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**Anaphylactic shock caused by antibodies in animals treated with antigen; reversed passive anaphylaxis.**

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Passive sensitization shows that the serum contains an antibody which has an essential part in the production of anaphylaxis. The presence of this antibody renders the animal sensitive to the action of the antigen and the character of the ensuing reaction is determined by functional peculiarities of various tissues of the body. If the union of antigen and antibody is sufficient to produce these changes it would be possible not only to sensitize animals to antigen by administration of antibody but to sensitize to antibody by previous treatment with antigen as well. One of us<sup>1</sup> has published observations which show that an animal treated with horse serum reacts with acute inflammation when serum of a rabbit immunized against horse serum is injected into its dermis. The usual procedure employed to produce the Arthus phenomenon has been reversed and inflammatory oedema is caused by the antibody injected into the skin of animals sensitized by antigen.

We have found that anaphylactic shock occurs in rabbits sensitized by previous injection of horse serum, beef serum or egg white when the corresponding anti-serum is injected into the blood stream. Guinea pigs have proven unfavorable for these experiments; on the one hand, rabbit's serum is toxic for guinea pigs in the amount required for the experiment and on the other hand antibody formation is relatively weak in guinea pigs so that guinea pig serum is ineffective.

It is noteworthy that when precipitin and its antigen are brought together, minimum precipitation occurs when the amount of anti-serum is several hundred times that of the antigen employed in its production. Likewise in the production of anaphylactic shock, the volume of antiserum required is greatly in excess of the corresponding antigen. Large rabbits were not suitable for these experiments because with them the production

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<sup>1</sup> Opie, E. L., *J. of Immun.*, 1924, ix, 255.

of anaphylactic shock requires quantities of antiserum larger than those conveniently obtainable. Young rabbits weighing from 200 to 400 grams were used.

One half cubic centimeter of horse serum sensitized young rabbits to the action of from 8 to 10 cc. of strong anti-serum obtained from animals which reacted with necrosis to subcutaneous injections of horse serum. Larger doses of weaker sera (10 to 20 cc.) were needed to produce the same result. The precipitin content of the serum is an index of its toxicity when injected into these sensitized animals.

The symptoms of this reversed passive anaphylaxis do not differ from those obtainable after active sensitization or in animals passively sensitized by the usual procedure. With shock following injection of anti-serum there is muscular weakness and diminished activity of reflexes; respiration is often for a time slow and labored; urine and feces are passed and convulsive movements may occur. The animal recovers its strength after 10 to 15 minutes. A larger quantity of anti-serum causes violent convulsions and death usually within five minutes but occasionally complete paralysis and death are almost immediate. All experiments have been controlled by the intravenous injection of anti-serum into normal animals. Rabbits of the size selected tolerate antiserum in quantities much in excess of their blood volume, if the serum contains no solid particles and is free from antigen.

In order to produce maximum sensitization an interval must elapse between the injection of antigen and of anti-serum but even when antigen has been followed by anti-serum within thirty seconds death has occurred in one instance and shock has been noted in six of nine experiments. After 4 to 6 hours, shock, occasionally with death, has occurred in all instances, but the reaction is not as severe as that observed after an interval of 12 hours, when maximum intensity is reached. These experiments indicate that there is a period of incubation during which tissues concerned in the reaction presumably acquire increasing concentration of antibody.

Nevertheless it is noteworthy that an incubation period is not essential to the production of the reaction, for, slight shock may follow the injection of antigen and antibody mixed immediately before introduction into the vein of a normal rabbit. When mixtures of anti-serum derived from several immunized rabbits are

employed, the presence of antigen must be excluded, for in some weakly immunized animals antigen persists during long periods within the blood stream.

This reversed passive anaphylaxis suggests a simple explanation of the phenomena of anaphylaxis. Characteristic reactions occur whenever antigen and antibody meet within tissues, which are in consequence of their peculiar functions susceptible to stimulation or injury. This explanation does not exclude the possibility that changes resulting in symptoms may occur within the blood stream. An analogous series of events are observed when antigen is injected into the skin of sensitized animals; acute inflammation (Arthus phenomenon) follows. This tissue sensitization may be produced passively and, as pointed out above, the usual procedure may be reversed, acute inflammation being produced by intracutaneous injection of anti-serum into animals sensitized by antigen. In this experiment the reversible relation of antigen and antibody to the changes which occur in the tissues is more evident than in anaphylactic shock but in each instance antigen and antibody has caused a reaction, the character of which is determined by functional peculiarities of the affected tissue.

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### Studies in adrenal insufficiency.

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*Duration of survival of pregnant dogs after adrenalectomy.*—The period of survival has been seen to be greatly increased in pregnancy. Two examples will be given: one in which the second adrenal was removed soon (probably no more than a week) after impregnation, and another in which gestation was from half to two-thirds over when the second adrenalectomy was performed. One dog (1036), known to have been impregnated in the interval between removal of the first and second adrenal, lived 46 days 3