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On the mechanism by which antigen is removed from the circulation.

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In studying the rate of disappearance of horse serum and the curves for circulating precipitin in a group of serum-treated patients it was noted that individuals who have severe serum disease are good precipitin formers and that at the time the precipitin in the circulation reaches the crest of its curve or soon thereafter the precipitinogen rapidly disappears from the blood stream. On the other hand in those individuals who after a first administration of foreign serum, show very mild or no symptoms of serum disease little or no precipitin is demonstrable in the patient's serum and the precipitinogen persists in the circulation for a long period. Intermediate types were also encountered. From these results it seemed at least plausible to assume that an important factor in determining the rate of disappearance of the foreign serum from the circulation was an intravascular union of antibody and antigen. That such an assumption is erroneous seems probable from the following experiments:

In one series of experiments 12 previously immunized rabbits were injected intravenously with amounts of horse serum (3.00 c.c. or 6.00 c.c.) comparable to the amounts used therapeutically in the group of patients studied. The animals were then bled every second or every third day and the precipitin and precipitinogen in the serum titrated. Six of the animals had a high titer (1:20,000 or higher) of precipitin in the circulation at the time of reinjection, 2 had a moderately high titer, 1 had only traces of precipitin, and 3 had no circulating precipitin. Two of the 3 rabbits with no circulating precipitin had been immunized 10 months previously and at that time had developed a high titer of precipitin which had entirely disappeared before the reinjection. Presumably such previously immunized rabbits which had shown

themselves to be good precipitin formers would form antibody in excess earlier than upon first immunization and would therefore dispose of injected antigen earlier than upon first immunization and earlier than fresh rabbits injected with the same amounts of antigen.

A control series of 11 normal rabbits was injected with the amounts of horse serum used in the previously immunized rabbits; precipitin and precipitinogen determinations were made similarly on the controls every second or third day. Of the rabbits receiving 3.00 c.c. of horse serum the time of disappearance in those previously immunized varied from 6 to 17 days with an average of 11.2 days and in the unimmunized controls the variation was 14 to 17 days with an average of 15.5 days. In the rabbits receiving 6.00 c.c. of horse serum the figures were: Immunized, variation 1 to 37 days, average 13.7 days. Unimmunized, variation 6 to 21 days; average 16.3 days. The difference, while in favor of the immunized animals, certainly falls short of theoretical expectations.

Following these preliminary and somewhat inconclusive observations an attempt was made to determine the rôle of intravascular union of antigen and antibody by a different experimental procedure. Normal rabbits were injected intravenously with 6.00 c.c. of horse serum and then twice every day given large amounts of high titer anti-horse rabbit serum intravenously. Precipitin and precipitinogen determinations were made daily during the period of the experiment. No conclusive evidence of accelerated disappearance of antigen was observed. One rabbit which received 97 c.c. of potent (1:20,000 to 1:500,000) anti-serum during the 48 hours following the injection of 6.00 c.c. of horse serum had the foreign serum in the circulation for 7 days. Another rabbit receiving 126 c.c. of potent (1:20,000 to 1:500,000) anti-serum during the 55 hours following the injection of 6.00 c.c. of horse serum continued to have the foreign serum in the circulation for 9 days after the antigen injection. While the rate of disappearance of antigen in these two rabbits is below the average for normal rabbits injected only with horse serum the rate is within the limits of variation of the control rabbits. If such a flooding of the circulation with specific anti-

serum produces little or no acceleration of the disappearance of antigen it seems justifiable to assume that intravascular union plays an unimportant rôle in the mechanism for removal of foreign serum from the circulation, and therefore that the cellular phase is of predominating significance.

It is also evident from the results on the whole group of 28 rabbits studied that individual variation extends over a wide range both in ability to form antibody and in the rate at which foreign serum is removed from the circulation.

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The effect of various proteins on streptolysin production.

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Variations in streptolysin production in horse and rabbit serum media were noted in a previous publication. In horse serum hemolysin was produced in titratable quantities later in the growth of cultures than in rabbit serum broth but the maximum concentration reached was greater. Unless glucose were present the curve of lysin production corresponded closely to that of growth since hemolysin was found in greater concentration during the period in which the bacteria were multiplying most rapidly. On account of these differences which were characteristic of these sera an attempt was made to discover the responsible factors. The albumen and globulin ratio was modified so that the horse serum contained the same proportions of horse-serum albumen and globulin as were found in rabbit serum, and rabbit serum the same percentages as were present in horse serum. Flasks prepared with 20 per cent. of these modified sera in plain infusion with 0.7 per cent. NaCl, were seeded with equal quantities of a 16-hour culture of hemolytic streptococcus in 20 per cent. horse serum broth. Hemolysin titrations were then made at intervals of an hour with a suspension of horse corpuscles in physiological salt.

The percentages of albumen and globulin in normal rabbit