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Source of Pfeiffer antibodies

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Bacteriolysis for Cholera & Typhoid
chiefly in bone marrow
Spleen & Lymph Glands

Pfeiffer, Marx, Wassermann -

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IMMUNE SERA

HÆMOLYSINS, CYTOTOXINS, AND PRECIPITINS

BY

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AUTHORIZED TRANSLATION

BY

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AUTHOR'S PREFACE.

During recent years that part of biology which concerns itself with the reactions resulting from the injection of organic constituents of one animal into the body of another has been worked up experimentally with great enthusiasm. This field, which in the beginning seemed to possess only a purely scientific interest, has now yielded numerous analogies to the results obtained in the experimental study of natural and artificial immunity against infectious diseases. Furthermore, the results of these investigations have been found applicable to many clinical questions, as well as to certain other problems of every-day life. It is with pleasure, therefore, that I heed the request of one of the editors of these "Clinical Lectures" [von Bergman] to present these highly interesting results to the medical profession at large. It is not my purpose to give the details of the many, oft-times complicated experiments undertaken by various authors to support or refute different theories. The following sketch is intended rather to introduce my colleagues to the essentials of the subject.

A. W.

TRANSLATOR'S PREFACE.

The subject of serum diagnosis and therapy, already grown to considerable proportions, is constantly increasing in importance. The lack in our language of any simple and concise exposition of the subject has led the translator to make this excellent treatise of Prof. A. Wassermann more readily accessible to the English-reading medical public. The presentation of the subject follows the author's course of lectures given at the University of Berlin in 1903. No changes whatever have been made in the translation. A table of contents has, however, been added.

C. B.

Brooklyn, January, 1904.

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HÆMOLYSINS, CYTOTOXINS, AND PRECIPITINS.

I. HÆMOLYSINS.

In 1898 Belfanti and Carbone showed that if horses were injected with red blood-cells of rabbits, the serum thereafter obtained from the horses would have acquired an appreciable toxicity for rabbits. Shortly after this Bordet published a very interesting series of experiments. He showed that the serum of guinea-pigs after these had been injected several times with 3 to 5 c.c. of defibrinated rabbits' blood acquires the property to dissolve rapidly and intensely, in a test-tube, the red blood-cells of a rabbit; whereas the serum of a normal guinea-pig is incapable of doing this, or does it in only a slight degree. Bordet could further show that this action is a specific one, i.e., the serum of animals treated with rabbit blood acquires this dissolving property only for the red cells of rabbits, not for those of any other species

of animal. For the latter, such a serum is no more strongly solvent than the serum of a normal animal. The same property that Bordet had demonstrated in the serum of guinea-pigs treated with rabbit blood could now be shown for the sera of all animal species treated with blood-cells of a different species. We can formulate this as follows: The serum of animals, species A, after these have been injected either subcutaneously, intraperitoneally, or intravenously with erythrocytes of species B, acquires an increased solvent action for erythrocytes of species B, and only for this species.* It is therefore a specific action. We call this *hæmolysis*, and the substances which effect the solution of the red cells, *hæmolysins* or *hæmotoxins*.

At about the same time, and independently of Bordet, similar experiments with similar results were published by Landsteiner and v. Dungern. As a result of this work, the acquired toxicity of horse serum, found by Belfanti and Carbone when they treated horses with red cells of rabbits, was explained. The serum of the horses so treated had become *hæmolytic* for rabbit blood, and therefore caused a solution or destruction of the red cells in the living body just as it did in a test-tube.

Agglutinating Power of Hæmolytic Serum.—As a further result of his experiments Bordet showed that in this hæmolytic serum still another property

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* We shall point out a few exceptions later on.

had been increased, namely, the power to clump the rabbit blood-corpuscles. This so-called *agglutination of the red cells* occurs previous to their solution. The increase in the agglutinating power of the hæmolytic serum is a specific one. For if an animal, species A, be treated with blood of species B, the serum derived from A will have acquired an agglutinating power which differs from that of normal serum of A in one very important particular, namely, in that it is specifically increased with respect to the red cells of species B or its nearest biological relatives.

That normal serum of an unrelated species possesses the power to clump the red cells of many other species had already been shown by Creite and Landois; and this clumping is not to be confounded with rouleaux formation. However, the single, specific increase of the agglutinating power with respect to a distinct and definite species of red cell by treatment with these cells was first demonstrated by Bordet.

Nature of Hæmolytic Sera—Active and Inactive Sera—The Two Parts of Hæmolysins.—This author now turned to a further study of the action of the hæmolysins, and was able to show that the solvent power of the specific hæmolysins depended on the combined action of two constituents of the specific serum. When the fresh hæmolytic serum was warmed for half an hour to 55° C., it lost its power. If to this *inactive serum* a very small

amount of the serum of a normal guinea-pig was added (a serum which of course was not hæmolytic for rabbit red cells), the full hæmolytic power was restored to this inactive serum. In other words, it had been *reactivated* by this addition.

This experiment permits of only one conclusion, namely, that the hæmolytic action of the specific hæmolytic serum depends on two substances. One of these is able to withstand heating to 55° C., and is contained only in the specific serum. The other is destroyed by heating to 55° C. and is contained not only in the specific hæmolytic serum, but also in the serum of normal untreated animals.

Alexin and Substance Sensibilatrice of Bordet—Rôle of the Substance Sensibilatrice.—Previous to this work of Bordet, and especially as a result of the researches of Buchner, it had been known that there were constituents of normal blood-serum which were actively destructive to corpuscular elements, bacteria, and other cells with which they came in contact. These substances had been termed *alexins* by Buchner. This term was retained by Bordet to designate that constituent of normal serum which did not withstand heating to 55° C., and which was one of the factors in the hæmolytic process. The other substance, which was found only in the specific serum and which withstood heating to 55° C., he termed *substance sensibilatrice.*

According to Bordet, therefore, the substances required for hæmolysis are the substance sensibila-

trice of the specific hæmolytic serum and the alexin which exists even in normal serum. The action of these two substances Bordet explains by assuming that the red cell is not vulnerable to the alexin; just as, for example, there are certain substances that will not take a dye without the previous action of a mordant. The substance sensibilatrice plays the rôle of mordant. It makes the blood-cells vulnerable to the alexin, so that the latter can attack the cells and dissolve them. The alexin he regards as a sort of ferment body with digestive powers.

Bordet says further, that the substance sensibilatrice sensitizes the blood-cells not only for the alexin derived from the serum of the same species as that from which it (the substance sensibilatrice) is derived, but sensitizes such cells also for the alexins of normal sera of other species. For example, in the foregoing experiment of Bordet, the substance sensibilatrice derived from the guinea-pig by treatment with rabbit blood sensitizes the red blood-cells of rabbits not only for the alexin of normal guinea-pig blood, but also for the alexins of other normal sera. In another experiment this author showed that rabbit red cells sensitized with an inactive specific hæmolytic serum derived from a guinea-pig would dissolve rapidly on the addition of normal rabbit blood. Here, then, the rabbit red cells, sensitized (according to Bordet) by the substance sensibilatrice of the guinea-pig,

dissolve on the addition of the alexin of their own serum.

The Exciting Agent.—If we now seek to discover the constituent part of the red cell which in the treatment excites in the animal body the production of the specific hæmolysin, we find this to be, according to Bordet and v. Dungern, the stroma of the red cells. This separated from the cell contents and injected into animals will likewise excite the production of specific hæmolytic serum. In opposition to this, Nolf assumes that the stroma excites the production of the above-mentioned agglutinins, and that the production of the substance sensibilatrice is called forth by the contents of the red cells.

Résumé.—Reviewing the important facts we have learned, we find them to be as follows: By means of the treatment of one species of animal with the red cells of a different one, the serum of the first species acquires an uncommonly increased power to dissolve and to agglutinate the red cells of the second species. This increased hæmolytic power shows itself not only in vivo, so that an animal so treated is able to cause red cells injected into it rapidly to dissolve and disappear, but it shows itself also in vitro when the serum of this animal is used. The process consists in the combined action of two substances, that which is excited in response to the injection, the substance sensibilatrice, and the alexin of normal serum.

Artificial Immunity against Bacteria—Bacteriolytic Power of Serum.—This specifically increased solvent action for foreign corpuscular elements on the part of sera of animals previously treated with the same, could not fail to be of the greatest interest to bacteriologists; for a most surprising similarity showed itself between this and the well-known facts of *artificial immunity against bacteria* as they had been developed by R. Pfeiffer. In order to make this clear to the reader, I must dwell for a moment on this subject of artificial immunity against bacteria—for example, against living cholera bacteria. A normal guinea-pig is able to kill and dissolve a number of living cholera bacilli if these be injected intraperitoneally. The freshly drawn serum of the animal possesses the same power. If this serum be heated to 55° C., or if serum be used that has stood for some time (eight to ten days), this property will have been lost. This power of normal serum and other body juices of the living animal to dissolve appreciable quantities of many bacteria, Buchner, as already stated, ascribed to certain constituents of normal serum which he called alexins.

These alexins are of very delicate constitution, decomposing when heated to 55° C., or spontaneously when kept outside of the animal body. If we inject into a guinea-pig a very minute not fatal dose of cholera bacilli, one which the animal is able by means of its alexins to overcome, and if we then

gradually increase the dose injected, it will be possible after a time to inject at one dose an amount of cholera bacilli that represents many times an ordinary fatal dose. If from this animal we now withdraw serum and inject it into another animal, we find that this serum, even in such small amounts as the fractional part of a centigram or even of a milligram, is able to protect the second animal against living cholera bacilli. Under the influence of these small amounts of serum of the treated animal, the organism of the untreated animal is able to dissolve large amounts of cholera bacilli, amounts which would otherwise be invariably fatal. This process, as R. Pfeiffer showed, is a specific one, i.e., the serum of the guinea-pig treated with cholera bacilli transmits an increased solvent power only for cholera bacilli, but not for any other species of bacteria. The active substance of such a bacteriolytic immune serum Pfeiffer called a *specific bactericide*. If we allow some of this specific cholera immune serum to remain for some time outside of the body, e.g. in a bottle, and then test it for solvent properties against cholera bacilli, not in a living body but in a test-tube, we shall find that its power is almost nil. If we add to this serum in the test-tube some fresh peritoneal exudate or some other body fluid, such as serum of a normal, untreated guinea-pig, as Metchnikoff first did, we find that this serum has now acquired the power to rapidly dissolve cholera bacilli even in a test-tube.

Bordet, in 1896, showed that in order for the specific immune serum to dissolve bacilli in a test-tube, it is unnecessary to add fresh normal serum or peritoneal fluid; but that immune serum freshly drawn from the vein is able even under these circumstances to dissolve the bacilli.

Analogy of the Bacteriolytic and Hæmolytic Processes—Active and Inactive Bacteriolytic Sera.—Now that the main points in cholera immunity are clear to us, the close analogy between this and the subject of hæmolysis is apparent. Just as, when immunizing an organism against cholera bacilli the organism responds with an increased solvent power for those bacteria, so does the organism respond when it is treated, i.e. immunized, with red cells of another species, by increasing the solvent power of its serum for those particular cells. Furthermore, just as the hæmolytic process was seen to depend on the combined action of two substances, one developed in the hæmolytic serum, the other already present in normal serum, so also in the bactericidal process just studied there are two factors. It is easy to understand, therefore, what formerly was not at all clear, why a specific bactericidal serum against cholera, typhoid, or other infectious disease should not act in a test-tube unless there had first been added some normal serum (according to Metchnikoff), or there had been employed a perfectly fresh serum (according to Bordet): simply because in either of these

ways the alexin necessary to co-operate with the substance sensibilatrice is introduced. This alexin no longer exists in the immune serum, if this be not perfectly fresh, for we have seen that it decomposes either on warming or spontaneously on standing. A bactericidal serum, therefore, that has stood for some time is incapable of dissolving bacteria. It is possible, however, to make an old inactive serum again capable of dissolving bacteria in vitro by adding a little fresh alexin, according to the suggestion of Metchnikoff. In other words, it is thus reactivated. Another obscure point was cleared up by these studies: why a specific bactericidal serum which is inactive in vitro should be intensely active in the living body. This is because in the living body the serum finds the alexin necessary for its working, which is not the case in the test-tube unless fresh normal serum be added. We see from all this that even the first experiments in hæmolysis have served to clear up a number of practical points in an important branch of bacteriology.

Ehrlich and Morgenroth on the Nature of Hæmolysis.—In continuing the study of hæmolysines we must note particularly the researches of Ehrlich and Morgenroth. These authors asked themselves the following questions: (1) What relation does the hæmolytic serum or its two active components bear to the cell to be dissolved? (2) On what does the specificity of this hæmolytic process de-

pend? Ehrlich was led to these researches particularly by his so-called Side-chain Theory, which we shall examine in a moment.

He made his experiments with a hæmolytic serum that had been derived from a goat treated with the red cells of a sheep. This serum, therefore, was hæmolytic specifically for sheep blood-cells; i.e., it had increased solvent properties exclusively for sheep blood-cells.

Basing his reasoning on his side-chain theory, Ehrlich argued as follows: "If the hæmolysin is able to exert a specific solvent action on sheep blood-cells, then either of its two factors, the substance sensibilatrice of Bordet or the alexin of normal serum, must possess a specific affinity for these red cells. It must be possible to show this experimentally." Such in fact is the case, and the experiments devised by him are as follows:

Experiment 1.—Ehrlich and Morgenroth, as already said, experimented with a serum that was specifically hæmolytic for sheep blood-cells. They made this inactive by heating to 55° C., so that then it contained only the substance sensibilatrice. Next they added a sufficient quantity of sheep red cells, and after a time centrifuged the mixture. They were now able to show that the red cells had combined with all the substance sensibilatrice, and that the supernatant clear liquid was free from the same. In order to prove that such was the case they proceeded thus: To some of the clear centri-

fuged fluid they added more sheep red cells; and, in order to reactivate the serum, a sufficient amount of alexin in the form of normal serum was also added. The red cells, however, did not dissolve — there was no substance sensibilatrice. The next point to prove was that this substance had actually combined with the red cells. The red cells which had been separated by the centrifuge were mixed with a little normal salt solution after freeing them as much as possible from fluid. Then a little alexin in the form of normal serum was added. After remaining thus for two hours at 37° C. these cells had all dissolved.

In this experiment, therefore, the red cells had combined with all the substance sensibilatrice, entirely freeing the serum of the same. That the action was a chemical one and not a mere absorption was shown by the fact that red blood-cells of other animals, rabbits or goats for example, exerted no combining power at all when used instead of the sheep cells in the above experiment. The union of these cells, moreover, is such a firm one that repeated washing of the cells with normal salt solution does not break it up.

The second important question solved by these authors was this: What relation does the alexin bear to the red cells? They studied this by means of a series of experiments similar to the preceding.

Experiment 2. — Sheep blood was mixed with normal, i.e. *not* hæmolytic, goat serum. After a

time the mixture was centrifuged and the two portions tested with substance sensibilatrice to determine the presence of alexin. It was found that in this case the red cells acted quite differently. In direct contrast to their behavior toward the substance sensibilatrice in the first experiment, they now did not combine with even the smallest portion of alexin, and remained absolutely unchanged.

Experiment 3.—The third series of experiments was undertaken to show what relations existed between the blood-cells on the one hand and the substance sensibilatrice and the alexin on the other, when both were present at the same time, and not, as in the other experiments, when they were present separately. This investigation was complicated by the fact that the specific immune serum very rapidly dissolves the red cells for which it is specific, and that any prolonged contact between the cells and the serum, in order to effect binding of the substance sensibilatrice, is out of the question. Ehrlich and Morgenroth found that at 0° C. no solution of the red cells by the hæmolytic serum takes place. They therefore mixed some of their specific hæmolytic serum with sheep blood-cells, and kept this mixture at 0°–3° C. for several hours. No solution took place. They now centrifuged and tested both the sedimented red cells and the clear supernatant serum. It was found that at the temperature 0°–3° C. the red cells had combined with all of the substance sen-

sibilatrice, but had left the alexin practically untouched.

It still remained to show the relation of these two substances to the red cells at higher temperatures. At 37°–40° C., as already mentioned, hæmolysis occurs rapidly, beginning usually within fifteen minutes. It was possible, therefore, to leave the cells and serum in contact for not over ten minutes. Then the mixture was centrifuged as before. The sedimented blood-cells mixed with normal salt solution showed hæmolysis of a moderate degree. The solution became complete when a little normal serum was added. The supernatent clear fluid separated by the centrifuge did not dissolve sheep red cells. On the addition, however, of substance sensibilatrice it dissolved them completely.

So far as concerns the technique of the experiments, I should like to observe that the addition of red cells in this as well as in all the following experiments was always in the form of a 5% mixture or suspension in .85%, i.e. isotonic, salt solution.

The significance of the last of the above-cited experiments is at once apparent. It is that the substance sensibilatrice possesses one combining group with an intense affinity (active even at 0° C.) for the red cell, and a second group possessing a weaker affinity (one requiring a higher temperature) for the alexin.

Nomenclature.—In place of the name substance sensibilatrice Ehrlich first introduced the term *immune body*, later on he called it the *amboceptor*. In the following pages we shall use the term *immune body*, as this had already been used by R. Pfeiffer to designate the same substance in bactericidal serum. Other names proposed for this substance have been *substance fixatrice* by Metchnikoff, *copula*, *desmon*, *preparator* by Müller. Instead of the name alexin, Ehrlich now uses the term *complement* in order to express the idea that this body completes the action of the immune body.

In contrast to the specific affinity which the red cells possess for the immune body, these cells possess no affinity whatever for the alexin, as has been shown by the second of Ehrlich's experiments. The alexin, therefore, possesses no combining group which can attach itself directly to the red blood-cell. It acts on these cells only through an intermediary, the immune body, which therefore must possess two binding groups, one which attaches to the red blood-cell and the other to the alexin of normal serum. As already stated, the group which attaches to the red blood-cell possesses a much stronger affinity than that which combines with the alexin. This follows from the last two experiments of Ehrlich before cited, in which he showed that at the lower temperature and with both substances present with the blood-cells only the immune body combined with the cells, while

the alexin remained uncombined. At the higher temperature the alexin also exerted its affinity, for then the red cells combined with all the immune body and with part of the alexin. We saw that after a time the red cells partially dissolved, but that complete solution occurred only after some fresh alexin had been added. This showed that although the red cells had combined with all the immune body necessary for their solution, they had been unable to bind all the alexin necessary. We may say, therefore, that that group of the immune body which combines with the red cell has a stronger affinity than that which combines with the alexin.

Rôle of the Immune Body.—According to Ehrlich, then, the rôle of the immune body consists in this, that it attaches itself to the red cell on the one hand and to the complement on the other, and in this way brings the digestive powers of the latter to bear upon the cell, the complement possessing no affinity for the red cell. Immune body and complement have no very great affinity for each other. At 0° C. they may exist in serum side by side, and they combine only at higher temperatures.

The amount of immune body which combines with the red cells may vary greatly, as the experiments of Bordet and of Ehrlich clearly show. Some red cells combine with only just enough immune body to effect their solution. Others are able to so saturate themselves with immune body that they

may have a hundred times the amount necessary for their solution.

On What the Specificity Depends.—From the preceding it follows that the specific action of the hæmolytic sera, and, I may at once add, of the bactericidal sera also, is due exclusively to the immune body. This possesses a combining group which is specific for the cells with which the animal was treated; e.g., the combining group of an immune body produced by treatment with rabbit blood will fit only to a certain group in the blood-cells of rabbits; an immune body produced by treatment with chicken blood will fit only to parts of the red cells of chickens; one produced by treating an animal with cholera bacilli will fit only to this species of bacteria and combine only with the members of it. Keeping to the well-known simile of Emil Fischer, the relation is like that between lock and key, each lock being fitted only by a particular key.

To repeat—for the point is of the greatest importance—the rôle of the immune body consists in tying the complements of normal serum, which have no affinity for the red cells or for the bacteria, indirectly to these cells so that their solution and digestion may be effected by the complements. In other words, the immune body serves to concentrate on the corpuscular element to be dissolved all the widely distributed complement found in normal serum.

The relation existing between complement, immune body (i.e., amboceptor) and erythrocyte is shown in the accompanying figure reproduced after Levaditi, a pupil of Ehrlich.

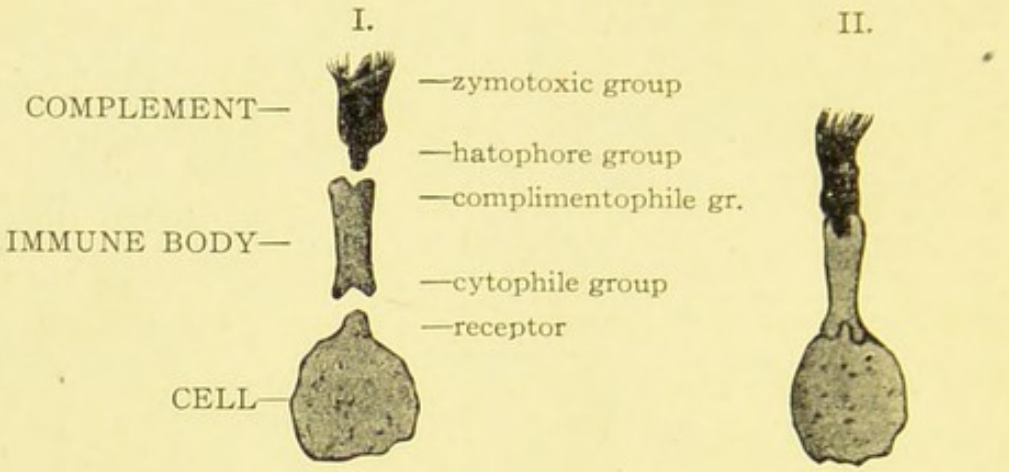

FIG. 1.

Difference between a Specific Serum and a Normal One.—*The difference, then, between a specific hæmolytic or a specific bactericidal serum and a normal one consists in this—that the specific serum contains an immune body which is specific for a certain cellular element and by means of which the complement present in all normal serum can be concentrated on this cellular element to cause its solution.* We shall return to this subject later.

Diverging Views of Ehrlich and Bordet.—Now if we recall the first experiments of Bordet and his conclusions respecting the manner in which the factors concerned acted, we shall at once see how Ehrlich and Bordet differ. Bordet assumes that the substance sensibilatrice (the immune body) acts as a kind of mordant on the red cells or bac-

teria, sensitizing these to the action of the alexin (complement). According to Ehrlich, however, the process is not analogous to a staining process, but follows definite laws of chemical combination, there being, in fact, no affinity whatever between the complement and the blood-cells or bacteria. Furthermore, according to this authority, the complement always acts only through the mediation of the immune body, which possesses two combining groups; one, the cytophile group, combining with the cell and another, the complementophile group, combining with the complement. Both observers have devised a series of ingenious experiments to support their views. But as these can interest only the specialist, I shall omit their discussion here. For such details the original articles may be consulted.

Ehrlich's Side-chain Theory.—The results of the experiments made by Ehrlich to determine the relation of immune body, complement, and cell to one another served as a further support for his so-called Side-chain Theory. This he had formulated several years before in order to explain the production of antitoxin and other specific anti-bodies. Because of the great importance of this theory, which laid the foundation for much of this work and which to-day occupies an important place in our literature, and also because it will serve to make the following more readily comprehensible, it will be well to devote a little time to its study.

Originally the side-chain theory was applied by Ehrlich only to the production of the specific *antitoxins*, i.e., substances in the blood which act not only on the living bacteria but also and especially on their dissolved toxins. Later on he extended it so as to apply also to the formation of specific bactericidal and hæmolytic substances in the serum of animals treated with living bacteria or with animal cells.

Toxins, their Toxophore and Haptophore Groups—Toxoids—Special Function of the Side-chains.—The basis of the theory is the fact that poison and counter-poison, toxin and antitoxin, combine directly in any given quantity. This combination always occurs in definite proportions following the laws of chemical combination; and, still following those laws, is slower at lower temperatures than at higher, stronger in concentrated than in dilute form. Ehrlich could further show that each poison for which by the process of immunizing one can develop a counter-poison possesses two groups which are concerned in the combination with the counter-poison or antitoxin. One of these, the so-called *haptophore group*, is the combining group proper; the other, the *toxophore group*, is the carrier of the poison. A poison molecule, therefore, might lose the one, the toxophore, and still be capable by means of its haptophore group of combining with antitoxin. Such a modified poison, which because of the loss of the toxophore group

can hardly be called a poison, but which still possesses the power to combine with antitoxin, Ehrlich calls a *toxoid.* Toxoids may be produced spontaneously in old poisons through decomposition of the poison molecule, or they may be produced artificially by causing certain destructive agents such as heat or chemicals to act on bacterial poisons. The toxophore group is a very delicate one and much more readily decomposed than the combining (haptophore) group. Ehrlich reasoned that in order for a poison to be toxic to an organism, i.e., in order that the toxophore group be able to act destructively on a cell, it is necessary for the haptophore group of the poison to combine with the cell. "In every living cell," Ehrlich says, "there must exist an active central body [Leistungs Kern] and a number of other chemical groups or side-chains. These groups have the greatest variety of function, but especially those of nutrition and assimilation."

The side-chains, then, according to this author, are able to combine with the greatest variety of foreign substances and convert these into nourishment suitable to the requirements of the active central body. They are comparable to the pseudopodia of the lower animals, which engulf food particles and assimilate the same for the immediate use of the organism. In order that any substance may combine with these side-chains it is necessary that certain very definite relations exist between

the combining group of the substance and that of the side-chain. To repeat the simile we used above, the relation must be like that of lock and key, i.e., the two groups must fit accurately. Hence not every substance will fit all the side-chains of an organism. It will combine only with those for which it possesses a fitting group.

Receptors—Weigert's Overproduction Theory.—This doctrine of the chemistry of the organism's metabolism Ehrlich applied to the action of toxins and antitoxins. "The toxin," he said, "can act only when its haptophore group happens to fit to one of the side-chains," or *receptors*, as he now prefers to call them. As a result of this combination, the toxophore group is able to act on the cell and injure it. If we take as an example tetanus, in which all the symptoms are due to the central nervous system, the side-chain theory assumes that the haptophore group of the tetanus poison fits exactly and is combined with the side-chains or receptors of the central nervous system. Other experiments, which we will not reproduce here, have shown us unquestionably that the action of the antitoxins depends on the fact that this combines with the haptophore group of the poison and so satisfies the latter's affinity. Ehrlich, therefore, concluded that the antitoxin is nothing else than the side-chains or receptors which are given off by the cells and thrust into the circulation. The way in which these side-chains or receptors are thrust

off as a result of the immunizing process, Ehrlich explains by means of *Weigert's Overproduction Theory*. Weigert, by his studies in new tissue formation, had shown that whenever there is a deficiency in the organism, the latter when replacing this is incapable of remaining within bounds, always producing more than is required. Ehrlich points out that owing to the combination of the toxin with the side-chain of a cell, these side-chains are practically lost to the cell; that the latter now produces new side-chains to replace this loss, but that this production always goes so far as to make a surplus of side-chains; that these side-chains are thrown off by the cell as unnecessary ballast and then circulate in the blood as antitoxin. The same substances, therefore, which when part of the cell combine with the haptophore group of the toxin, enabling that to act on the cell, when circulating free in the blood combine with and satisfy this haptophore group of the toxin and prevent the poison from combining with and damaging the cells of the organism.

Using Ehrlich's comparison, this may be likened to an iron bar within a building which owing to its attraction causes the lightning to strike the building. The same iron bar, however, acts as a protection for the building if it be placed outside of the same. Let us bear this comparison in mind as we glance at the facts in tetanus. This is the easiest disease in which to study the relation of the

various substances and processes one to another, as all of the symptoms are referable to one organ, the central nervous system. In this disease the antitoxin against the tetanus poison must consist of side-chains or receptors thrust into the circulation by the cells of the central nervous system.

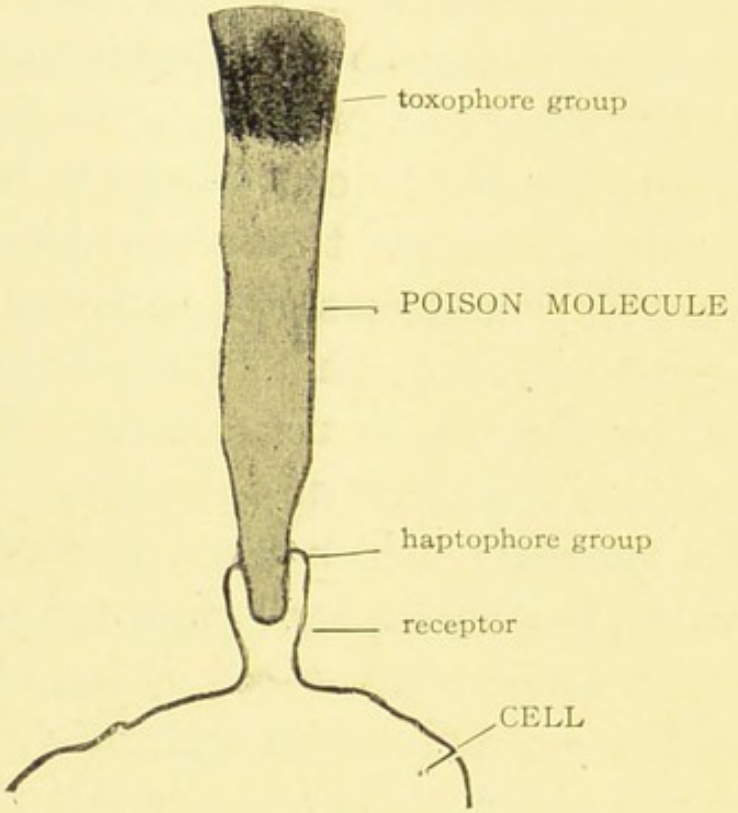

FIG. 2.

The action of the antitoxin then would be this, that these free receptors combine with the haptophore group of the tetanus poison as soon as this reaches the circulation, and thus prevent this poison from combining with and injuring the cells of the central nervous system. This I was able to prove experimentally by showing (1) that the central nervous system of most animals susceptible to tetanus is able to combine with the tetanus poison in vitro;

and (2) that such a mixture of tetanus poison and normal central nervous system is innocuous to animals; because certain substances present in the central nervous system combine with and thus satisfy the affinity of the haptophore group of the poison. This of course prevents the latter from combining with any of the cells of the organism.

Organs other than the central nervous system do not possess this property of combining with tetanus poison, just as the central nervous system is, on the contrary, incapable of combining with diphtheria poison which clinically does not show any pronounced affinity for the central nervous system. This combination, then, of central nervous system and tetanus poison is a specific one in conformity with the side-chain theory. Furthermore it has long been known that it is possible to immunize animals (and so produce antitoxins) with toxoids, i.e., with poisons that possess only a haptophore group. This supports the view of Ehrlich that the essential feature of antitoxin formation is the combination of the haptophore group of the poison with certain definite parts—the receptors—of the cell. Conversely, poisons or cells the affinity of whose haptophore group has previously been satisfied are unable to excite the production of any antitoxin—excite any immunity. That is because they are no longer able to combine with receptors of the cells. v. Dungern, for example, showed that blood-cells which had previously been saturated

with their immune body—in other words, whose haptophore group had been satisfied—were unable to excite the production of any hæmolysin when injected into animals.

All of the specific relations which we have seen exist between toxin and antitoxin, Ehrlich and Morgenroth in their experiments above noted found to exist also between immune body and the specific blood-cell. The immune body must therefore possess a haptophore group which fits exactly to certain receptors or side-chains of the red cells, just as the anti-body according to the side-chain theory possesses a group that fits exactly into the specific combining group—i.e., haptophore group—of the toxin or toxoid used for exciting the immunity.

If, for example, we produce a hæmolytic serum specific for red cells of a rabbit by injecting an animal with these cells, the haptophore groups of this serum, i.e., the free side-chains thrust off, must possess specific combining relations with the red cells of rabbits. That such is the case in the hæmolytic immune serum we saw from the experiments of Ehrlich and Morgenroth.

The Theory Applied to the Production of Other Anti-bodies.—In consequence of all this, Ehrlich widened the application of his side-chain theory so as to include not only the production of antitoxin but also the production of bactericidal, hæmolytic, and other immune bodies. He expressed this

somewhat as follows: *If any substance, be it toxin, ferment, constituent of a bacterial or animal cell, or of animal fluid, possess the power by means of a fitting haptophore group to combine with side-chains (receptors) of the living organism, the possibility for the overproduction and throwing off of these receptors is given, i.e., the possibility to produce a corresponding anti-body.*

Specific anti-bodies in the serum as a result of immunizing processes can only be produced, therefore, by substances which possess a haptophore group and which, in consequence, are able to form a firm union with a definite part of the living organism, the receptor. This is not the case with alkaloids, e.g., morphin, strychnin, etc., which according to Ehrlich enter into a loose union, a kind of solid solution with the cells. It is for this reason that we are unable to produce any anti-bodies in the blood serum against these poisons. Ehrlich says further that all of the substances taking part in the production of immunity, including of course complement and immune body, have certain definite affinities for each other, and in order to act they must fit stereochemically to each other.

As we have already seen, we are able by means of the injection of a variety of substances or cells to produce a similar variety of immune bodies in the serum. Thus we can immunize a rabbit so that its serum will possess specific hæmolytic bodies against the red cells of guinea-pigs, goats,

chickens and oxen and specific bactericidal bodies against cholera and typhoid bacilli, etc., and as we shall see, still other groups of anti-bodies.

Multiplicity of Complements.—Under these circumstances an important question presents itself: Is there in normal serum one single complement which completes the action of all these various immune bodies, one, for example, which in the above illustration will fit all the hæmolytic immune bodies as well as all the bactericidal ones, or are there a great many different complements? Ehrlich, as a result of his experimental work with Morgenroth, claims that the latter is the case; namely, that it takes a different complement to fit the immune body specifically hæmolytic for guinea-pig blood than it does to fit that specific for chicken blood.

Bordet, on the other hand, assuming that the immune body plays the rôle of mordant, believes, as does also Buchner, that there is but one single complement in the serum. According to him, this complement is able to dissolve blood-cells as well as bacteria after these have been sensitized by their specific immune body. Each of these authors supports his claims by means of ingenious experiments, for the details of which, however, we must refer to the original articles, as they require the knowledge of a specialist for their comprehension. As a result of my own work I accept Ehrlich's view, that of the multiplicity of the com-

plements. One thing at least I regard as proven, that the complement which fits to the bactericidal immune body is different from that for the hæmolytic immune body. According to his most recent work this view is also shared by Metchnikoff. Later on we shall see that this is not merely an academic question, but one of great practical importance.

Normal Serum, its Hæmolytic and Bacteriolytic Action.—Inquiring now into the essential difference between a specific hæmolytic or bactericidal serum and a normal one, we must first of all study the behavior of normal serum toward foreign red cells and bacteria. It has long been known to physiologists that fresh normal serum of many animals has the power to dissolve blood-cells of another species. This was studied especially by Landois. One-half to one c.c. of normal goat serum, for example, is able to dissolve 5 c.c. of a 5% mixture (in normal salt solution) of rabbit or guinea-pig red cells. In the same way these red cells are dissolved by the sera of oxen, of dogs, etc. This *normal globulicidal* property of the serum corresponds to another which fresh normal serum was found to possess, namely, the property to dissolve appreciable quantities of many species of bacteria. This analogy was pointed out by Fodor, Nutall, Nissen, and especially by Buchner. We call this the *bactericidal* property of fresh normal serum. Buchner, as we have already seen, had studied

this carefully and ascribed the action to a substance found in all normal serum, which he called *alexin*. According to his experiments, this is a very unstable substance, decomposing spontaneously on standing or on heating for a few minutes to 55° C., or readily on the action of chemicals. According to this author all the globulicidal and bactericidal functions of normal serum are performed by this one substance, the alexin.

Active and Inactive Normal Serum.—Ehrlich and Morgenroth now took up the study of the hæmolytic action of normal serum. They sought particularly to discover whether in normal serum the hæmolytic property depended on the action of a single substance, the complement (Buchner's alexin), or whether here as in the specific hæmolytic serum it depended on the combined action of two substances. For this purpose they used guinea-pig blood, which is dissolved by normal dog serum. If this serum was heated to 55° C., it lost its hæmolytic power. It was necessary now to show that in this inactive dog serum there remained a second substance which could be reactivated after the manner of reactivating an old specific hæmolytic serum. This had its difficulties, for they could not add normal dog serum. This, as we saw, is already hæmolytic for guinea-pig blood. "Possibly," said they, "there exists a complement of another animal which will fit the hypothetical second substance of this dog serum."

This proved to be the case, the complement of guinea-pig blood fulfilling the requirements. If they added to the inactive normal dog serum about 2 c.c. normal guinea-pig serum, the hæmolytic property was restored and the guinea-pig red cells dissolved completely. This can only be explained by assuming that in guinea-pig blood there exists a complement which happens to fit the haptophore group of the second substance, or inter-body, of the normal dog serum. This combination of guinea-pig blood, inactive normal dog serum, and a reactivating normal guinea-pig serum is the best possible one to demonstrate the existence in normal dog serum of an inter-body; for the guinea-pig serum should be the best possible preservative for the guinea-pig red cells. The hæmolysis following the addition of this serum shows positively the existence of a substance in the dog serum which has acted with something in the guinea-pig serum.*

Inter-body and Complement.—We see, then, that the hæmolytic action of normal sera depends, just

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* Of such combinations, i.e., combinations in which a complement derived from the same animal from which the red cells are derived fits to the inter-body of other species of animals, causing the solution of red cells of the latter, Ehrlich and Morgenroth found still other examples. For instance, guinea-pig blood, inactive calf serum, guinea-pig serum; goat blood, inactive rabbit blood, goat serum; sheep blood, inactive rabbit blood, sheep serum; guinea-pig blood, inactive sheep serum, guinea-pig serum.

as that of the specific hæmolytic sera, on the combined action of two bodies: one, the *inter-body*, which corresponds to the immune body of the specific sera, and a second or *complement*. In speaking of the constituents of *normal* serum, Ehrlich and Morgenroth prefer to use this term *inter-body* to distinguish it from the *immune bodies* of *specific* hæmolytic sera.

Action Not Entirely Specific.—It has also been found that there frequently exist normal sera which are hæmolytic not only for one species of red cell but for several. We saw, for instance, that normal goat serum dissolved the red cells of guinea-pigs and rabbits. The question now arises, Is this property of normal goat serum due to two inter-bodies existing in the serum side by side, one fitting the red cells of the guinea-pig, the other those of the rabbit? Ehrlich and Morgenroth answered this in the affirmative, for in the following experiment they succeeded in having each of the two inter-bodies combine with its respective cell. To some inactive normal goat serum they added rabbit blood and centrifuged the mixture. To the separated clear fluid they again added some rabbit red cells as well as normal horse serum to reactivate the mixture. Horse serum is not hæmolytic for rabbit red cells. The mixture remained unchanged, no hæmolysis taking place. If, however, they added some of this normal horse serum to the centrifuged red cells, the latter imme-

diately dissolved. Now, to the clear centrifuged fluid, which as we have seen would not dissolve rabbit red cells, they added guinea-pig red cells and again some normal horse serum to reactivate the mixture. The guinea-pig red cells all dissolved. This proved conclusively that in the normal goat serum there had existed two specific inter-bodies. One, for rabbit red cells, had been tied by these cells and carried down with them in centrifuging; the other, specific for guinea-pig red cells, had remained behind.

Multiplicity of the Active Substances.—These investigators were able to prove still more in regard to the multiplicity of the substances in normal serum which are concerned in hæmolysis. They showed that beside the two inter-bodies just mentioned there existed in goat serum two specific complements, one for each inter-body, and they were able by means of Pukall filters to separate these two. In this filtration the complement fitting the inter-body for rabbit blood remained behind for the greater part, while that fitting the inter-body for guinea-pig blood mostly passed through.

Whereas then, according to Buchner, only one substance, the alexin, is concerned in the hæmolytic action of this normal goat serum, these experiments of Ehrlich and Morgenroth show us four substances, viz., two inter-bodies and two complements. This at once makes clear the opposing

views of these authorities. But the number of active substances in normal serum is still greater, for in the experiments of the last-named authors it oftens happens that a specific inter-body shows itself to be made up of several inter-bodies, all, to be sure, fitting the same specific red cell, but differing from each other by their behavior toward different complements. Ehrlich, therefore, regards the substances concerned in hæmolysis which occur in normal serum to be of great number and variety. Buchner and Bordet, on the other hand, assume that only one substance is concerned.

The facts which we have thus far developed in regard to the hæmolysins of normal serum apply equally well to its *hæmagglutinins*. As we mentioned in the beginning of this article, Bordet showed that not only was the hæmolytic action of a specific serum increased for certain red cells, but its agglutinating power was increased for the same cell. According to this, then, as a result of the immunizing process there are formed not only hæmolysins but also hæmagglutinins.

Hæmagglutinins of Normal Serum.—Analogous to the hæmolytic action of *normal* serum on the red cells of certain other species, we find that *normal* serum is able to agglutinate the red cells of many other species and bacteria. For example, normal goat serum agglutinates the red cells of man, pigeon, and rabbit; normal rabbit serum

agglutinates typhoid and cholera bacilli. Bordet could show that the bacterial agglutinins are governed by the same laws of combination that Ehrlich and Morgenroth showed governed the interbodies of normal sera. Thus if to a normal serum which agglutinates both typhoid and cholera bacilli some typhoid bacilli be added and the mixture centrifuged, the clear fluid will no longer be able to agglutinate typhoid bacilli. It will still, however, readily agglutinate those of cholera. The typhoid agglutinin has in this way been tied to the typhoid bacilli first added, and with them it has been carried down in the centrifuged sediment. If the experiment be reversed, so that cholera bacilli are first added and then the mixture centrifuged, the clear fluid will contain the typhoid agglutinin, but not that of cholera. These points, brought out by Bordet for bacterial agglutinins, I have had Malkoff study regarding the hæmagglutinins of normal serum, and this investigator has found the same facts to apply to these substances. To normal goat serum, which agglutinates the red cells of man, rabbits, and pigeons, he added human red cells and then centrifuged the mixture. In this way the agglutinin for these cells was abstracted from the serum, which then was capable of agglutinating the red cells of rabbits and pigeons, but incapable of agglutinating human red cells. When he used pigeon blood instead of the human blood, the agglutinin for pigeon blood was abstracted,

leaving the agglutinins for the red cells of man and rabbits, etc.

These experiments of Bordet and Malkoff on the selective combination of the cells show that with the agglutinins as with the lysins (solvent substances) it is a question of numerous substances and not of a single one. When, for example, normal goat serum is able simultaneously to agglutinate several, say three, species of blood-cells, this action is not due to a single agglutinin which affects all three species, but is the work of three distinct substances, each specific for a certain red cell.

Nature of the Agglutinins.—The agglutinins are fairly resistant substances which withstand heating to 60° C., and lose their power only on heating to 65° C. It is possible, therefore, to make a serum hæmolytically inactive by heating to 55° C., and still preserve its agglutinating power. Corresponding to the specific combining power of these agglutinins, they possess a haptophore group which effects the combination, and a second group, easily decomposed by acids, which effects the clumping. In the bacterium as well as in the blood-cell there exists a substance not yet closely studied, called the *agglutinable substance.* This also has two groups, a haptophore, which combines with the haptophore group of the agglutinin; and a second, more delicate group, which is acted on by the functional group of the agglutinin.

These points have only very recently been brought out by Eisenberg and Kraus, and by the author.

This agglutination then is a chemical combination between the agglutinating substance of the serum and the agglutinable substance of the red cell or bacterium and it proceeds in definite chemical proportions. The chemical and physical aspects of the process itself are still the subject of various theories. These I shall not discuss here, as they lack experimental support. The relation of the agglutinins to the precipitins is still obscure, so that I shall not venture an opinion on the subject.

Agglutinoids.—Agglutinins which have lost their agglutinophore group through the action of acids, etc., but which still possess their haptophore group, are called *agglutinoids*, just as toxins which have lost their toxophore group are called toxoids. Such agglutinoids, then, may still combine with the blood-cells or bacteria without, however, being able to produce any clumping or agglutination.

Purpose of Agglutination. — It is not yet clear what the purpose of the agglutinating function is. Gruber, the first to thoroughly study and appreciate the bacterial agglutinins, assumes that the process injures the affected cell, preparing it for solution and destruction. After numerous experiments I have not been able to convince myself of any damaging influence of the agglutinins on the affected cell, be this blood-cell or bacterium, and

the observations of other authors confirm this opinion. Agglutinated bacteria are capable of living and of reproduction, and agglutinated red blood-cells are no more fragile or easier to destroy than normal, not agglutinated cells. Neither can anything be discovered microscopically which would indicate any injury to their structure.

One thing is certain: that the agglutinins are in no way related to the lysins found in serum, and so, of course, are not identical with these. The simultaneous occurrence in a serum of immune bodies, inter-bodies, complements, and agglutinins is an entirely independent phenomenon which is no way regular. There are sera which dissolve certain cells without agglutinating them, and others which agglutinate cells without dissolving them.

Difference between a Normal and a Specific Immune Serum. — Practical Application. — Returning now to the question of the difference between a specific immune serum and a normal one, we find this to be as follows: Normal serum contains a great variety of inter-bodies, in very small amounts, and a considerable amount of complements. In immune serum, on the other hand, the amount of a specific inter-body, the one which fits the haptophore group of a certain cell, is enormously increased. This specifically increased inter-body, it will be remembered, is called the immune body. The complement, as shown by v. Dungern, Bordet, Ehrlich and Morgenroth, and myself, is in no way increased by the im-

munizing process. The increase affects solely the immune body. It is therefore possible to have a serum which contains more immune body than complement to satisfy it, and if we withdraw such a serum from an animal we shall find that it contains some free immune body. This serum can only then exert its full power when the full amount of complement is present, i.e., when some normal serum is added. If we treat a rabbit with the red cells of an ox, as v. Dungern did, we shall obtain a serum which is hæmolytic for ox blood. 0.05 c.c. of this freshly drawn serum suffices to dissolve 5.0 c.c. of a 5% mixture of ox blood. If now we add to this hæmolytic serum a little normal rabbit serum, we shall find that only one-tenth of the amount of serum is required; i.e., only 0.005 c.c. to dissolve the same quantity of ox blood. This means that through the addition of the rabbit serum, which, of course, is not hæmolytic for ox blood, a sufficient amount of complement was added to enable all the immune body of the specific serum to act. This specifically increased power of the immune serum to act on certain definite cells depends on the fact that the immune body resulting from the immunizing process concentrates the action of the complement scattered through the serum, on cells for which it has definite affinities. If 2 c.c. of normal guinea-pig serum are able to dissolve, we will say, 5 c.c. of a 5% defibrinated rabbit-blood mixture, and if we find that after the immunizing process

0.05 c.c. of the guinea-pig serum suffice to dissolve the same amount of rabbit blood, we conclude that through this process the inter-body, i.e. the immune body, has been increased forty times. We know that the complement has not been increased, but this is now able to act by means of forty times increased combining facilities. This increase, however, is exclusively for rabbit blood-cells. In a bactericidal immune serum this specific increase is sometimes as much as 100,000 times that of normal serum. The practical idea to be gained from this for the therapy of infectious diseases is this: that with the injection of an immune serum we supply only one of the necessary constituents to kill and dissolve the bacteria, and that is the immune body. We do not, however, supply the second, i.e. the complement, for this we have seen is not increased by the immunizing process. As matters stand, then, the use of a specified immune serum for therapeutic purposes assumes that the complement which fits exactly to the immune body and which is essential for the latter's action will be found in the organism to be treated. Because in certain infectious diseases the required complement is present in too small amounts in the organism, I have suggested that the curative power of many bactericidal sera might be increased by the simultaneous injection of the sera of certain normal animals in order to gain in this way an increased amount of complement; but we shall soon see that this pro-

cedure, while of great value in animal experiments, presents certain difficulties.

All that has here been said regarding the specific increased hæmolytic power of sera applies equally to the specific increased agglutinating power following the injection of animals with certain cells. As a result of such injections, that agglutinin which stands in specific relation to the blood-cell injected is increased according to the laws of the side-chain theory, and such a serum therefore possesses an increased agglutinating power for these particular cells. With the agglutinins this increase in power is sometimes an enormous one. If, for example, a normal serum is just able to agglutinate a certain cell when diluted 1 to 10 with normal salt solution, it is possible by means of the immunizing process to obtain a serum which in dilutions of one to several thousands will still completely agglutinate the cells.

In such a sketch as this, I cannot dwell on the practical importance that this specific increased agglutinating power has in the serum diagnosis of certain infectious diseases, such as typhoid, etc.

Nature of the Immune Body—Partial Immune Bodies of Ehrlich.—Turning now to a closer study of the nature of the immune body, we again find a difference of opinion. Whereas Bordet, Metchnikoff, and Besredka assume each immune body to be a single definite substance, Ehrlich and Morgenroth as a result of their experiments hold to a plurality of bodies. These authors say that each immune

body is built up of a number of *partial-immune bodies*, a point to which we have already alluded. In support of this view they offer the following experiment. On immunizing a rabbit with ox blood, they obtained a serum hæmolytic not only for ox blood but also for goat blood; on immunizing a rabbit with goat blood they obtained a serum hæmolytic for goat blood and ox blood.*

According to Ehrlich's theory, then, the red cells of the ox possess certain receptors which are identical with receptors possessed by the goat red cells. From this it follows that in a single red cell there are several or many groups each of which is able, when it finds a fitting receptor, to take hold of a single immune body. Ehrlich and Morgenroth, therefore, claim that the immune body of a hæmolytic serum is composed of the sum of the partial immune bodies which correspond to the individual receptors used to excite the immunity. It may be assumed, then, that not all of the combining groups of a cell, be this a blood-cell or a bacterium, will find fitting receptors in every animal organism, and that therefore not all the possible partial immune bodies will be equally developed. In one animal there may be receptors which are not present in another, and in this way there might be a different variety of partial immune bodies in the two

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* We have already called attention to these exceptions to the rule of specific action.

animals. This would lead to the possibility of the occurrence of immune bodies, for the same species of blood-cell or bacterium, differing from each other in the partial immune bodies composing them, according to the variety of animals used in preparing the serum.

Metchnikoff's Views—Practical Importance of the Point.—This view is directly opposed to that of Metchnikoff and Besredka, who believe that a certain immune body, e.g. one specific for ox blood, is always the same no matter from what animal it is derived. The point is not merely theoretical, but under certain circumstances of great practical importance. If we believe, as Ehrlich does, that the immune body differs according to the species of animal from which it is derived, i.e., that it is made up of different partial-immune bodies, then we must admit that we have better chances for finding fitting complements if we make use of immune bodies derived from a variety of animals. We would, for instance, be likely to achieve better results in treating a typhoid patient with a mixture of specific bactericidal typhoid sera derived from a variety of animals than if we used a serum derived only from a horse. For in such a mixture of immune bodies the variety of partial-immune bodies must be very great and the chances that the complements of the human body will find fitting immune bodies, and so lead to the destruction of the typhoid bacilli, are greatly increased. Ehrlich and his pupils have

actually proposed such a procedure in the use of bactericidal sera for therapeutic purposes.*

Support for Ehrlich's View.—Besides the above experiments we possess others which support the theory that the immune body is not a simple but a compound substance. v. Dungern had already shown that following the treatment of an animal with ciliated epithelium from the trachea of an ox, there were developed immune bodies which acted not only on the ciliated epithelium but also on the red cells of oxen. We must assume, therefore, that the ciliated epithelium and the red cells of the ox possess common receptors. Analogous to this is the action of the immune body resulting from the injection of spermatozoa, as was pointed out by Metchnikoff and Moxter.

We see, then, that the specific action of immune bodies is not so limited as to apply only to the cells used in the immunizing process, but extends to other cells which have receptors in common with these.†

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* Reasoning along similar lines, namely, that the human complement must fit the immune body of the therapeutic serum, Ehrlich has also proposed that these bactericidal sera be derived from animals very closely related to man, e.g., apes, etc.

† The same holds good for the agglutinins and the precipitins still to be studied. In these the action extends also to closely related cells and bacteria, or in the case of the precipitins to closely related albumins, as these possess a number of receptors which are common to them and to the cells or substances used for immunizing.

Coming now to the question as to what part of the cell it is which excites the production of the hæmolytic immune body, we find this, according to v. Dungern, to be the stroma of the red cells. If this be so, it must be the stroma which combines with the immune body. Nolf, however, claims that the cell contents are factors in the production of the immune body. So far as concerns the site in the organism where the substances used in immunizing find their receptors, this is not known for the hæmolytic immune body. For the bactericidal immune bodies of cholera and typhoid, however, we know from the researches of Pfeiffer, Marx, and myself that this is chiefly in the bone marrow as well as in the spleen and lymph bodies.

Anti-hæmolysins: their Nature—Anti-complement or Anti-immune Body?—A further step in the study of hæmolysins is one discovered independently by Ehrlich and Morgenroth on the one hand and Bordet on the other. These authors succeeded in producing an *anti-hæmolysin*. The procedure is closely related to the results gained by immunization against bacterial poisons. A specific hæmolysin, one, for example, specific for rabbit blood, derived by treating a guinea-pig with rabbit red cells, is highly toxic to rabbits. Injected into the animals intravenously in doses of 5 c.c. it kills the animals acutely, causing intra vitam a solution of the red cells. Such a hæmolytic serum, then, acts the same as a bacterial poison, and it is possible to

immunize against this just as well against a bacterial poison. For example, to keep to our illustration, rabbits are injected first with very small doses of this specific hæmolytic serum. The dose is gradually increased until it is found that the animal tolerates amounts that would be absolutely fatal to animals not so treated. If some of the serum of this animal is now abstracted and added to the specific hæmolytic serum, it is found that the power of the latter will be inhibited. This shows that an *anti-hæmolysin* has been formed. As we know that the action of the hæmolysin depends on the combined action of two substances, the immune body and the complement, the question arises to which of these two the anti-hæmolysin is related. Is it an anti-immune body or an anti-complement? A study of this question has shown that both these substances are present. In the serum of the rabbit treated with specific hæmolysin, both an anti-immune body and an anti-complement have been found. For the details of the experiments of Ehrlich and Morgenroth and of Besredka, which demonstrated this, I must refer to the original articles. The first-named authors were further able to show that the action of the anti-complement depended on a haptophore group which it possessed, enabling it to combine with the haptophore group of the complement, thus satisfying this and hindering its combination with the complementophile group of the immune body (see figure).

Anti-complement. — Since the complements are constituents of normal serum, it should be possible to produce anti-complements by injecting animals merely with normal serum; and they can, in fact, be so produced. If rabbits are treated by injecting them several times with normal guinea-pig serum, a serum may be obtained from these rabbits which contains anti-complements against the complements of normal guinea-pig serum. A serum

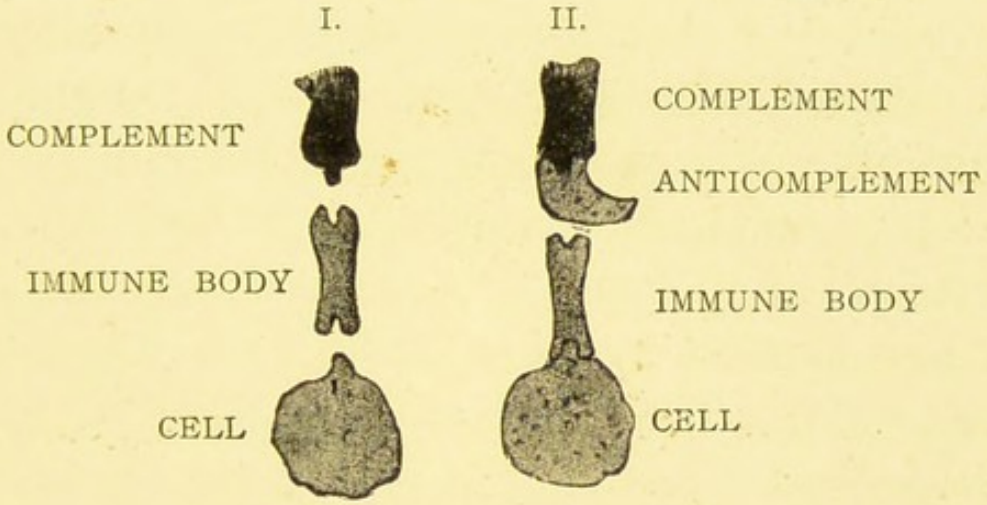

FIG. 3. (After Levaditi.)

obtained in this way of course contains only one of the anti-hæmolytic bodies, the anti-complement, and not the anti-immune body. This is because normal serum is too poor in immune body (inter-body) to excite the production of any anti-immune body.

If to a hæmolytic serum derived from guinea-pigs we add an anti-complement serum derived, as just stated, from rabbits and containing an anti-complement specific for guinea-pig complement, the

hæmolytic action of the former will be inhibited for the reason that the complement necessary for the hæmolysis to take place has been bound by the anti-complement. (See Fig. 3.) One must, however, observe the precaution to heat the anti-complement serum of the rabbit to 55° C. before so mixing it, in order to destroy the complement which it contains and which would otherwise reactivate the guinea-pig immune body.

From the foregoing we see that either anti-immune body alone or anti-complement alone is able to inhibit the hæmolytic action. Hæmolysis cannot take place when either of the two necessary factors is bound and prevented from acting.*

The anti-complements are specific bodies, i.e., an anti-complement combines only with its specific complement. Thus an anti-complement serum derived from rabbits by treatment with guinea-pig serum combines only with the complement of normal guinea-pig serum, not, however, with the complements of other animals. Exceptions to this are those cases in which the complement of the other species possess receptors identical with those of the first.

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* By treating animals with normal sera of certain other species it is possible to produce not only anti-complements but also specific anti-bodies against certain other constituents of normal serum. These are, for example, anti-agglutinins, which inhibit the action of the hæmagglutinins of normal serum, and anti-precipitins, which we shall discuss later.

In order that a normal serum of species A, injected into species B, produce anti-complements there, the side-chain theory demands that the complements of A find fitting receptors in species B. According to Ehrlich, however, normal serum contains many different complements and not merely a single one. Under the circumstances it is easily possible that only a few of the complements in the serum of A find fitting receptors in species B. We shall then obtain an anti-complement serum which inhibits the action of some but not of all the complements of species A. Thus it might inhibit the action of a complement fitting to a certain bactericidal immune body, and not of one contained in the same serum which fitted a certain hæmolytic immune body, etc.

Auto-anticomplements. — A question of great practical importance now arises. Is it possible under certain conditions for an organism to manufacture within itself anti-complements against its own complements, i.e., *auto-anticomplements?* The complements, owing to their ferment-like digestive power, must play an important rôle in the living organism; for this concerns itself not only with the destruction of bacteria, etc., an important factor in the natural immunity against diseases, but also, according to Ehrlich, Buchner, and the author, with the solution and digestion of all kinds of foreign albuminous bodies which enter the organism. Any inhibition of this important function would there-

fore be followed by severe disturbances, particularly, however, by a decreased resistance against infectious diseases. The author succeeded in demonstrating that animals injected with anti-complements to tie up their complements were much less resistant to certain infectious diseases.

The *spontaneous* development in an animal of auto-anticomplement, i.e., substances developed within the organism against its own complements, has not yet been demonstrated. Ehrlich and Morgenroth were able in a rabbit to excite the production of an auto-anticomplement by treating the animal in a certain way. Ordinarily, normal rabbit serum is slightly solvent for guinea-pig blood. If the rabbits are treated with goat serum, the rabbit serum loses this solvent power for guinea-pig red cells. Even if fresh normal rabbit serum is now added the hæmolysis does not take place, although we know that this fresh serum is hæmolytic. This shows that in the serum of the rabbit treated with goat blood an anti-complement has been formed which combines with the complement of normal rabbit blood, for it was able to inhibit the action of the complement of the normal freshly added rabbit serum. In the rabbit's body, then, as a result of this procedure, an anti-complement has been formed against the complement of its own serum, a true auto-anticomplement.

Now, according to the side-chain theory, there are no receptors in an organism for the complements

of the same organism. The formation of these auto-anticomplements, according to Ehrlich, can only be explained by assuming that in normal goat serum there are present complements which are almost identical with those of the rabbit serum, but which differ from them in that they find receptors in the rabbit serum whose haptophore group fits to their own.

Fluctuations in the Amount of the Active Substances in Serum.—As already said, we have thus far been unable to show that the complements of an organism are decreased through the action of spontaneously formed anti-complements. We have, however, come to know certain conditions under which there may be a decrease of certain complements in normal serum. Ehrlich and Morgenroth showed that in rabbits poisoned with phosphorus and in whom, therefore, the liver was badly damaged, the serum on the second day (the height of the disease) had lost its power to dissolve guinea-pig blood, and that this was due to a disappearance of the complement. Metchnikoff also reported that in an animal suffering from a continuing suppurating process the complement had fallen considerably in amount. Especially interesting are the experiments of v. Dungern, who showed that animal cells, hence emulsions of fresh organs, are able to attract and combine with complements.

Fully as important as the question of a decrease in complements or an inhibition of their action, is

that of the possibility to artificially increase them. A number of authors, among them Nolf and Müller, have answered this question in the affirmative. They believe they have noticed such an increase following the injection of an animal with all sorts of substances, such as normal serum of another animal, sterile bouillon, etc. v. Dungern, as well as myself and others, have not been able to convince ourselves of the possibility of such a definite increase. I tried to excite the increased production of complement by injecting guinea-pigs for some time with anti-complement. This being the opposite of the complement, I hoped to be able by immunizing to excite an increase of the complements. In this I was unsuccessful, though of course it may be possible with another species of animal.

Despite all this we must believe that the amount of complement as well as the amount of other active substances of the blood, inter-bodies, agglutinins, anti-toxins, ferments, anti-ferments, etc., is subject to great fluctuations even in the same individual, a constant change going on within the organism. Ehrlich, in particular, has pointed out these individual and periodic variations and has insisted on their importance. Very likely, under circumstances of which we now know very little, these substances are at certain times produced in greater amounts, at other times in lesser; sometimes they may be absent entirely in an individual in whom they were previously present. For example, the serum of a

dog will at times dissolve the red cells of cats, rabbits, and guinea-pigs, at other times not. Furthermore, the serum of one and the same animal may possess specific hæmolytic properties for certain cells, and later on may lose this property entirely. In human serum these same individual and periodic variations may be demonstrated, as I was able by many experiments to prove. However, the circumstances on which these variations depend are as yet entirely unknown to us. Possibly we are dealing here with subtle pathological changes.

Source of the Complements—Leucocytes as a Source—Other Sources.—*Where do the complements or alexins originate?* This question has been studied particularly by Metchnikoff and by Buchner, also by Baïl, Hahn, Schattenfroh, and others. These investigators believe that the leucocytes are the source of the complements or alexins. There is, however, this difference between the views of Metchnikoff and Buchner; whereas Buchner believes the alexins to be true secretory products, Metchnikoff believes that they originate on the breaking up of the leucocytes, i.e., that they are decomposition products. Metchnikoff bases his belief chiefly on the work of his pupil, Gengou, who showed that although the serum was rich in alexin (i.e., complement) the plasma contained none at all.

Other authors, as Pfeiffer and Moxter, as a result of their experiments, are not willing to assume the existence of any relationship between the alexins

and the leucocytes. Gruber as well as Schattenfroh are ready to believe the leucocytes to be the source of *an* alexin, but claim that this is different from that found in serum. I myself believe that the leucocytes are a source of complements (alexins); for I succeeded in producing anti-complement by means of injections of pure leucocytes which had been washed free from all traces of serum, and which had been obtained by injections of aleuronat. Because of the plurality of the complements, I have expressed the view that the leucocytes are probably *one* source, but not the only one, for the complements of the serum. Landsteiner and Donath have confirmed my views experimentally. They succeeded in producing anti-complement by the injection not only of leucocytes, but of other animal cells. Furthermore, the experiments of Ehrlich and Morgenroth already mentioned, in which the complements disappeared after the destruction of the liver function, show that the liver cells are concerned in the formation of complements.

Structure of Complements—Haptophore and Zymotoxic Groups — Complementoids. — The structure of the complement has been studied particularly by Ehrlich and Morgenroth, and by P. Müller. We have seen that the complements lose their power when heated to 55° C. If, however, we inject animals with a normal serum that has previously been heated to 55° C., we shall still excite in these animals the production of anti-complements. This

shows that the heating has not destroyed the entire complement body, but only that part which effects the digesting, solvent action. The part of the complement concerned with the combination with the inter-body or immune body, in other words, that part called by Ehrlich the haptophore group, must have remained intact. It is clear, therefore,

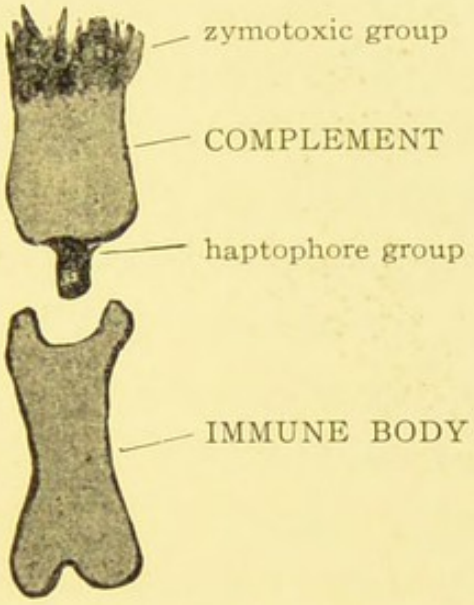

FIG. 4.

that anti-complements can only be formed when there remain in the complements haptophore groups that fit certain receptors in the organism of the animal injected. From this it follows that the complements consist of a combining *haptophore group* which withstands heating to 55° C., and another more fragile group which possesses the actual solvent properties, and which Ehrlich calls the *zymotoxic group*. There is a perfect analogy between this and the toxins already studied. These, it will be remembered, consist of a haptophore and

a toxophore group. And just as those toxins which had lost their toxophore group were called toxoids, so Ehrlich and Morgenroth purpose to call complements which have lost their zymotoxic group *complementoids*.

Isolysins — Autolysins — Anti-isolysins.— All of the preceding studies in hæmolysis have concerned themselves with the results obtained by injecting animals of one species with blood-cells of another. Ehrlich and Morgenroth now sought to discover what the result would be if they injected an animal with blood-cells of its own species. They injected goats with goat blood, and found that when the amount injected at one time was large the serum of the goat injected acquired hæmolytic properties for the blood of many other goats but not for all. The substances thus formed the authors called *isolysins*. These, then, are substances which will dissolve the blood of other individuals of the same species. Substances which dissolve the blood-cells of the same individual are called *autolysins*. But autolysins have so far been demonstrated experimentally only once (by Ehrlich and Morgenroth). If one tests the properties of an isolysin of a goat on the blood of a great many other goats, it will be found that this will be strongly solvent for the blood of some, slightly for the blood of others, and not at all for still others.

By using a blood that was readily dissolved by the isolysin, and proceeding in the same series of

experiments which we have already studied under hæmolysis, Ehrlich and Morgenroth showed that the isolysins, like the hæmolysins, consist of an immune body and a complement of the normal serum. The experiments undertaken by these authors were made on thirteen goats and the surprising fact developed that the thirteen resulting isolysins were all different. For example, the isohæmolytic serum of one goat dissolved the red cells of goats A and B; that of a second goat those of C and D; of a third those of A and D, but not of C, and so on. If now they produced *anti-isolysins* by injecting animals with these isolysins, they found that these anti-isolysins were specific; i.e., the anti-isolysin of A would inhibit the action only of isolysin of A, but not of C, etc. These results are of the highest clinical interest, for they show *a difference in similar cells of the same species*, something that had never before been suspected(?) In the above the blood-cells of species A must have a different biological constitution than those of species C, etc.

The fact that after injections of large amounts of cells of the same species isolysins develop, but that autolysins are almost never formed, caused Ehrlich and Morgenroth to assume that the body possesses distinct regulating functions which naturally prevent the formation of the highly destructive autolytic substance. It is obvious that if there were no such regulating facilities the absorption of

large bloody effusions and hæmorrhages might lead to the formation by the organism of autolysins against its own blood-cells. Gengou, a pupil of Metchnikoff, in a very recent work, believes to have shown experimentally that the destructive action of these autolysins is hindered by the simultaneous production of an auto-anti-immune body which immediately inhibits their action.

In order that isolysins may be formed, it seems necessary to overwhelm the organism once or several times with large amounts of cells or cell products of the same species; to produce, as Ehrlich says, an *ictus immunisatorius*. I tried, by using various blood poisons, such as hæmolytic sera, toluylenediamine, etc., for a continued length of time, to cause the formation of these isolysins, but without success, although in these experiments each injection was followed by an appreciable destruction of red cells and absorption of their decomposition products. The gradual and even repeated absorption of not too large quantities of decomposed red cells does not therefore lead to the formation of isolysins; but, as already said, a sudden overwhelming of the organism by large amounts of the cells or their products is necessary.

II. CYTOTOXINS.

Cytotoxins—Definition—Leucotoxin—Nature of the Cytotoxin—Anti-cytotoxin.—After it had been found that the injection of an animal with red blood-cells of another animal was followed by the production of definite, specific reaction substances, investigators experimented to see whether this was also the case if other animal cells were used. Injections were made with white blood-cells, spermatozoa of other animals, etc., and there resulted a series of reaction substances, entirely analogous to the hæmolysins, which were specific for the cells used for injection. These sera Metchnikoff calls *cytotoxins*. After Delezenne had published a short article on a serum hæmolytic for white blood-cells, Metchnikoff undertook a study of the substances produced in sera of animals treated with leucocytes of another species. He injected guinea-pigs with the mesenteric glands and bone marrow of a rabbit. He also injected for several weeks half an Aselli's pancreas at a time, at intervals of four days. If he withdrew serum from such a guinea-pig he found this to be intensely solvent for white blood-cells of a rabbit. He called this serum *leucotoxin*. This

leucotoxin is very poisonous for these animals, and kills them within a few hours. Non-fatal doses at first excite a marked hypoleucocytosis, which is followed after a few days by a compensatory hyperleucocytosis. Leucotoxin destroys the mononuclear as well as the polynuclear leucocytes of the animal, as was shown by Funk. Leucotoxin which had been derived by injection of the leucocytes of horses, oxen, sheep, goats, or dogs acted only on the leucocytes of that species, not on the leucocytes of man. So far as the mechanism of the cytotoxic action is concerned, it has been found that this is the same as that of the hæmolysins. The action of the specific cytotoxic serum is always due to the combined action of two substances in the serum, a specific immune body, and an alexin or complement present also in normal serum. The cytotoxic sera, like the hæmolytic sera, are rendered inactive by heating to 55° C. In other respects also the cytotoxic sera maintain the analogy to the hæmolytic sera. Thus it is possible by immunizing with a cytotoxin to obtain an *anti-cytotoxin*. Metchnikoff, for example, was able to produce an anti-leucotoxin by injecting animals with leucotoxin. This anti-body inhibited the action of the leucotoxin.

Spermotoxin.—Another specific cell-dissolving serum was produced by Landsteiner, Metchnikoff, and Moxter, by injecting animals with the spermatozoa of other animals. Such a serum rapidly

destroys the spermatozoa of the animals whose product was injected. This cytotoxin was named *spermotoxin*. If animals are treated with spermatozoa there is produced a serum which is not only a spermotoxin, but which is also hæmolytic for the red cells of that animal. This was demonstrated by Metchnikoff and Moxter, and has already been referred to in discussing hæmolysins. If, for example, we inject the spermatozoa of sheep into rabbits, we shall obtain a serum that is spermotoxic for sheep, as well as hæmolytic for sheep red cells. This is the case even when the greatest care is exercised to exclude every trace of blood in obtaining and injecting the spermatozoa. The hæmolysin, however, differs somewhat from that obtained by injecting sheep red cells, and its production is not hard to explain if we hold fast to the side-chain theory. We assume that these spermatozoa possess certain receptors in common with the red blood-cells of the same animal.

Anti-spermotoxin — Auto-spermotoxin.—By treating an animal with its spermotoxin we can produce an *anti-spermotoxin* which will inhibit the action of the former. Metalnikoff, a pupil of Metchnikoff, has demonstrated the occurrence of *auto-spermotoxin*. This, however, is only of scientific interest, and I mention it here only for the sake of completeness.

Cytotoxin for Epithelium.—v. Dungern has produced an *anti-epithelial* serum by treating animals

with the ciliated tracheal epithelium of oxen. This serum is rapidly destructive for this particular kind of epithelium. In this serum there is formed at the same time a specific hæmolytic body, just as in the case of the spermotoxic serum, and for the same reasons. The ciliated epithelium possesses a receptor group common to it and to the red blood-cells. It is therefore able to produce an immune body which is made up of two partial immune bodies.

This anti-epithelial serum is of further interest in that it leads us to hope that eventually we shall be able to produce sera which are cytotoxic for other varieties of epithelial cells, particularly those of pathological origin, as carcinoma. There have, however, been no further contributions to this subject worthy of mention.

Lindemann, a pupil of Metchnikoff, and Nefedieff have treated animals with an emulsion of kidney cells of another species, and have found that a serum was produced which was specific against the kidney cells of the second animal, and which produced an albuminuria in these animals intra vitam.

In similar fashion, Delezenne and Deutsch have produced a serum specifically cytotoxic for *liver cells*.

Neurotoxin.—Delezenne and Madame Metchnikoff have injected animals with central-nervous-system substance, and so produced a specific *neurotoxin*. They injected ducks intraperitoneally, giv-

ing them five or six injections of 10 to 20 grammes of dog brain and spinal cord mixed with normal salt solution. The serum of these ducks injected intracerebrally into dogs in doses of one-half c.c. caused the dogs to die almost at once in complete paralysis, whereas if normal duck serum was injected in the same way no effects of any kind were produced. If smaller doses of the specific neurotoxic serum were administered, say 0.1 to 0.2 c.c., various paralyses and epileptiform convulsions set in, from which the animals sometimes recovered. The action of this serum is also specific, i.e., the serum of ducks treated with dog brain causes these symptoms only in dogs, while on rabbits it acts no differently than normal duck serum.

These are the most important of the cytolytic or cytotoxic sera, though, of course, the list can readily be extended experimentally. In all this we are evidently dealing with a general biological law which we can express somewhat as follows: *An animal, species A, into whose body are injected cells or cell products of species B, reacts by producing specific substances in its serum against these cells or cell products, provided, of course, that the incorporated cells or cell products find fitting receptors in the body of A.*

Practical Applications of the Cytotoxins.—With a number of these sera therapeutic experiments have been made in the human subject Those of Metchnikoff and his pupil Besredka deserve men-

tion. They used a hæmolytic serum derived from goats which had been treated with human blood. One volume of this was able to dissolve an equal volume of human blood within a few minutes. This specific serum was injected into patients suffering from lepra, in doses of one-half to seven c.c., subcutaneously. As a result there was, of course, first a reduction of red cells, due to hæmolysis. This was followed after about six days by an increase of the same, and also by an increase in their hæmoglobin content. Certain other symptoms which showed themselves on the leprous nodules Metchnikoff ascribes to the leucotoxin which the serum contains. These experiments have, however, had no further practical results.

III. PRECIPITINS.

Definition.—All of the foregoing experiments have concerned themselves with the results obtained by injection of cellular material of one animal into another. In the further study of this subject, experiments were made to discover what happens when *dissolved* albuminous bodies of one species are injected into animals of another species. This line of investigation was first pursued by Tsistowitsch, who injected rabbits with the serum of horses and of eels. On withdrawing serum from such rabbits and mixing it with horse or eel serum, the mixture became cloudy, owing to the precipitation of part of the albumin of the horse or eel serum by that of the rabbit. Normal rabbit serum does not possess this property. Bordet was able to demonstrate that the same thing takes place if rabbits are treated with chicken blood. On mixing such a serum with chicken serum a precipitate formed. These substances which develop in the serum by treating an animal with albuminous bodies of another animal, and which precipitate these albumins when the sera of the two animals are mixed, are

called *precipitins*.* This power of the organism to react to the injection of foreign dissolved albuminous substances has been found to be very extensive.

Lactoserum — Other Specific Precipitins. — Bordet, by injecting cows' milk into rabbits, was able to produce a serum which precipitates the casein of cows' milk. He called this *lactoserum*. Ehrlich, Morgenroth, the author, Schütze, Myers, and Uhlenhuth showed that by treating a rabbit with chicken albumin a precipitin is formed which precipitates chicken albumin. Myers, by treating animals with Witte's pepton and globulin, produced a serum that contained specific anti-peptons and anti-globulins. Pick and Spiro, by using albumose, produced anti-albumoses. Lechainche and Vallée, Stern, Mertens, and Zülzer treated animals with human albuminous urine and produced a serum which contained a precipitin specific for this substance. Schütze, by treating rabbits with a vegetable albumin, as well as with human myoalbumin, produced a precipitin specific for these albumins. This does not exhaust the recital of the work done in this field, and there is a host of other albuminous bodies which, when injected into an animal, are able to excite the production of specific precipitins. The production of precipitins for the albuminous

* It will be recalled that, besides the production of precipitins, the above procedure causes the formation of other anti-bodies such as anti-complements, anti-agglutinins, etc.

bodies found in bacterial cultures had previously been shown by Kraus.

Nature of the Precipitins.—The precipitins are fairly resistant bodies, whose power gradually declines at a temperature of 60° C., but is not lost until 70° C. is reached. The resulting precipitate is soluble in weak acids and alkalies. Peptic digestion destroys the substances which effect the precipitation. Concerning the chemical nature of the precipitins, we have an admirable study by Leblanc, who finds in the case of a large number of precipitins that they are precipitated with that fraction of the serum which Hofmeister calls the *pseudo-globulins*. The pseudo-globulins constitute that part of the total globulins which is soluble in distilled water, while the rest, the euglobulins, are insoluble. The nature of the resulting precipitate has also been studied by Leblanc. He finds that it is a combination of the precipitated albumin with the anti-body, a pseudo-globulin, of the specific serum. In this combination the properties of the pseudo-globulin predominate, showing that it is the specific serum which furnishes the greater part of the precipitate.

Action Not Entirely Specific.—Of special interest is the inquiry as to how far the action of these precipitins is specific. The first experiments of Bordet had shown that the specificity is not complete; that the serum of rabbits injected with chicken serum is a precipitin not only for chicken serum but also for that of pigeons. The author and Schütze,

as well as Stern, were able to show that the serum of rabbits treated with guinea-pig serum is a precipitin also for the serum of monkeys. Probably this is because the sera of guinea-pigs and of monkeys possess common receptors. For this reason also the injection of a serum from one animal into a closely related animal does not excite the production of a precipitin, e.g., the serum of chickens injected into pigeons or that of rabbits into guinea-pigs. We may assume that in these closely related animals the serum of the one fails to find receptor groups with which to combine; on the contrary, it finds groups similar to its own, and these cannot react on one another. In line with this is the work of Uhlenhuth, who showed that the serum of animals treated with chicken egg albumin is a precipitin for egg albumin of other closely related birds.

Practical Application.—These precipitins have very recently found a practical application. Fish, Ehrlich, Morgenroth, the author, and Schütze investigated the specific action of lactoserum. They found that a serum derived by treating an animal with cows' milk contained a precipitin which reacted only on the casein of cows' milk, but not on that of human milk or goats' milk.. The serum of an animal treated with human milk was specific for the casein of human milk, etc. Ehrlich, Morgenroth, and the author also experimented with the serum resulting from treatment with chicken egg albumin,

and found that this, while not strictly specific so far as closely related species are concerned, is yet so against other species. *The precipitins, therefore, react on closely related albumins, but are absolutely specific against those of unrelated species.*

Wassermann's Method of Differentiating Albumins—To Test Blood Stains.—As a result of these researches the author proposed, at the Congress for Internal Medicine, 1900, to use these sera as a means of differentiating albumins, i.e., to distinguish the different albumins from one another and particularly to distinguish those derived from man from those of other animals. This proposal thus to use the Tsistowitsch-Bordet precipitins had important practical and theoretical results. Uhlenhuth, Wassermann, Schütze, Stern, Dieudonné, and others showed that a serum could be produced from rabbits by injecting them with human serum, by means of which it is possible to tell positively whether a given old, dried blood stain is human blood or not. The procedure is as follows: The suspected clot is mixed with a small quantity of normal salt solution and then filtered. To some of this in a test-tube about ~~the~~ double the amount of the specific serum (derived as above) is added. The specific serum is first, however, tested as to its activity. As a control test we place a little blood of another species, e.g., of an ox, in a second test-tube together with some of the specific serum and a little normal salt solution. In a third test-tube we place some of the

suspected blood solution, and in a fourth some of the specific serum, both without any additions. All four tubes are placed in an incubator at 37° C. for one hour or are left at normal room temperature for several hours. If the clot be that of human blood, the first tube must show distinct evidences of precipitation, while all the control tubes must have remained clear. This reaction is absolutely specific, with one exception, as was pointed out by the author, Schütze, and Stern. A serum derived by treating an animal with human serum reacts also to the serum of monkeys. It does not, however, react to the sera of any other animals thus far investigated. This method, then, furnishes the surest differential diagnosis for forensic purposes, as has been proved by the researches into the subject by Ziemke.

The Method Applied to Distinguish Albumins.—The A. Wassermann method of diagnosis by means of precipitins has found further application. Leblanc showed that the serum of an animal treated with pseudo-globulin causes a precipitate only in a solution of pseudo-globulin; one derived from an animal treated with serum albumin, only in a solution of serum albumin; one derived by treatment with hæmoglobin, only in a solution of hæmoglobin, etc. One is enabled, therefore, by this method to distinguish the different albuminous bodies. Leclainche and Vallée as well as Mertens showed by this method that the albumins of blood and milk

are different, and that therefore the albumin of milk is not a mere transudation product, but is a true secretion. Kowarski and Schütze, as already mentioned, could show a difference between vegetable and animal albumin. Jess as well as Uhlenmuth used the method to differentiate various kinds of meat in the markets.

The principle and the method are the same in all these various applications. We treat animals with the albumins which we wish to differentiate, and so obtain sera specific, each for its particular kind of albumin. These sera, then, produce precipitates only in solutions of their respective albumins. For example, if we wish to determine whether a given sample of meat is horse-flesh or not we must inject an animal with horse serum, or, if we prefer, with an extract of horse-flesh. The serum derived from this animal will then produce a precipitate in the aqueous extract of the meat if this be horse-flesh, but not if it be beef. Animals treated with dog serum yield a serum which precipitates an aqueous extract of dog-flesh, etc. The future will undoubtedly show further practical applications of this method.

Anti-precipitins — Iso-precipitins.—Biologically, the precipitins are found to behave like the substances already studied. It is possible, for example, by injecting an animal with a precipitin, say lactoserum, to obtain an *anti-precipitin*, an anti-lactoserum, which counteracts or inhibits the ac-

tion of the precipitin. This is entirely analogous to the anti-hæmolysins, the anti-spermotoxin, etc.

If rabbits are treated with rabbit serum, a serum is obtained which will, in certain cases, precipitate the serum of other rabbits. This was done by Schütze, and he called this serum *iso-precipitin.*

IV. CONCLUSION.

Clinical Applications of Immune Sera.—In closing this general résumé of the subject it may be well to mention some of the most important work done in the application of these discoveries to clinical purposes. Monaco and Panichi have shown that in malaria the blood of the patients very early shows the presence of iso-agglutinins, so that the serum of these patients is able to agglutinate the red cells of other persons. Grünbaum claims to have proved the same for typhoid and scarlet fevers. The most thorough work on this subject has been done by Eisenberg, who after examining a large number of cases of all kinds finds that iso-agglutinins and isolysins may be developed in all diseases in which there is destruction of red blood-cells or other cell material and a consequent absorption of their products. According to the studies thus far made we cannot, in man, ascribe any specific diagnostic value to the occurrence of isolysins or iso-agglutinins. Rather may they be regarded as delicate indicators which show that there has been destruction and absorption of living cell material in those cases in which they appear.

Diagnostic Value of Iso-agglutinins and of Isolysins.—As a result of my own observations, made on patients in the Institute for Infectious Diseases, I attach no particular value to the occurrence of *iso-agglutinins* in the serum of one patient for the erythrocytes of another. In this procedure, especially in the case of human erythrocytes, there are great sources of error. The erythrocytes of many persons have an inclination to agglutinate on the addition of any human serum, so that even the serum of the same person will agglutinate these red cells. In my opinion, therefore, it is unwise to attach much importance to the occurrence of *iso-agglutinins;* we should rather look for the occurrence of *isolysins* in the different diseases. In the isolysins the sources of error just mentioned do not obtain.

E. Neisser, Döring, and Lacqueer were able to show that in cases of uræmia substances appeared in the serum which acted very much like auto-anti-complements. The number of the observed cases, however, is too small to draw definite conclusions.

Immunization against Other Substances.—For completeness' sake it may be mentioned that it has been possible to immunize against a great variety of ferments; thus against emulsin (Hildebrandt), certain ferments in bacteria (v. Dungern), rennet (Morgenroth and Briot), and against fibrin ferment (Bordet and Gengou).

With all these sera the results obtained experimentally have thus far been applied clinically to too

few cases to allow of any conclusive opinion as to the merits of this method of treatment. Without doubt carefully conducted researches in this field might lead to discoveries of great value to the sick, and give us an insight into most delicate disturbances of the organism.

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running exps is
to allow the serum (or its separated Constituents)
to act in Vitro on the cells
and to then
Centrifuge out & Test the action on
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of different
Constituents of
serum which
are separated &
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1 Centrifuge & Thermometer are used.
for these exps.

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alexin
serum sensibilatrix

P-40

an immune serum may
have as much as 100,000
units to unit of immune body
present in normal Ser.

See also p 23

WHEW!

Addendum b. HG

Opsonins

Wright & Douglas Roy. Soc. Proc Vol 72 273
(County bacterin Wright Lancet July 4 1902)
Bulloch & Atkin Proc R S Vol 74 Jan. 1905
from latter the following conclusions :—

1. Opsonin is present in the normal Serum.
2. opsonin is thermolabile (60° C. 3 mins inactiv)
3. It rapidly disappears from the serum when latter is mixed with bacteria at 37° C or at 0° C.
4. After the opsonin has united with the bacteria the mixture of serum & cocci can be heated to 60° C for long periods without abolition of the opsonic effect.
5. The Leucocyte is practically an indifferent factor when the phagocytic power of different bloods is compared

6. The capacity of bacterial emulsions for extracting opsonin from the serum is only slightly diminished by subjecting these emulsions to very high temps over prolonged periods.

7. The action of heat is to destroy the opsonin, & not merely to convert it into a non-opsonisable modification

8. The opsonin is not identical with any of the antibodies hitherto discovered in the serum *

9. The opsonin is of relatively simple constitution; where these experiments cover the same ground as those of Wright & Douglas the observation of these authors are confirmed.

(* antitoxins, agglutinins, lysins
latter dep on { complement } & { immune body
{ thermolabile } } thermostable
see P 382 of B & H's paper.)

JMM
24/10/53