Contributed and Selected

INFECTION AND IMMUNITY—A REVIEW.

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6. SPECIAL PHENOMENA OF IMMUNITY. It has been shown that antitoxins, according to Ehrlich's scheme, are cast-off receptors of the first order, and that in order to explain other phenomena occurring in immunity, as agglutination, precipitation, cytolysis, bacteriolysis, and hemolysis, it becomes necessary to demonstrate other orders of receptors.

Agglutinins. In 1895 Grüber and Durham discovered that when a few drops of an antibacterial serum were added to a suspension of homologous or corresponding bacteria, the micro-organisms within a short time would be found in clumps. This phenomenon was termed agglutination, and was said to be due to definite bodies in the serum called agglutinins. The practical application of this reaction to the diagnosis of typhoid fever was brought out independently by Grünbaum and Widal, although Widal was the first to publish his results. The Widal reaction, or the phenomenon of agglutination, may be produced by most of the antibacterial serums, and observed, therefore, in many of the bacterial infections, although the reaction is variable, and is more specific and definite in some than others. The cast-off receptors or agglutinins, which have to do with the formation of the clumps in the phenomenon of agglutination, have not only a haptophore affinity as in the case of receptors of the first order, but also another group, called a zymophore group. When an animal is immunized to a certain micro-organism, these receptors of the second order are formed along with others, and many of them of course are liberated. These cast-off receptors or agglutinins, therefore, attach themselves to the specific bacteria by means of the haptophore affinity, and produce the agglutination by means of the zymophore group acting upon these attached micro-organisms. The haptophore group selects and picks up the bacteria, while the zymophore group produces the reaction.

Precipitins. The receptors concerned in the precipitation reaction are formed similar to those in the agglutination reaction. When the blood or serum of a human being is repeatedly injected into the peritoneal cavity of a rabbit, the serum of that rabbit acquires the property of precipitating the human serum, if mixed in the test tube. The receptors or precipitins are formed and liberated

during the injections of serum into the rabbit. These receptors have a haptophore affinity which attaches itself to the serum of the human being, while the zymophore group produces the precipitation. If the serum of this rabbit is mixed with the serum of any other animal, the reaction will not take place, for this haptaphore group can only attach itself to human serum, and the zymophore group can only react when the haptophore group is thus attached. The reaction is, therefore, a specific test for the presence of blood.

Cytolysins. It has been found that when suspensions of various cells are injected into an animal, certain substances are formed in that animal and found in the serum which are injurious to cells similar to those injected. The cells injected may be bacterial cells, blood cells, epithelial cells, renal cells, hepatic cells, and others, but it must be borne in mind that the destructive bodies are specific only for the kind of cells injected. For instance, if we inject red blood cells from a human being into a rabbit, then the serum of that rabbit will be injurious to human red blood cells but not to kidney cells or liver cells, and not red blood cells of any other species. It can be seen that in order to explain this phenomenon it becomes necessary to have a more elaborate receptor or side chain than for any of the previous combinations. At least two distinct substances are formed which react upon the cells in question, and these two substances must be able to combine with each other before the reaction can take place. These two combining substances are termed amboceptor and complement. The amboceptor, the immune body or receptor, is formed by the body cells during the process of injecting the red blood cells, bacteria or other cells, while the complement is always present, and, therefore, a normal constituent of the serum. The immune body or amboceptor, which is the cast-off receptor, must not only be able to unite with the specific cell, similar to the antitoxin of the first order, and the agglutinin of the second order, but go a step further and unite with another substance or body, the complement. It therefore must have two haptophore affinities, one for the complement and one for the specific cell. The final reaction, the destruction of the cells, is produced, however, by the complement, and although this is present in the normal serum, it cannot perform its function without the aid of the amboceptor, which is only formed by the injection of the cells.

Opsonins. In studying the action of phagocytes on bacteria, it has been found that it is not primarily a reaction between the leucocytes and bacteria, as was thought by Metchnikoff and his school, but is a more complicated reaction. Wright and Douglas have demonstrated that certain substances in the blood serum are necessary before the reaction can take place. These substances which act upon the bacteria and prepare them for the leucocytes, are called opsonins. What sort of changes the opsonins produce in the bacteria, rendering them susceptible to the action of the leucocytes, is not known.

Hektoen and Rurdiger have shown that the opsonins resemble the toxins, in that they apparently have a toxophore and haptophore group, one to unite with the bacteria and the other with the leucocytes. The relationship between the opsonins and the other immune substances, as the agglutinins and cytolysins,

has practically been proven, so it appears that the opsonic theory represents a connecting link between the phagocytic theory of Metchnikoff and the side-chain theory of Ehrlich. It may possibly be demonstrated, in the future, that Ehrlich's theory is simply an aid in explaining the action of the phagocytes in infection, and that, after all, the leucocytes may have the most important part to play in the phenomena of immunity.

7. ANAPHYLAXIS AND SERUM SICKNESS. One of the best descriptions of anaphylaxis is given by Hiss and Zinsser. "By anaphylaxis is meant the following train of phenomena: When a foreign proteid is introduced by subcutaneous, intraperitoneal, intravenous or subdural injection (or in some cases by feeding) into the animal body, after a time there will appear a specific hypersusceptibility of the animal for this proteid. After a definite interval, a second injection of the same substance, harmless in itself, will produce violent symptoms of illness and often rapid death in an animal so prepared. The phenomena are not limited to any given class of proteids, but are manifest in the case of animal, vegetable and bacterial proteids, and within certain limits are specific." A typical reaction may be seen in a guinea pig which has been injected with normal horse serum. Following an extremely small initial dose of the proteid (0.004 cc.) the anaphylactic state usually develops after ten to fourteen days. After a large dose the time required for the development of the anaphylaxis is usually longer; it may even extend over weeks or months. Many theories have been offered for the explanation of the phenomenon of anaphylaxis, but none are at all satisfactory. Without going into the exposition of these different theories,, we will take up one which seems to offer the most plausible and at the same time the simplest interpretation of all.

It has been found that the proteid molecule, on being split up by chemical methods, contains a toxic and a non-toxic substance. It has also been determined that this toxic substance is unlike the toxin formed by the diphtheria bacillus, in that it does not produce a neutralizing body similar to antitoxin, when injected into an animal. It does seem to produce, however, a substance or body resembling the hemolysins, termed proteolysin, which is capable of breaking up *any* molecule of the same substance, which may be subsequently injected after a certain length of time. The hemolysins break up the red blood cells, setting free the toxic portion. The toxic portion of the proteid molecule is extremely poisonous, and if enough is set free in the animal, fatal results will follow within a few minutes. By making a direct application of this theory, let us see how anaphylaxis may take place in a guinea pig. A small amount of horse serum (0.004 cc.) is injected into a guinea pig. The proteid of this serum contains a toxic substance, which, acting upon the guinea pig, produces a body we have called proteolysin. The body does not form at once, but appears to take about ten days, and when once formed will remain in the guinea pig for the remainder of its life. Now after the required interval the guinea pig is again injected with horse serum, this time, however, with a much larger dose. The body or substance, the proteolysin, which was formed by the guinea pig following the first dose of serum, now acts upon the proteid of the second dose of

serum, splitting it up at once into the toxic and non-toxic parts. On account of the large amount of serum constituting the second dose the amount of toxin set free must be relatively large, and acting upon the tissues of the guinea pig produce a train of symptoms recognized as the phenomenon of anaphylaxis. Vaughan and Wheeler, of Ann Arbor, were able to separate the proteid molecule into a toxic and non-toxic portion, and with the toxic portion experimentally produce symptoms similar to anaphylaxis, so it would seem that the theory so far is well founded.

The facts as regards anaphylaxis of which we are practically certain are as follows:

1. A condition of hypersusceptibility or hypersensitiveness is produced when a small quantity of proteid is injected, and a condition of immunity is produced when a sufficiently large dose is given.

2. The symptoms are more severe and specific the smaller the first or sensitizing dose, to a certain limit.

3. If a dose is given the animal some time between the first or sensitizing dose, after the first day, and the second or fatal dose, a condition of antianaphylaxis is produced which immunizes the animal to the fatal dose.

4. The condition of anaphylaxis may be transmitted from a sensitized animal to another through the serum, which is termed passive anaphylaxis.

5. The condition of anaphylaxis may be transmitted from mother to offspring.

6. Animals sensitized to one proteid are not sensitive to subsequent injections of other proteids; the reaction, therefore, being more or less specific.

7. The quantity for the second injection should be considerably larger than the first or sensitizing dose.

8. Animals recovering from the second injection are thereafter immune to the same substance.

9. After ten days following the sensitizing dose the animal is always susceptible to the second dose.

Other phenomena somewhat of this nature, which probably depend upon the principles involved in anaphylaxis, or at least in hypersensitization (allergy), are seen in the tuberculin and mallein reactions. The animal or individual is probably sensitized by the primary infection, while the injection of the mallein or tuberculin produced the typical reaction, which is slight, and which is due to the small amount of the dose. If the dose is large very severe symptoms or even death have been known to follow. Another condition or reaction, which has been compared to anaphylaxis, is that of serum-sickness. It has been known for several years that the injection of antitoxic sera in human beings is often followed by various skin eruptions, pain in the joints, swelling of the lymph glands, often albuminuria and fever. These symptoms appeared after an incubation of from two to ten days. It was also early found that these symptoms had nothing to do with the antitoxic reaction of the serum, but were dependent upon properties peculiar to the serum itself. Normal horse serum will produce

the same symptoms. It seems certain that anaphylaxis has something to do with these conditions, but we are unable to determine the exact relationship. Anaphylaxis in animals only follows the second injection, whereas serum-sickness often follows the first injection. The patient is the more liable to the condition the greater the number of injections given. The size of the dose does not seem to make much difference in serum-sickness. The phenomenon of serum-sickness is seen in about 20 per cent. of the cases injected with antitoxic serum. The symptoms may at times be troublesome, but fatal cases traceable to serum-sickness are unknown, or at least have not been proven. There are a few cases on record where death followed suddenly on the injection of antitoxic serum, but these are very rare, although very magnified by opponents of serum-therapy. This condition has been termed sudden death. While it would appear, in explanation of this condition, that the fatal symptoms were traceable in some way to anaphylaxis, other suggestions have been offered which seem much more plausible, as they have been to a certain extent, backed up by the post-mortem findings, such as the shock of the injection upon an already overburdened heart, or upon one suffering from the condition known as status lymphaticus.

Knowing that the larger part of the antitoxin is contained in the globulins of the serum, it has been found advantageous to use these globulins in the prophylaxis and treatment of diphtheria in place of the whole serum. As a result, the percentage of cases of serum sickness have been greatly reduced. This is explained on the assumption that as the amount of proteids injected are necessarily decreased, the chances of proteid poisoning are lessened. Although serum sickness is of less frequent occurrence than formerly, showing the relative increase in the safety of the globulin over the whole serum, yet a point has been raised as to the relative immunizing value of the globulins as compared to the whole serum, and, along the same line, the relative value of serums of high antitoxic potency as compared to those of low. It has been suggested that we do not obtain the same results, unit for unit, with serums of concentrated antitoxic content as we did when this method of specific therapeutics was first inaugurated and large quantities had to be injected due to the low antitoxic content of the serums. That is to say, some maintain that we do not obtain relatively the same therapeutic results, from the immunity point of view, with 1 cc. of a globulin containing 3000 units per cc. or 3 cc. of a serum containing 1000 units per cc. as we did with 10 cc. of a serum containing only 300 units per cc. This is a point which only time and experience can answer.

The following table will compare fairly well the three conditions, according to the facts we have been able to obtain up to the present time:

Anaphylaxis.	Serum Sickness.	Sudden Death.
1. Condition is manifest only after second injection.	1. Condition often manifest after first injection.	1. Condition usually manifest after first injection.
2. Symptoms appear within an hour. Difficult to kill within five minutes.	2. Symptoms usually appear after an incubation from two to ten days.	2. Symptoms appear immediately.
3. Very severe symptoms, usually resulting fatally.	3. Symptoms disappear within a few days and leave no bad results.	3. Symptoms always result fatally.
4. Fatal dose must be very large in proportion to therapeutic dose for man. 5 cc. for a guinea-pig, corresponding to 3 pints for a man.	4. Size of dose of little importance.	4. Size of dose apparently not important.
5. Animal must be "sensitized" by a previous dose of the same proteid, with an interval of at least 10 days.	5. Previous dose apparently not necessary.	5. Previous dose apparently not necessary.
6. If a dose is given the animal some time between the first dose and the fatal or second dose, the animal will be immunized to the last dose.	6. Not known; experimental.	6. Not known.
7. The condition of anaphylaxis may be transmitted from a sensitized animal to another through the serum (Passive Anaphylaxis).	7. Not known.	7. Not known.
8. The condition of anaphylaxis may be transmitted from mother to offspring.	8. Not known; may be possible.	8. Not known.
9. Animals sensitized to one proteid are not sensitive to subsequent injections of other proteids.	9. Not known; probable.	9. Not known.
10. Animals recovering from the second injection are thereafter immune to the same substance.	10. The patient is the more liable to the condition the greater the number of injections given.	10. .....

8. RELATION OF BIOLOGIC PRODUCTS TO IMMUNITY.

Bacterial Vaccines (dead bacteria), active immunity.
Smallpox Vaccine (attenuated virus), active immunity.
Blackleg Vaccine (attenuated organisms), active immunity.
Anthrax Vaccine, Pasteur (attenuated organisms), active immunity.
Antitoxic Sera (blood serum), passive immunity.
Antibacterial Sera (blood serum), passive immunity.
Tuberculins (dead bacteria and bacterial products), active immunity.
Rabies Vaccine (attenuated virus), active immunity.

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