been left off was related. Besides psoriasis it was also sometimes successful in lichen planus, and in the worst forms of lichen acuminatus, in all of which its action was probably direct on the diseased epithelial cells, but it was always a slow remedy in these affections, often required the dose to be raised to the verge of the patient's tolerance, and many cases were much better treated by other means. It was often advantageous on recurrent angio-neuroses, such as some forms of erythema, especially erythema haemorrhagicum in which a toxin origin was often to be inferred, in chronic