A REVIEW OF CURRENT THEORIES REGARDING IMMUNITY.

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Concluded from page 285.

Two questions. In concluding our review of this division of the subject, which deals with the parts played by the bodily presence of cellular protoplasm as contrasted with the activity of the chemical products of that protoplasm, which from their solubility may act at a distance from the cell producing them, there are two points which may be alluded to. Firstly, it is difficult to see how, granted that two substances are necessary for bactericidal action, these substances can in the first instance at least meet the bacterium except within a cell. Unless all immune bodies are represented in the serum by go-betweens (Zwischenkörper),—by bodies of an identical nature and differing only in that they are subservient to the normal metabolism of the body—how, when a bacterium gains entrance to the blood, does it come in contact with the immune body for which its protoplasm has the affinity? The receptor, which fixes the group in the bacterium corresponding with it, is within a cell,—how can the affinities be satisfied until the bacterium gets within the cell? It is not till the cell has been robbed of the use of these receptors and they become over-regenerated that the immune body becomes free and can be found in the serum. It is possible that all immune bodies are represented by go-betweens, and that a certain amount of the latter must be kept free in the serum for ordinary metabolism, and it is also possible that when the gradient —to use a physical phrase—between the cell and the blood plasma becomes great so far as the amount of go-betweens present in the latter is concerned that the cell becomes more active and secretes more

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of the material which is being more rapidly taken up than is usual in ordinary metabolism. Thus while the extra-cellular destruction of bacteria is easy to understand in the later steps of immunisation there is a difficulty about the earlier stages.

Secondly, if it is the case that in order to their destruction bacteria must meet in a cell immune body and complement produced by the same cell, why is it that during the process of immunisation only one of these cytases, to use Metchnikoff's phrase, is produced in excess? Why should the cell manifest so much activity in overproducing one of its products and manifest so little activity in producing another and an equally necessary substance?

The possible relationship of the processes occurring in immunity against bacterial action to processes normally occurring in the body.

In our review of the factors concerned in this variety of immunity we have seen that there is evidence of the vital activity of cells giving rise to the presence in the circulating fluids of the body of materials concerned in the death of bacteria. The question now to be looked at is whether the functions brought into play in the production of the protective bodies are called into existence only for protection against bacteria, and other noxious agents of a similar kind, or whether these functions are concerned in the normal activities of the cells. Two lines of enquiry might throw light on this matter, firstly, that concerned with asking the normal functions of the cells producing protective bodies; and, secondly, that which is directed to investigating whether or not bodies similar or identical with protective bodies occur in the sera of animals not the subjects of infection. To look first of all at this matter from the point of view of the cells. Here it is evident that the question arises of the normal functions of all the cells we have enumerated as concerned in the reactive processes already studied. Of these, we have seen reason to believe, the most important are the leucocytes, and we may direct our attention chiefly to them. What are the normal functions of these cells? Of this subject very little is known, and in fact it is probably by the study of immunity that information will be gained as to what under ordinary circumstances these cells do. From what indications we have we may say that they may have one or other of two functions. Firstly, their sole use may be to guard the body against infection. Secondly, such a function may be subsidiary to other functions. With regard to the

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former of these possibilities we have to remark that in his early work on inflammation Metchnikoff [102] looked upon the leucocytosis which occurs in this process as its essential feature. This deduction was largely based on the phagocytic activities of wandering cells in the different types of the whole animal series from the lowest invertebrates upwards. In the lower animals such a phagocytic function of cells is simply the same process by which the animal seizes particulate bodies from the digestion of which it derives its food, and in many such animals these cells are the main, and it may be sometimes the only means by which food is obtained. The occurrence of phagocytic cells in practically all animals may be granted, though the homologies of the cells concerned in different species still require much investigation. Even, however, if the leucocytes of the mammalia are the homologues of the wandering cells of lower forms it does not follow that the functions of digestion and protection are parts of the same vital activities. As digestion in the higher forms has become chiefly a function of certain specialised tissues derived in the main from the hypoblast, it is possible that that of protection is the specialised function of the leucocytes; and while the latter do undoubtedly contain proteolytic bodies it is, as has been already pointed out, an assumption that these are identical with the bactericidal substances. There is little doubt that the body is more or less constantly exposed to the absorption of bacteria from the intestinal tract, though the extent of this risk requires further investigation, and there is little doubt that infection does not follow every such absorption, but the constant presence of bacteria in the neighbourhood of the intestinal lumen would not account for the marked leucocytosis which in mammals occurs after a meal is partaken of. It is to be remembered, however, that leucocytes can be attracted by such non-particulate substances as bacterial proteines, albumoses, etc., and it is a possibility that harmful materials of a similar nature require constantly to be disposed of in order that the body may not suffer injury. On the other hand it is quite possible that the occurrence of an increase of leucocytes in the circulating blood during digestion may indicate a digestive function on the part of these cells, though we have no facts by which we may judge what changes they may originate in the fluids being absorbed from the intestine. The general view of physiology is that the albuminous constituents of the blood are formed from peptone in the intestinal wall, *i.e.* during absorption, though as we shall see presently it is doubtful if the methods of physiological chemistry are sufficient to appreciate very fine differences which may exist between albumins. There is no doubt there is thus an opening for further elaboration taking place in the fluid elements of the blood after absorption, and in these processes the white cells might play a part. If, as may thus be gathered, the functions of the leucocytes are obscure it is evident that it is still more difficult to form a conception of the parts ordinarily played in the body by the great variety of phagocytic cells to which we have alluded. In connection with this aspect of the subject there are numerous lines of enquiry opened out which would well repay following up.

Enquiries into the normal functions of the leucocytes being thus to a large extent barren, we proceed to ask if under normal circumstances substances analogous to protective bodies occur in the body. Here is involved the question of the co-relation of the bactericidal actions of normal sera with those of the sera of immunised animals, and regarding this the chief results of research have already been given. We have seen that complementary substances occur in ordinary sera which have a bactericidal action just as they form a very important part of the sera of immune animals, but we have seen that it is a matter of dispute whether they occur in the circulating blood. With regard to the free occurrence of immune bodies the case is different. We have adduced one instance where there occurs in a normal serum a body corresponding in all its properties with an immune body, and we have raised the question whether the bactericidal action of normal sera may not be always due to the presence of such bodies in addition to complements. The instance given was that of the body in the normal serum of the goat, which with the aid of complement from the horse will haemolyse rabbit's corpuscles. A very great number of such bodies having the properties of immune bodies have been discovered in normal sera, and the question arises what their normal function is, for it is, of course, inconceivable that, say, in the case given, the substance should exist in the goat's body for the purpose of haemolysing rabbit's corpuscles, when the latter happened to get into the goat's body. Just as in looking at this question from the point of view of the cells producing complement and immune body so here there are two main possibilities,—either the substances are concerned in the protection of the animal against infection or they are concerned in the elaboration of materials needed in ordinary metabolism. It is to the last view that Ehrlich inclines. A point which may be cited in its favour is derived from the analogies of what we have seen as probably happening in the case of tetanus toxine. The toxine molecules are, as has been observed, very

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probably allied in nature to those which form the normal food of the cells fixing them. Here there is no question of the cellular receptors having a protective action, for it is because of these receptors being present in the cell that the latter becomes susceptible to the toxic action of the toxophorous group of the toxine.

But the probability that the substances we are concerned with are of use in ordinary metabolism is indicated by the fact that when materials analogous to the ordinary food materials of the body, and so far as we know incapable of harmful action, are introduced into the blood they are acted on by substances precisely similar to those which act on such a harmful agent as a bacterium. It was noticed by Bordet[103] that when rabbits were treated by intra-peritoneal injections of fowl's blood not only was a haemolytic serum obtained, but the serum when added to fowl's blood produced a precipitate somewhat like a coagulum. Subsequent investigations of similar conditions have shown that the reaction is one produced by the presence of the serum, and especially by the globulins of the blood injected. Of the results of such enquiries those of Myers[104] may be taken as an example. This observer found that intra-peritoneal injections, extending over two months, of crystallised egg-albumin into the rabbit's peritoneum produced a serum which caused a precipitate when added to solution of hen's egg-albumin. This precipitate was soluble in 2 per cent. sodium chloride solution and gave ordinary proteid reactions. The solubility of the precipitate thus marked the phenomenon off from a true coagulation. The serum had a slight effect on duck egg-albumin, but none on sheep globulin, sheep serum albumin, bullock serum, or Witte's peptone. The intra-peritoneal injection of serum globulin from the sheep into the rabbit gave rise to a precipitin (as the anti-bodies in this class of sera are called) capable of precipitating the globulin which originated it, but which had no reaction on bullock globulin or Witte's peptone. The injection of bullock globulin gave a precipitin which besides its specific action on the causal globulin also slightly precipitated sheep's globulin. The injection of Witte's peptone gave a precipitate with peptone, which precipitate, however, did not give the biuret reaction though soluble in 2 per cent. salt solution. The first three precipitins were not weakened by half-an-hour's heating at 56° C., and thus differed from immune sera, but in the case of the last precipitin a weakening occurred the effect of which, however, could be neutralised by the addition of serum from the normal rabbit. This precipitin therefore corresponded exactly with an immune serum. The important points regarding these precipitins are, firstly, that bodies closely allied to the normal constituents of an animal's blood can originate in that animal's body substances capable of producing an effect upon themselves; secondly, that the anti-bodies thus produced in some cases resemble in their nature the anti-bodies of the serum of an animal immunised against bacterial infection, though in many cases this is not true; thirdly, that these anti-bodies are not so specific in their reactions as is the case with immune sera but are capable often of having a definite effect on substances allied to those which stimulated their origin. It is evident that by the discovery of these precipitins the way is opened up for believing that the go-betweens ("Zwischenkörper") often present in serum may have as a normal function the elaboration for the use of the body of the food materials after their preliminary digestion in the intestinal tract. How the precipitins originate has still to be investigated, and it is not known whether they are the products of leucocytic activity or what cells are concerned in their genesis, nor are their effects at all understood, for the nature of the precipitation which they cause is unknown. In fact it is doubtful if their effect *in vitro* is the same as their action when introduced into the body of an animal which contains in its blood materials on which they are capable of acting. Bashford[105] has pointed out that in a rabbit with a serum capable of precipitating peptone the injection of the latter substance into the ear-vein does not produce embolism which the injection of a precipitate caused by the same serum *in vitro* does. A final point may be noticed with regard to these bodies. The facts known indicate that in bodies so apparently identical when considered from the standpoint of ordinary physiological chemistry as serum globulin from the ox and that from the sheep, differences in constitution really exist which can be distinguished by this more delicate method of analysis by physiological reaction.

These facts regarding the appearance of substances in normal sera allied in nature to those found in immune sera, and the development of analogous substances by the injection of materials closely resembling the substances which must occur in the blood after a meal, open up the way for believing that in all probability the events of immunisation are closely related to what occurs under normal conditions in the elaboration of the many bodies required for cellular nutrition. Such nutrition may depend in many ways on the inter-action of affinities in food materials for receptors in the cells, and, from what we already know, we can realise that the process may be extremely complicated in nature. This has been made clear by certain observations of Ehrlich and others. Not only can there be developed in the course of immunisation immune bodies and complements, but it is possible in many cases to get substances which can antagonise the actions of these. Thus if a serum containing complement be injected into the body of another animal there appears in the serum of the latter an anticomplement, *i.e.* a substance which when mixed with the latter and introduced along with an appropriate immune body can prevent the complement from acting with the immune body, and thus prevent the latter having any action whatever. Examples of the development of an anti-immune body are more rare, but Ehrlich has found evidence of their occurrence in the case of the immune bodies concerned in haemolytic action though they are apparently less common, if they can be developed at all, in connection with the immune bodies concerned in anti-bacterial action. In connection with this subject a very interesting and important matter arises. If an animal is treated with the corpuscles of another animal of the same species it will develop a serum haemolytic to the blood corpuscles of the second animal. It might be thought that this serum would be haemolytic to its own corpuscles, but this is never the case, although such a serum is frequently haemolytic for the corpuscles of other individuals of the same species. The following experiments illustrate this principle. Goat A was injected with the blood of three other goats, 1, 2, 3, and a haemolytic serum was obtained which acted on the corpuscles of goats 1, 2, 4, 5, 6, 9; it also acted slightly on the bloods of goats 3 and 8, and not at all on the blood of goat 7. Its own blood was also unaffected by the serum. Thus while there was evidence of an isolysin, *i.e.* a serum dissolving the blood corpuscles of animals of the same species, there was no evidence of the presence of an autolysin, *i.e.* the presence of a substance dissolving the animal's own blood corpuscles. Ehrlich has never obtained any evidence of the existence of such autolysins. Now if an ordinary haemolysin such as for example exists normally in the serum of the dog or the goat is injected into another animal there is produced an anti-haemolysin. Can such anti-bodies to the isolysin of the goat be produced? The serum of goat A was injected into a goat 10, and it was found that an anti-isolysin was produced, that is to say a body which protected some of the bloods mentioned as being susceptible to serum A against it. At the same time as goat A another goat B had been injected with the same bloods and it was found that at first for 14 days its serum showed the presence of very little isolysin. Afterwards an isolysin appeared in it, but it was found to differ from that present in the serum of goat A in that bloods which were susceptible to A were not very susceptible to B. It was also found that the anti-isolysin of A had not the power to protect bloods against the isolysin B. Another goat C was treated in the same way as the two others, and again an isolysin was obtained which again showed different properties from A and B. Further, all these haemolysins A, B, and C, dissolved sheep's blood, so that in the latter there must have been three groups, one to take up the receptor of each of the three sera. The theoretical considerations involved in these three cases are very complicated, and Ehrlich states them as follows. Suppose that in a given red blood corpuscle there exists a group α and in the body of the animal into which it may be injected for the purposes of immunisation (in the case under consideration let the latter be one of the same species) there is an affinity which satisfies it which we shall call receptor α. Now under ordinary circumstances the latter will first be saturated and then reproduced in excess and cast off into the serum as immune body. But suppose that not only does group α exist in the red blood cell of the blood introduced for immunisation, but also in the blood cells or somewhere in the body of the host which is undergoing the immunisation process. If now receptors α are cast off in great numbers they may combine with the α groups, and if the latter are in the red blood cells, the fact that there is complement present in the serum may lead to haemolysis; this would be a case of the occurrence of an autolysin. But if the α receptors were only cast off at first in small numbers, and (as we have seen in the case of tetanus antitoxine) this may quite well be the case, then they would unite in small numbers with the α groups, would rob the cells containing them of material required in normal metabolism, would stimulate them in turn to be over-reproduced and to be shed off into the serum. The latter would then contain an anti-autolysin. Hitherto no evidence of the formation of such bodies as the latter has been obtained.

Evidence has, however, been brought forward of the possibility of the development of auto-anticomplements. Ehrlich and Morgenroth made the following observations. The normal serum of the rabbit possesses a complement and also a go-between which acting together can dissolve guinea-pig corpuscles, and further there is in the rabbit's blood also a complement which can activate the immune body present in rabbits treated with ox blood. It was found however, that if rabbits had been a week previously injected with goat serum in-

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activated by heat these capacities were lost, and it was shown that the serum of these rabbits, especially when heated to 56° C., could prevent the complement normally present in rabbit's serum from acting. An anti-complement in other words had been developed, and, taking into account the fact that there was no complement present in the goat's serum, the formation of the anti-complement must have been due to a substance having a receptor identical with one already existing in the rabbit's body (*i.e.* in the normal complement of the rabbit). The anti-complement must thus have been of the nature of an auto-anticomplement. Such is the only exception that has as yet been found to the fact that the body seldom, if ever, produces anti-bodies to receptors already existing within it. It is the expression of what Ehrlich calls a "horror autotoxicus," on the part of the animal body. It is evident that these facts have a most important bearing on the co-relation of the processes of immunity with the enormously complex processes of normal metabolism. We may now therefore give a brief indication of their applicability in this direction.

From the consideration of the facts regarding the fixation of toxines Ehrlich [106] first arrived at the conception that unlike such materials as strychnine, etc., which show no tendency to become fixed to the cellular protoplasm the bacterial toxines have the capacity of being assimilated. Thus they proclaim their affinity to the food-stuffs of the cell which manifest the same property. This conception found support in the facts which have been detailed with regard to the effects produced in the body by the injection of serum globulin, peptone, etc. His view is that there exists in the protoplasm of the active cell a nucleus of vital activity with which the special capacities of the cell are associated. To this vital nucleus there are attached as side-chains atoms or atom-complexes which play an essential part in the work performed by the cell but which are not necessary to its life. Among these side-chains are the unsaturated affinities which normally fix food materials to the cell and which may fix such materials as toxines, the protoplasm of bacterial cells, etc. These fixative affinities are of very varied character, being adapted to the varying requirements of the cell. First of all there is the simplest form, which consists of a simple affinity and which is concerned in the fixing to the cell of relatively simple materials such as ferments, toxines and other cellular secretions. These simple affinities Ehrlich calls receptors of the first order. Such receptors when cast off in excess into the serum form such an antitoxine as that of diphtheria. If the molecules to be absorbed into the cell are of large size then more complicated receptors are necessary. For making such a molecule fit for absorption it may be necessary that a preliminary digestive process should take place. Here the fixing receptor is supposed to fix the molecule by one affinity while another arm carries a ferment-like capacity by which the fixed molecule is broken up. These are Ehrlich's receptors of the second order. The example which he gives of such a receptor is the class of bodies concerned in agglutination. These substances can be heated to 70° C. before they lose their effect, and the addition of normal serum of the animal from which the agglutinine was derived has no effect in causing the agglutinating properties to return. The principal group of receptors, however, are those of the third order, which besides being attached to the cell contain two haptophorous groups, one of which fixes the food particle while the other fixes the ferment-like body (complement), the action of which is necessary for the breaking up of the particle fixed. These receptors include by far the greater number of the bodies we have been studying in connection with immunity against infection. When they are cast off into the blood by the same mechanism as in the case of antitoxine production, they form if they are normal factors in the latter the go-betweens, whereas they constitute the immune body if they are freed by a process of immunisation. To include both of these varieties, differing only in the stimulus calling them into existence, Ehrlich uses the term "amboceptors." To the whole orders of receptors, from the fact of their containing haptophorous groups, he gives the name of "haptines," it is by them that a cell is able to attach its food to its centre of vital activity. According to his view there exist in the bodily cells innumerable such affinities concerned in the preparation of food for cells and in elaborating substances for the use of other cells. Their multiplicity may be judged of by the numerous examples of free receptors already known, lysins, agglutinins, precipitins, complements, ferments, antitoxins, anticomplements, antiferments, etc. The multiplicity of closely allied haptines may be judged of by the specificity of the numerous haemolysins for their corresponding bloods, and even when only one blood is under consideration the existence of a number of immune bodies concerned in the same reaction may be judged of by the facts given regarding the occurrence of almost identical immune bodies in connection with the isolysin experiments.

The consideration of the theories advanced at the present day to account for the phenomena of immunity thus leads on to results which

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have a deep biological significance. If looked at from the chemical standpoint alone they form a contribution, it may be said to be the as yet most far-reaching contribution, to our understanding of the complex processes by which living matter manifests itself as active. Not only so, but they lead to the possibility of understanding functions of cells, the laws which govern their activity, and the ways in which groups of cells in the complicated household of the animal body contribute to each other. Thus not only the pathologist but the biologist and physiologist are concerned in the solution of the problems which are opened up.

ERRATA.

p. 218, line 8 from top:—"an animal immunised against the filtered toxines of the cholera vibrio was not immune against an injection of the living organisms and further that the serum of one animal immunised against the latter did not protect another animal against a fatal dose of the filtered toxine" should read "the serum of an animal immunised against the cholera vibrio did not protect another animal against intestinal infection with the cholera vibrio, *i.e.* was incapable of neutralizing the toxines produced by the latter which constitute the active pathogenic agent in such an infection."

p. 243, line 16 from top:—after "Bordet" read "working with guinea-pigs treated by intraperitoneal injections of rabbit's blood and,"

p. 243, footnote:—for "*sensibilatrice*" read "*sensibilisatrice*."

p. 253, second line from bottom:—for "2 c.c." read "twice the simple dissolving dose."

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