A SUMMARY AND ANALYSIS OF RECENT OBSERVATIONS AND THEORIES

AS TO

THE PROCESSES OF INFECTION AND PROTECTION IN THE ORGANISM.

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(Continued from p. 846.)

III.—BACTERIOLYSIS AND HAEMOLYSIS.

Characters of Amboceptor.

THE immune body has been spoken of as amboceptor because it anchors the complement and the red cell. Its action is merely that of a coupler, but it is specific in a sense, inasmuch as only a suitable receptor can be made use of by a single type of complement. The specificity depends further on the presence of a specific binding group, which anchors it to the red cell. The amboceptor is produced specifically by the introduction of the blood cells of a species into the organism of another, or it may exist normally in the blood of certain species.

Now it has been shown that antibodies are nothing more than receptors cast off from the cells, and as the amboceptor is a side chain produced by the red corpuscle, it must be accepted that what was previously spoken of as a receptor of the blood cell, after being cast off, becomes an amboceptor. This applies to bacteriolysin as well as to haemolysin. Bel-

Fig. 3.—Varieties of amboceptor. b' , b'' = Varieties of amboceptors; c = part of red blood cell; g' , g'' = varieties of receptors.

fanti and Carbone¹ were the first to show that the injection of the blood cells of one species into another produced a product derived from the red blood cells, which rendered the serum of the injected animal highly poisonous. Bordet² showed that this poisonous product corresponded to haemolysin, and von Döngern³ and Langsteiner⁴ confirmed this. All cells are capable of giving rise to an amboceptor. Thus Langsteiner,⁴ Metchnikoff,⁵ and Moxter⁶ produced a serum active against spermatozoa (spermotoxin); von Döngern,³ a serum active against ciliated epithelium; and Metchnikoff,⁵ a serum active against leucocytes and renal epithelium (leucotoxin). Thus it can be seen that the amboceptors are the analogues of the haptophoric groups of toxin. They occur in variety, according to the source of production, and are not uniformly similar bodies. The polyvalence of the amboceptor would be more difficult to understand if the whole doctrine of lysis action did not point to the fact that in normal serum there may be a very large number of freed side chains which correspond to agglutinins, ferments (enzymes), antiferments, cytolytins (for example, haemolysin, bacteriolysin), etc.; and, under pathological conditions, a still larger quantity may be formed. Every normally functioning cell throws off large numbers of side chains, either as isolated complexes, or in connexion with complement. These side chains are spoken of as haptines (Ehrlich⁷).

Since amboceptors exist specifically, they are capable of forming antibodies, and the existence of these (anti-immune bodies) can be readily demonstrated. Before detailing this, however, it is necessary to consider the variations of specific effect, which are due to peculiarities of production of the amboceptor.

Isolysin.

By the injection of a red blood cell of a strange species a specific side chain is formed as soon as the cell is absorbed.

¹ Belfanti and Carbone, *Ann. de l'Inst. Pasteur*, 1896.

² Bordet, loc. cit.

³ Von Döngern, *Munch. med. Woch.*, Nos. 20 and 28, 1901.

⁴ Langsteiner, *Centrabl. für Bacteriol.*, Nos. 10 and 11, 1900.

⁵ Metchnikoff, loc. cit., and *Revue Générale des Sciences*, No. 1, 1901.

⁶ Moxter, *Centrabl. für Bacteriologie*, vol. xxvi.

⁷ Ehrlich and Morgenrath, loc. cit., fourth communication.

It would therefore appear that if the red blood cells of the animal were absorbed by any inherent means (for example, after haemorrhage into the body cavities, tissues, etc.), a specific side chain would be formed. Were this so, there would be a greater danger to the organism from endogenous poisons than from heterogeneous ones, unless some special regulation process, which can neutralize it, existed. That such a process is theoretically possible can be shown by analogy; that it actually exists can be proved. By injecting a goat with the blood of another goat a haemolytic serum is produced, which is active toward the blood cells of other goats. Ehrlich calls the lysis thus produced isolysin. He has succeeded in obtaining twelve different varieties, each presenting some anomalous or individualizing feature; but in no case did the specific body act as autolysin, that is, they were incapable of dissolving the blood cells of the injected goat. The possible explanations for the absence of autolytic action are:

1. That the red cells produce no corresponding receptors; in this case the amboceptors would accumulate in the serum, but being unattached to the cells of the blood would produce no harmful effect, while on being transferred (in the serum) to a mixture containing cells with corresponding receptors (goat's blood), the conditions for the production of haemolysis (isolysin) would be present.

2. There may be suitable receptors, but these may be easily thrown off, and thus anti-autolysin will be at once produced. Ehrlich failed to demonstrate this latter possibility, but could not exclude it.

Bullock⁸ refers to Michaeli's case of a woman who was attacked with haemoglobinuria after a profuse haemorrhage into one of the body cavities. The extravasated blood was resorbed, and autolysis actually took place.

Some forms of haemoglobinuria and of very severe anaemia may be due to special poisons, and quite recently Ehrlich has returned⁹ to the regulation arrangements which prevent the occurrence of autolysis. He points out that since resorption of body cells (liver, kidney, etc.) frequently takes place, and yet autolysis in the form of hepatotoxin, nephrotoxin, haemolysin, etc., is rarely if ever found, some antibody must be formed (as described above) to prevent this.

Metchnikoff¹⁰ discovered in the blood of a guinea-pig which had been injected with the spermatozoa of guinea-pigs a body which was capable of destroying the spermatozoa of the injected animal, and therefore could be called auto-spermotoxin. This, however, only occurred in the test tube, and not in the living body; it is probable that only a specific amboceptor, and no complement corresponding to it, was present in the serum, and thus the autolysis was incomplete. Max Neisser and Wechsberg¹¹ found that an analogous condition was present in the serum of rabbits in connection with certain bacterial amboceptors, for example, those of typhoid fever, Metchnikoff's vibrio and Nordhafen's vibrio. When injected in large quantities the serum did not render the specific amboceptors of these bacteriolysins active. Loeffler and Abel¹² found that an overdose of the immune serum of bacteria coli communis is as incapable of protecting an animal against infection as is an insufficient dose. Pfeiffer¹³ also found that medium doses of immune serum against cholera were the most active, and Leclainche and Morel¹⁴ found the same for the serum against malignant oedema. In Neisser's experiments a quantitative examination was made of the dose of inactive rabbit's immune serum (against the micro-organisms mentioned above) which, in addition to a given dose of normal rabbit's serum, was capable of destroying a definite quantity of a twenty-four hours' old culture, and a quantitative estimation was made of the dose of normal serum, which would render a certain quantity of inactive immune serum active. In every case it appeared that no bacteriolytic action occurred with large doses. M. Neisser and Wechsberg suggested that this would be due to all the complement added in the form of normal serum, being anchored to those amboceptors which, being formed in excess, were free in the serum; while those amboceptors which were anchored to the bacterial receptor found no complement. If this were true the addition of more complement

⁸ Bullock, *The Practitioner*, December, 1900.

⁹ Ehrlich, 73. *Versammlung Deut. Naturforscher und Aerzte in Hamburg*, *Munch. med. Woch.*, 1901.

¹⁰ Metchnikoff, *Ann. de l'Inst. Past.*, No. 9, 1900.

¹¹ Max Neisser and Wechsberg, *Munch. med. Woch.*, No. 37, 1900, and No. 13, 1901.

¹² Loeffler and Abel, *Centrabl. für Bacteriologie*, vol. xix, 1896.

¹³ Pfeiffer, *Zeitschrift für Hygiene*, vol. xx, 1895.

¹⁴ Leclainche and Morel, *La Sérothérapie de la Septicémie Gangreneuse*, *Ann. de l'Inst. Past.*, No. 1, 1901.

would be capable of completing the action. E. Neisser and Doering¹⁵ show by analogy that the want of action in this case is due to the presence of antilynsins.¹⁶ It is therefore very likely that the action of autolysin is disturbed by the production of anti-auto complement.

The following observations of Ehrlich and Morgenroth further strengthen this view. A normal rabbit's serum is capable of dissolving guinea-pig's red blood cells, and contains a complement which can render active the amboceptor produced in the rabbit by injection of ox blood. But if a rabbit is injected with goat's serum (that is, complement), these characters are lost. This process will, according to the side-chain theory, lead to the production of an anti-complement, and as this will exert its antibody functions in the organism of the injected rabbit, it must be regarded as an auto-anti-complement. The production of such a body varied in quantity in different experiments. On the one hand, there might be complement in excess and a small amount of the antibody, in which case the complement remaining untouched after the antibody had neutralised as much as it could cover, would exert a certain amount of lysis action; and, on the other hand, the excess might be of anticomplement, in which case, all the complement would be neutralised, and thus all action prevented. The matter is, however, somewhat complicated by the fact, that, when a complement is introduced into the organism of a strange species, the serum of which contains an identical complement, no anti-complement is formed. An example of this is observed, when the serum of a goat is injected into a sheep. The complements must, however, be identical, and the same restriction does not apply to those which have identical haptophoric groups, but which are otherwise different. These related complements are capable of forming auto-anti-complements. It has so far not been possible to definitely determine the exact factors at work, which prevent the occurrence of autolysis.

There are conditions under which no antilynsins can be formed, as may be observed when a dog is injected with the serum of a sheep which has previously been treated with dog's blood. In some cases, this is due to the peculiarities of the receptor of the red cell. The receptor may be "sessile," so that the casting off necessary for the production of antibody does not take place, or may be altogether absent. In the latter case the antibody may be produced, if another organism in which the red cells possess the capability of forming suitable receptors' is chosen to supply the serum.

Further Varieties of Amboceptor and Anti-Immune Body.

In bacteriolysis anti-immune body is less likely to be produced, because the cells of the body are not stimulated to throw out the receptor by the injection of amboceptor into the organism, while the natural antagonistic groups to the amboceptor will be found in the bacterial cells themselves. In this way bactericidal serum rarely contains inhibitory bodies, save where a great excess of amboceptor is used.

Experiments with ox blood injected into rabbits¹⁷ show that varieties of amboceptor exist, in which two or more kinds may possess their complementophilic groups in common, but may differ in respect of their cytophile groups, and, therefore, require special receptors of the red cells. There are exceptions to this specificity of the receptor and amboceptor, inasmuch as it has been shown that the injection of a certain amboceptor may call into existence a side chain which is capable of anchoring another amboceptor beside the one introduced. For example, von Dungern has shown that the injection of ciliated epithelium produces an amboceptor which can be used as a haemolytic as well as against ciliated epithelium. Weigert¹⁸ showed that certain forms of receptor have a very wide distribution in the various animal species. Ehrlich found that receptors capable of taking up ricin, croton, ganglion cells, etc., are also suitable for tetanus plasma and the botulism poison. Wassermann showed that tetanus toxins are capable of being anchored to a variety of cells in the remote organs of the body. Ehrlich and Morgenroth succeeded in obtaining a very active immune

serum by injecting a goat with the inactive serum of a rabbit which had previously been treated with ox blood. The action of this immune serum depended on anti-immune body, and in the experiments with it, it was shown that when the complement supplied was derived from the guinea-pig the antilytic action was maximal, but when this was derived from the goat it was nil. The experiments were conducted as follows:

0.4 c.cm. of inactive (anti-immune body) serum was added to varying quantities of inactive serum of a rabbit treated with ox blood. The mixture was brought up to a certain volume by the addition of normal saline fluid, and was then brought into contact with 1 c.cm. of a 5 per cent. suspension of ox blood cells and 0.15 c.cm. of normal guinea-pig's serum—that is, to a serum containing anti-immune body was added amboceptor and red blood cells of the specific kind, and this mixture was rendered active by a complement. For the control experiment normal inactive goat's serum was used instead of anti-immune body serum. In the experiment 0.0175 c.cm. of amboceptor was capable of causing complete solution in spite of the presence of anti-immune body, while 0.0018 c.cm. was completely neutralized. In the control 0.001 c.cm. of amboceptor produced complete solution, and 0.005 produced "moderate solution." When the complement was derived from the goat instead of guinea-pig 0.057 c.cm. of amboceptor in both experiment and control produced complete solution, and with 0.014 c.cm. or less no solution occurred in either case.

Fig. 4.—Amboceptors with anti-amboceptors attached, leaving other amboceptors with different haptophoric groups unaltered. *a* = Complement; *a'* = a second variety of complement; *b* = amboceptor; *B* = a second variety of amboceptor; *h* = antibody.

In a variety of attempts they found that ten to thirty times the quantity of goats' complement as compared with guinea-pigs' was required to complete the solution. They proved that this was not due to lack of complement, and therefore assume that the immune serum contained two varieties of amboceptors, which were present in the ratio 10 : 1. The cytotoxic groups of these amboceptors differed from each other, as may be readily understood from the schema.

The action of the varieties of amboceptors depends largely on the haptophoric group and on the receptor of the red cell. Buchner¹⁹ and Nolf²⁰ have shown that the amboceptors have a specific affinity for the protoplasm of the red cell and none for the paraplasm, as represented by the haemoglobin; but they, as well as Niccoli,²¹ regard the affinity in the light of a level attraction, like that of the carbon molecule, while Ehrlich likens it to the selective affinity of the diazo group to the phenols on the one hand, and the aldehyde group to the cyanogen bodies on the other. Diazo-benzaldehyde is capable of binding phenol and prussic acid through itself, although these substances alone do not enter into chemical combination.

Ehrlich and Morgenroth further proved that varieties of amboceptors could be produced by the injection of ox blood into rabbits and into goats. In the serum of dogs and of rabbits treated with ox blood they found that certain amboceptors of each corresponded except as to their cytophile groups. The same variation also exists in bacteriolytic amboceptors.

Amboceptors may be homologous save for differences in their complementophilic groups. In some cases these groups may be multiple, and then the immune body will consist of one cytophile and two, three, or more complementophilic groups—triceptor, quadriceptor, etc. The multiplicity of the complement has already been spoken of, and corresponding forms of complementophilic groups of the immune body exist. Further, certain complements exist as partial complement, which are identical, as far as their haptophoric groups are concerned, in different animals. Corresponding to the partial complements, partial amboceptors are met with.

The whole importance of the complementophilic groups of amboceptor turns on the multiplicity and variety of complement and of its haptophoric group. It is possible that the complementophilic group may be produced by the mere presence of complement of a strange species. The variety of this

¹⁵ E. Neisser and Doering, *Berl. klin. Woch.*, No. 22, 1901.

¹⁶ These observers carried out experiments with human blood, and showed that the laws of haemolysis applied equally to the human as they do to other species.

¹⁷ Von Dungern, *Münch. med. Woch.*, No. 20, 1900. Ehrlich and Morgenroth's Fourth Communication.

¹⁸ Weigert, Lubarsch-Ostentag's *Ergebnisse der Pathologie*, 1837, p. 141.

¹⁹ Buchner, *Ann. de l'Inst. Past.*, 1900.

²⁰ Nolf, *Ibid.*

²¹ Niccoli, *Revue Générale des Matériaux Colorantes*, Nos. 43 and 44, 1900.

relationship between the latter and the receptor of the red blood cell, while the various kinds of complement whose haptophoric groups are of such a constitution as to be fitted for a certain kind of amboceptor will, generally speaking, find the possibility of anchoring themselves to that body, be it by means of a pre-existing side chain or be it by means of a side chain called into existence for the purpose.

RECEPTORS.

While agglutinin and haemolysin are independent of one another, they in all probability act at times side by side. The same laws, to a certain extent, hold good for both, but a very marked difference of the active group must be recognized, in that the action of agglutinin, unlike most haemolysins, is not disturbed by heating to 55° to 60° C. There is no amboceptor as such, but the body consists of a zymophoric group (cf. complement) and a haptophoric group (cf. cytophoric group of the amboceptor). Grüber attaches much too much importance to the part played by agglutinin in connexion with bacteriolysin and haemolysin.

Fig. 5.

Fig. 7.

Fig. 6.

The above figures (types of receptors) represent the anchoring of lysins, toxins, etc., in a pictorial form.

a = Complement.

c = Part of a cell.

e = Haptophoric group.

k = Complementophile group.

l = Toxophoric group.

m = Zymotoxic group.

n = Nutrient molecule.

z (in Fig. 5) represents a receptor of the first order, corresponding to toxin, etc.

y (in Fig. 6) represents a receptor of the second order, corresponding to agglutinins, etc.

z (in Fig. 7) represents a receptor of the third order, corresponding to haemolysin, etc.

We have three distinct varieties of receptor formations which are represented diagrammatically in the accompanying schemata. The first order, which is capable of anchoring toxins, ferments, and simple cell secretions, consists of an arrangement for the reception of the haptophoric groups of the toxin, etc. The second order is adapted for the anchoring of coagulins, agglutinins, etc. This one consists of a haptophoric group for the reception of a nutrient molecule (fraction of the giant molecule), and a second group, to which the ferment attaches itself. The third order is more complex, and is the arrangement which enables haemolysins, bacteriolysins and the like to become attached to the cell. It consists of a haptophoric group for the reception of a nutrient molecule, and a second haptophoric group which, on being cast off, functionates as the amboceptor or immune body.

That the production of receptors depends on the nutrition and vitality of the cell is obvious, since it has been observed group is of less importance than that of the cytophile group, for the great chemical affinity necessitates an exact specific that certain receptors,²² which were present at one time, may

be wanting at a later date; that is, new receptors of the same kind are not made by the cell, after the old ones have been cast off, and, inversely, new receptors may appear of a type which had previously not been present. Ehrlich explains the interesting observation of Kossel that rabbits which are used for the production of immune serum against eel's blood lose their susceptibility toward the poison by assuming that the receptors for the poison are no longer manufactured. He points out that the receptors are naturally called into existence for the purpose of anchoring certain products of metabolism. They are produced in excess by the injection of the poison, and therefore form antibodies, some of which anchor the poison, while others anchor that product of metabolism, and in this way prevent the necessary cell stimulation, which can call forth a further production of these receptors. This occurs more readily when the product is one which the tissue economy can easily dispense with—for example, sugar—which can be replaced by fats. They found that the blood cells of newly-born rabbits were incapable of anchoring eel poison. This can only be explained by the assumption of such an absence of receptors.

Taking haemolysis as a type of the processes in question, we must accept that the same laws hold good for the action of other cell poisons. Uhlenhuth²³ (whose work on the medico-legal recognition of the blood of various species has attracted much attention) deals with precipitins, Metchnikoff²⁴ with spermotoxins and leucotoxins, von Dünern²⁵ with trichotoxin, Lindemann with nephrotoxin, and Enriquez and Sicard with neurotoxin. Widal and Durham described the occurrence of agglutination, and Grüber²⁶ applied this exactly to the requirements of the side chain theory (cf. the action of some of the phytalbumoses). Of the secretions of bacteria the lysins (corresponding in their actions to haemolysins) have attracted much attention since Pfeiffer first described the process. Ehrlich and Madsen have studied tetanolysin, van de Velde, M. Neisser, and Wechsberg staphylotoxin, von Lingelsheim the poison of streptococci, and Bulloch that of pyocyanus. The last-mentioned poisons, as well as tetanus toxin (studied by Wassermann) deal with the toxin group, while the first, as well as typholysin, the lysin of cholera (Wassermann, Pfeiffer, and Marx) belong to the lysin group. It rests with Wassermann to have first clearly shown beyond doubt that the side-chain theory could be demonstrated in his experiments with tetanus toxin.

(To be continued.)

CONTRACT MEDICAL PRACTICE.

PRIVATE MEDICAL CLUBS.

DR. F. W. D. MCGACHEN (Littlehampton) writes to express the opinion that private medical clubs are even more objectionable than medical aid companies; the latter, he says, do their work openly, while canvassers of private clubs work quietly, and get as much both for new business and for collections. He thinks that the General Medical Council should include the private medical clubs, in which canvassers to whom commission is paid are employed, in any condemnation of canvassing.

INTERNATIONAL CONGRESS OF ELECTRICITY IN MEDICINE.—The Second International Congress for Electricity in Medicine and Radiography will be held at Berne, September 1st to 6th, 1902. The following questions are proposed for discussion:—(1) The Present State of Electrodiagnosis (to be introduced by Dr. Cluzet, of Toulouse, and Dr. Mann, of Breslau); (2) Surgical Electrolysis (to be introduced by Dr. Guilloz, of Nancy); (3) Radiography and Radioscopy of the Internal Organs (to be introduced by Dr. Bécélère, of Paris, and Professor Grunmach, of Berlin); (4) Accidents caused by X Rays (to be introduced by Dr. Oudin, of Paris); (5) the Danger of Industrial Electric Currents (to be introduced by Dr. Battelli, of Geneva). An international exhibition of all electrical instruments of physiological, electrotherapeutic and radiographical interest will be held in connexion with this Congress. All communications should be addressed to the Secretary, Dr. L. Schnyder, 38, Rue Fédérale, Berne.

²³ Uhlenhuth, *Deut. med. Woch.*, No. 6, 1901.

²⁴ Metchnikoff, *Ann. de l'Inst. Past.*, 1900.

²⁵ Loc. cit.

²⁶ Grüber, *Münch. med. Woch.*, 1896; *Wien. klin. Woch.*, 1896

²² Ehrlich, *Schlussbetrachtungen*, Nothnagel's *Speziellen Pathologie und Therapie*, 1901.