An Address

ON

THE ACTIVITY OF THE CELLS AND FLUIDS OF THE BODY IN THE PREVENTION AND CURE OF DISEASE:

A PLEA FOR MORE THOROUGH PATHOLOGICAL INVESTIGATION.*

BY

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THE advances which have taken place in pathological science within recent years have been so great that specialization in certain directions has been forced upon the workers on the subject. Such specialization, like specialization in any other direction, has led observers to magnify one aspect in the problem of disease and to minimize another, which may, after all, be the more important. In fact, I do not think it is too much to say that the effects, because they are the most obvious and because they lend themselves more easily to the investigator, are often very fully worked out, whereas no attempt is made to get at the cause. The history of careful blood examination in disease does not go back very many years, and yet we find diagnoses made and even new diseases "discovered," or, at any rate, new names for these diseases coined, from blood examination alone. Medical literature is becoming burdened with new names, because people will not take the trouble to study the fundamental problems on which the cellular and other reactions which characterize disease in general are founded. To take only one instance: blood examinations are extremely valuable, but unless the interpretation of the changes which are seen is based on an intelligent grasp of the processes underlying them, and unless these changes are regarded merely as an aid to the problem which has to be solved, erroneous statements and wrong diagnoses are certain to be made.

I wish to deal with only one of these problems, that one, however, which I think the most important and certainly that which promises greatest things in both preventive and curative treatment—the activities of the cells and fluids of the body.

Phagocytosis.

It is to the work of Elias Metchnikoff that we owe so much of our knowledge of the cellular activities of the body. It is now a well-established fact that many cells are specially active in the destruction of bacteria. There can be no doubt that the bacteria are first ingested and then digested. The actual process by which this ingestion takes place is not fully understood. It has been established that certain chemical substances have the power of attracting leucocytes, while others do not possess this power. It may therefore well be that the bacteria or the bacterial products exert a similar action. However the matter be explained, the fact is perfectly definite that with the introduction of bacteria there is, in almost all cases, an increased number of leucocytes in the circulating blood; and that numbers of these leucocytes pass through the walls of the blood vessels, migrate to the area of infection, and there become active phagocytes; and that in minor infections, at any rate, the action of these leucocytes is to overcome the bacteria and bring about the repair of any damage which they or their products have effected.

The importance of this positive chemiotaxis, and the ingestive and destructive power of the leucocytes is obvious, and it is of special interest that these functions can be modified in various ways. It has been shown that in the active immunization of an animal certain bodies are produced which at any rate aid in the destruction of the bacteria, and with the development of these, increased phagocytosis is obvious. Whether this increase is due to the direct action of these bodies on the bacteria them-

selves or on the phagocytic cells is a matter which has led to a great deal of controversy. Numerous experiments have shown that virulent bacteria—for example, virulent strains of streptococci—are not phagocytosed by the leucocytes of the body *in vitro*, but that if certain bodies produced during the process of immunization—such as those contained in antistreptococcal serum—are added to the mixture of leucocytes and streptococci, phagocytosis almost immediately becomes a marked feature. Much recent work, especially that in relation to opsonins, has shown that at any rate one factor in this process is a directly injurious action on the bacteria of these antagonistic substances. There can be no doubt, however, that living and active bacteria are ingested by the leucocytes, and that intracellular destruction of these takes place; but I think we must also recognize that though bacteria may be ingested by the leucocytes, they may not be digested. One cannot imagine that the enormous numbers of gonococci which are found in the cells of gonorrhoeal pus, and which retain their power of infection, are in any way injured by the intracellular activities of the leucocytes. The same may be said of the bacillus of tuberculosis or the bacillus of leprosy. In fact, there seems evidence that an actual multiplication of some of these bacteria takes place in the cytoplasm of the leucocytes.

I have already referred to the non-phagocytic action of the leucocytes to virulent streptococci *in vitro*, but this reaction is also seen in the animal body during life. The experiments of Bordet and of Marchand are of very great interest and importance in this connexion. Bordet noted that streptococci injected into the peritoneal cavity of laboratory animals set up a marked leucocytosis which ended in the ingestion and digestion of almost the whole of the streptococci. There generally remained a few individuals which resisted the action of the leucocytes and were not ingested. Further injections of the organisms showed that the leucocytes were still active, but more streptococci remained free. Thus a new generation of organisms was produced which was able to resist the action of the leucocytes, or, at any rate, which was not actively phagocytosed by them. Carrying his experiments further, Bordet established that it was not a weakening of the phagocytic function of the leucocytes which had taken place, for if he injected a rather feeble organism into the peritoneal sac just at the time when the ingestion of the streptococci had ceased, the leucocytes at once became actively phagocytic to these new organisms. They thus appeared to have a positive attraction for one kind of organism and a negative for another.

Marchand, who repeated these experiments with similar results, showed also that it was the more virulent strains of the organisms in which the leucocytes did not act; and he concluded that "an attenuated streptococcus is a streptococcus readily devoured by phagocytes," whilst "a very virulent streptococcus is a microbe that is not attacked by the leucocytes"; and he adds that "a streptococcus is virulent because it is not devoured by phagocytes."

The facts which I have stated and the experiments which I have recorded are only a few of the many evidences we have of the very great importance of phagocytosis, not only in the natural cure of disease, but also in the preventive and therapeutic measures which are so constantly employed. For an active phagocytosis it is essential that there should be a well-marked leucocytosis. Blood examination, therefore, will reveal to the clinician whether this leucocytosis is or is not present, and the simple process of testing the phagocytic power of the leucocytes devised by Leishman may also be of great value in testing the virulence of the offending organism. Leucocytosis is undoubted evidence that the case is one of organismal or of toxic origin, but it may also give much information in regard to prognosis, etc.

It is now a well known fact that in most infective diseases a polynuclear leucocytosis is always to be regarded as favourable, whereas the absence of it is a very grave sign. The positive side is, from the point of view of prognosis, much less important than the negative. It is true that up to a certain point the leucocytosis increases with the extent of the infection, and that a marked leucocytosis may indicate a widespread involvement of the affected organ or organs, but it is always an indication

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that the leucocyte forming tissues are functioning well. The other side of the picture is much more important, for in infections in which leucocytosis is the rule, its absence or its diminution and disappearance without a corresponding improvement in the symptoms must always be regarded as a very grave sign. The reactive power of the tissues is lost or is in abeyance, and in consequence the toxæmia remains unchecked.

Every clinician knows the grave prognosis of pneumonia in alcoholics, and an examination of the blood of these cases generally reveals an aleucocytosis. Ferguson has shown that in that very fatal disease, hæmorrhagic small-pox, aleucocytosis is again a marked feature.

A study of the bone-marrow has afforded an explanation of the leucocytosis and also of the aleucocytosis. The polynuclear cells are formed from the myelocytes in the marrow. In the normal long bones this leucocyte-forming tissue is mainly found near the extremities, but in the majority of infective diseases this tissue is very greatly increased at the expense of the fat; and the whole of the medullary cavity may become converted into a leucocyte factory. But the marrow, like other tissues, may become exhausted or may undergo degenerative changes, and then, no matter what stimulus may be applied to it, it cannot react. I need not enter into the details of these changes.

There are inevitable dangers of applying too rigidly the facts obtained from one source of investigation either in giving a diagnosis or a prognosis. Blood examination, as I have already said, can only be regarded as an auxiliary—truly a valuable auxiliary if we have clear views as to the rationale of it. There are cases, however, in which toxic agents are definitely at work, in which no polynuclear leucocytosis occurs. Of these I need only mention typhoid fever, influenza, measles, and acute tuberculosis, and the onset of leucocytosis in such cases is generally the precursor of some complication by which other bacteria or other toxic substances are called into play.

I have also pointed out, and I would again emphasize the fact, that an abundant leucocytosis may be called forth and yet the leucocytes may have practically no action in the causal organisms. They multiply apparently irrespective of the leucocytosis. For some reason that we do not clearly understand they do not become the prey of the leucocytes.

So far we have dealt principally with the polynuclear cell as a defensive agent, for the obvious reason that we know most about it, and can work out its reactions very readily, but there seems little doubt that all the other cells of the body, and at any rate all the migratory cells, have important functions to discharge. Thus the constant increase of the eosinophiles in the blood as a result of infection by parasites has been largely used as a means of diagnosis in ankylostomiasis and other parasitic conditions, but we cannot conceive that these cells are there simply to aid the clinician. They no doubt have an important function, though at present we do not know what it is. So with many of the mononucleated cells. Proliferation of these takes place very markedly, though usually locally, in many infective and toxic conditions. They often act as direct phagocytes, but there is much evidence that they are more concerned with the production of substances which in various ways aid in the defences of the body. To this subject I shall refer later.

If these cells occupy the important position which I have given them, it is obvious that an increase in their number, or a stimulation of those existing, or an increase of their products, should be of extreme value in the prevention and in the cure of disease. Much has already been done along these lines, and it is only necessary to recall the work of Mikulicz, who, in operations in the peritoneal cavity, produced a preliminary leucocytosis by the injection of nucleic acid. We are all familiar with the rapid healing of an old sluggish ulcer or an old sinus after it has been thoroughly scraped or cauterized, or the healing of an abscess after it has been opened. No doubt, in these cases many of the organisms have been got rid of in one way or another, but there is little doubt that the healing is largely brought about by the influx of fresh cells and fresh lymph to the damaged area.

Little work has yet been done with leucocyte extract, but the results, both in animals and in the human subject, which have been recorded by Hiss and Zinsser are, to say the least, extremely hopeful. It will be a great triumph

when the clinician can treat his cases of pneumonia, not with drugs that simply keep him going till the crisis comes, but with substances which can overcome the cause and antagonize the toxic products, and so hasten the period of crisis. This seems to have been the result if the work of Hiss and Zinsser is to be accepted. In the light of the facts which careful pathological research has brought out, it would seem as if we should have to alter not only our line of attack on many diseases, but also revise our conception of the therapeutic action of some of our familiar drugs. The whole fabric of the treatment by vaccines is founded on the increased activity of the cells of the body which is produced by the injection. The pharmacologist does not tell us how the salicylates act in acute rheumatism. Does the drug act directly on the causal agent, or does it act by increasing the defensive agents of the body? Strong believer as I am in the bacteriological cause of acute rheumatism, I naturally turn to the leucocyte-producing tissues for an explanation. In acute rheumatism there is a marked leucoblastic reaction in the bone marrow, and in the healthy individual leucocytosis is produced by the exhibition of salicylates; I have not sufficient evidence to dogmatize, but I throw out the suggestion. May not the beneficial action of salicylates in certain cases and its absolute failure in others—a fact which has led to the disuse of the drug in certain schools—be explained by a careful study of its reactions on the cell activities of the body? It may succeed, when the leucocyte-forming tissues are healthy, either by stimulating them to a greater production of leucocytes or by intensifying the activity, phagocytic or chemical, of the leucocytes which are present; it may fail because the leucocyte-forming tissues have already been over-stimulated or have undergone degenerative changes, and cannot therefore respond to any new stimulus, or it may fail because the leucocytes fail to act upon the causal organism—or, perhaps, being a worker in this field and therefore a biased witness, I should say causal agent.

Antitoxin and Bactericidal Fluids.

So far I have dealt with the cells of the body as defensive agents in the protection against and in the cure of disease, and though, strictly speaking, this cellular activity cannot be separated from the antitoxic and bactericidal action of the fluids of the body, it is convenient to deal with them separately.

It is well known that many of these protective substances are present in small quantities in the normal body fluids, and that by the process of immunization or vaccination, either artificially or as a result of an attack of some infective disease, they are increased, and may become curative agents.

It may be stated generally that these protective substances, whatever their nature, are present normally in the serum or in the cells. Some of them can be easily demonstrated, and others are probably present in or in combination with the complex protoplasm of the cells. They probably have a chemical affinity for particular organic substances, and are formed in excess or secreted in excess when these substances are introduced. Those which are of importance may for convenience be divided into three groups:

1. Those which have with other substances a combining affinity only.
2. Those which have not only this combining affinity, but which, as a result of the combination, produce physical changes in the medium in which they are present.
3. Those which, in virtue of their combination with other substances, are able to bring about destructive changes.

In the first group we have the antitoxins, which by combination with the toxins produce what is, so far as we know, an inert substance. A toxin saturated with antitoxin is not able to combine with the cells of the body, and therefore can cause no destructive action in these cells. If this toxin-antitoxin mixture is an inert body, and if, as we believe, the antitoxin, at any rate when given for the first time, is also harmless, strong support is given to the school which advocates large doses of antitoxin. The toxin is the destructive agent, and the whole object of the antitoxin is to neutralize that toxin.

The amount of toxin in the general circulation may be enormous, and if sufficient antitoxin is not given to neutralize the whole of this toxin, then the uncombined toxin goes on with its destructive work; if, on the other hand, the antitoxin is in excess, no harm results.

In the second group we have the agglutinins, precipitins, etc. With the precipitin combination takes place, but there is an alteration in the physical condition producing a cloudiness in the serums to be tested. The agglutinins are even more striking examples of this group. They combine with the bacteria, but also produce clumping, and thus give us evidence of their specific character. This specificity is of extreme importance in diagnosis. Thus, the agglutinin found in the serum in cases of typhoid fever exhibits its most intense effects on the *B. typhosus*, and though on this reaction a definite diagnosis can be made in a very high percentage of cases, yet the specificity is not absolute. The agglutinin acts, though to a less extent, on allied bacilli. The probable explanation of this is that the agglutination reaction is a definite chemical process, the agglutinin combining with certain of the molecules contained in the body of the bacilli. The structure of the bacillary protoplasm is very complex, and it may well be that the combining affinities for the agglutinin of typhoid fever are numerous in the typhoid bacilli, but are present, though in smaller proportion, in the other bacilli of the group. It is, therefore, obvious that if this agglutination be, as we have said, a chemical process, the importance of the quantitative factor is very great. By diluting the agglutinin we lessen its combining properties, and therefore, if with considerable dilution we still get definite agglutination, the reaction becomes the more specific. Thus a dilution of a typhoid agglutinin to 1 in 5 or 1 in 10 may give clumping with, say, Gaertner's bacillus, whereas a 1 in 20, to a 1 in 50, or 1 in 100 dilution shows no agglutinative action on any organism except the *B. typhosus*. This factor is one on which too little emphasis is placed, and I am convinced that much of the odium which has been cast on the agglutinative reaction as a test in typhoid and other infective conditions is due to the inaccurate and indefinite methods which are so commonly used in working out the reaction.

The third group is perhaps the most important. This group of antisubstances—the immune bodies—combines with the substances on which the members act, but needs to produce its destructive effect the co-operation of a substance normally present in the serum—the complement of Ehrlich.

It is now a well-known fact that if the cells of one animal are injected a few times into an animal of a different species, the serum of this latter animal attains properties which are destructive to the cells originally injected, and that this destructive action can be prevented simply by heating the serum or even by keeping it exposed for some time, and further that the destructive property can be restored by adding some fresh normal serum.

To take a specific example: if the washed red blood corpuscles of a sheep are injected into a rabbit, the serum of the rabbit develops an immune body which in its fresh, unheated condition is capable of hæmolyzing the red corpuscles of the sheep. This property is very soon lost, but the serum can be reactivated by the addition of some normal unheated serum, say from a guinea-pig. This reactivation is due to the addition of complement, which, as I have already said, is present in the normal serum, and which is therefore also present in the immune serum when it had been freshly withdrawn. This reaction is an extremely important one—one of very common occurrence in the animal kingdom, and one on which is dependent many pathological changes seen in disease; and on which is based some of the more recent and extremely interesting methods of diagnosis. There is some evidence, for example, that the breaking down of the red corpuscles in cases of pernicious anaemia is brought about by the action of bodies resembling these antisubstances. Perhaps of more interest is the Wassermann-Neisser-Bruck reaction in syphilis, which is occupying so much attention at the present time. This reaction is entirely dependent on the interaction of a specific immune body present in the blood of syphilitics and normal serum, or, rather, normal complement.

I have said enough to emphasize the importance of these protective substances, the study of which is still in its infancy. The whole subject of the general treatment by vaccines is based upon the fact that these substances are present normally, that they can be artificially increased, and that by this increase the body is protected against the invasion of bacterial and other agents which are causal in disease, or, perhaps we should say more correctly, is protected against the destructive action of these agents when they reach the unprotected body. But not only are they protective agents, they are curative ones as well. Nothing need be said in medical circles of the great protection against small-pox, or of the curative action in diphtheria of these antisubstances. It is yet too early to speak with any definiteness of the cure of tuberculosis by vaccines, or of the cure of cerebro-spinal meningitis by antiserum; but the work of Wright and his school, no matter what may be our views as to the methods employed, or the deductions drawn from them, and the work of Flexner and of Kolle, must be regarded as epoch-making.

To-day advance is being made all along the line by utilizing the facts which have been elicited by a study of Nature's method of dealing with disease. If I might take one more illustration: A study of acute pneumonia has shown us that the cellular reaction is exemplified in the very highest degree. The blood shows a very marked leucocytosis, and the bone marrow exhibits a pronounced leucoblastic transformation. But we find, also, that substances antagonistic to the causal organism and its toxin are developed in the serum, no doubt derived, as we must believe all these substances are derived, from the various cells of the body. The antisubstances, possibly both antitoxic and antibacterial, gradually increase in quantity, as a result of the infection, and it seems highly probable that the crisis occurs when they have reached a sufficient amount or a sufficient intensity of action.

Attempts have been made to increase these protective agents, and though at present we cannot point to great success, still advance has been made, and some extremely hopeful results have been recorded. I would again refer to the work of Hiss and Zinsser, who have been using extract of leucocytes with, to say the very least, some success in the treatment of pneumonia, and also in staphylococcal infections. The basis on which their work is founded is certainly good. The failure in the disease is very often an imperfectly cellular reaction. Phagocytosis is thus lessened, and, what is perhaps of more importance, the protective substances produced by the cells is not in sufficient quantity to overcome the poisons. The rational procedure, therefore, seems to be to increase these protective substances, either indirectly by stimulating the cells, or directly, as Hiss and Zinsser have done, by introducing the products of the activity of the cells.

CONCLUSION.

I have attempted to sketch some of the main facts which have been occupying pathologists for very many years, and I think I may say that the importance of them justifies my plea for a continued and even more thorough pathological investigation of disease. The pathologist of to-day must of necessity spend a great deal of his time in his laboratory with test tube as well as with microscope; but the pathologist who neglects the *post-mortem* room or even the bedside cannot fully realize the greatest problems of disease. In his work, therefore, he must be assisted by the clinician, and in their hearty co-operation, both in eliciting the fundamental causes of disease and in the application of the most important scientific discoveries, the advance in scientific medicine must be greatly aided. Much has been done, but much remains to be done. A *post-mortem* examination in every case of death, no matter how uninteresting it may seem, is highly desirable. This would, I believe, be easily accomplished, at any rate in our great hospitals, with a little tact and determination. The examination of blood and morbid secretions of various kinds is now undertaken more or less generally, and one rejoices to see the fitting up of clinical laboratories in many of our hospitals; but clinical laboratories will be of little value if they are mere workrooms for dilettanti, and are not at least controlled by men not only enthusiastic in their work, but with a satisfactory training for the proper accomplishment of it.