A STUDY OF ANTIANAPHYLAXIS.*

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Many authors have already made studies of antianaphylaxis produced by the injection of an antigen into the peritoneal cavity of sensitized animals. There has, however, been no experiment on what kind of phenomena would occur in the case of repeating the intravenous injection. Having studied the nature of antianaphylaxis, especially of that produced by repeated injections, I have found the following facts.

1) Influence of passive anaphylaxis upon the active sensitization.

A number of guinea-pigs were divided into two groups, according to their sensibilities to passive anaphylaxis produced by the injection of serum of guinea-pig or rabbit immunized against the horse serum. I have observed in each of the groups the severity of anaphylactic symptoms produced by the reinjection of horse serum, this being given 14 days later, and have found that the passive anaphylaxis exerts no influence upon the active sensitization and also that the reaction to the reinjection was weaker in the guinea-pigs injected with two kinds of antigen (horse and rabbit serum) than in those injected with one (horse serum).

2) The antianaphylaxis produced by the repetition of injection.

In the case of repeating proof-injections at a certain interval in the guinea-pigs, which have been actively sensitized and survived from proof-injection of a sublethal dose, the following facts have been observed. In the case of repeating the injection at an interval of from 10 minutes to 1 hour, the animals which have passed one shock, showed no symptom in a dose less than 3 times that of the first injection, but when the dose was

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increased 4–10 times, the animals all struggled from an attack of severe shock and a few of them fell down to death, and when the animals were injected with more increased dose, say 16 times, all of them died. In cases, where the injections were repeated at an interval of 1–3 days, the animals in the same state as mentioned above showed no anaphylactic reaction to the administration of the same dose as in the first injection, but almost all the animals suffered from anaphylactic shock and in a few of them the injection resulted in death, when the dose was increased 2–3 times. At an interval of 4–8 days, the same dose as in the first injection was enough to kill 33% of the experimented animals. In cases, where the interval was extended from 9 to 19 days, the original dose killed 50% of injected animals and 1.6–3 times the dose caused the death in almost all the animals. In the animals which survived the shock 2 times and 3 times, no symptom has been observed in the case of injecting them the maximal dose of the pre-injected, at an interval of one day. When the interval was allowed to elapse from 2–3 days and an injection of the same dose as above given, most animals showed anaphylactic symptoms and sometimes a few died. By administrating the same dose at an interval of 4–30 days, anaphylactic symptoms were produced in almost all animals and 21% of those which endured the shock 2 times and 12% of those which endured 3 times fell down to death. The anaphylactic symptoms produced in the animals, which survived the shock 4 times or more, by a proof-injection at an interval of 3–40 days were generally slight and almost none of them died from the attack. In the case of injecting the same dose at an interval of 70–160 days, a half of the animals died and at an interval of more than 200 days all of them fell down to death. In short, the duration of antianaphylaxis is extended and its intensity is increased according to repetition of shock.

3) Specificity of antianaphylaxis.

The guinea-pigs, sensitized with two kinds of antigen (horse and rabbit serum) and being in an antianaphylactic state by the repetition of proof-injection with one antigen (horse serum), showed
almost no resistance to the proof-injection of the other (rabbit serum). And the guinea-pigs, which were sensitized passively with the immune serum against two kinds of antigen (horse serum and egg white) and survived the sublethal dose of the one antigen, have shown symptoms similar to those produced in the control animals.

When the immune serum against two kinds of antigen (horse serum and egg white) has been mixed with the one antigen in vitro, the precipitin for the former has diminished while the precipitin for the latter remained as it was, and the sensitizing power of the mixed serum for the mixed antigen has also diminished, but was quite indifferent to the other antigen. From the above facts, I can not recognize the opinions of Bessau, Opitz and Preusse, that in the state of antianaphylaxis there is the loss of sensibility to the so-called anaphylatoxin and also that there is the phenomena of "Fällungs-antianaphylaxie." In other words, antianaphylaxis is strictly specific.

4) Hinderance of the production of anaphylactic symptoms by the free antibody in the circulating blood.

Notwithstanding that the duration of existence of free antibodies in the circulating blood of a highly sensitized guinea-pig seemed to be parallel to that of antianaphylaxis, according to the results of the experiments with a few guinea-pigs, I could find no relation between free antibody and antianaphylaxis in the experiments with a large number of sensitized guinea-pigs, measuring free antibodies and observing the severity of anaphylactic symptoms produced by proof-injections.

In the guinea-pigs, sensitized by injecting horse and rabbit serum as antigens, a measurement has been made with regard to the quantity of antibodies and the severity of anaphylactic symptoms. From this it has been found that the anaphylactic symptoms were severer in those animals, which have a large quantity of antibodies in the circulating blood than in those which have less antibodies.

These facts, contrary to Weil’s opinion, show that the phenomena of antianaphylaxis can not be explained by presence of a large quantity of free antibodies.
5) Neutralization of anaphylactic antibody with antigen in vivo and in vitro.

In the experiments on neutralization of anaphylactic antibody with antigen in vivo and in vitro, I have found that the dose for neutralizing antigen is in an inverse proportion to the lethal dose in the case of proof-injection and also that the power of antigen neutralizing antibody in vivo is 4 times stronger than that in vitro. These results do not agree with those from the experiments made by Weil.

6) Passive sensitization in antianaphylactic guinea-pigs with immune serum from homogeneous and heterogeneous animals.

In spite of injecting serum from the guinea-pig immunized against horse or rabbit serum into guinea-pigs, which are in an antianaphylactic state to horse or rabbit serum by repetition of proof-injection, the passive sensitization could not be produced. On the contrary, with serum from heterogeneous animals (rabbits), the antianaphylactic guinea-pigs have been sensitized to horse serum.

7) Passive sensitization in guinea-pigs which are antianaphylactic to an antigen, by injecting them with a serum from homogeneous animals (guinea-pigs) immunized against other antigen.

In spite of being injected with the serum from homogeneous animals (guinea-pigs) immunized against rabbit or horse serum, the guineapigs, which are in a state of antianaphylaxis against horse or rabbit serum, have remained quite antianaphylactic against horse or rabbit serum as before.

8) Transmission of anaphylactic antibody from mother guinea-pigs to children.

In the children, which were born from a mother, once sensitized with horse serum, severe anaphylactic symptoms were produced by a proof-injection of horse serum, and this sensitiveness in children has remained quite as it was for 40 days after the birth, and then it has begun to diminish. In all the children
from a mother having borne 3 times in the course of 305 days, anaphylactic symptoms were caused by the proof-injection.

From the above experiments, I am of opinion as follows. It is now generally believed that anaphylactic shock appears when a combination of sessile antibodies present in a certain number of sensitized cells with antigens takes place, giving rise to a change in them.

A cell, which is capable of working as a cause of anaphylactic shock when a combination of an antibody with an antigen takes place in it, seems to have a number of antibodies, and may be thought as a sensitized cell. The intensity of sensitization of the cell may probably be proportional to the number of antibodies present in it. When a combination of the antibody with the antigen occurs in a sensitized cell and all the antibodies are neutralized by antigens, it must become a complete desensitized cell. This desensitized cell, different from a sensitized cell, should have no antibody, and also being different from a non-sensitized cell (normal cell), it would not be capable of having any antibody again. When a part of antibodies in a sensitized cell is neutralized by corresponding antigens, it would be desensitized incompletely, and should have both the properties of a sensitized and desensitized cell. But from the experiment above mentioned, it may be said that the desensitized cell must return again to a normal cell in a course of from fifty or sixty to one hundred and fifty or sixty days. It will be worthy of note that the complete sensitized and the desensitized cells can have neither auto-antibodies nor antibodies from homogeneous animals while they can receive antibodies from heterogeneous animals because the antibodies are heterogeneous in character.

When an antigen is injected into a sensitized animal, the antigen combines with the antibody present in the sensitized cell of the animal, and the sensitized cell, in which the combination of the antibody with the antigen has occurred, becomes a desensitized cell. Antianaphylaxis may be thought as a state in an animal whose cells are desensitized. The animals which are completely antianaphylactic must have only desensitized cells,
but practically we can not get such animals. So-called antianaphylactic animals have sensitized, desensitized and normal cells, and if in these animals the number of desensitized cells would increase and that of sensitized cells decrease by repetition of proof-injections, a higher antianaphylaxis may be produced in them. These antianaphylactic animals react to the proof-injection slightly as do weakly sensitized animals do, because both the animals have only a small number of sensitized cells. The antianaphylactic animals, however, react weakly to the proof-injections for a long time (50-150 days), during which time the desensitized cells probably return to normal. When the desensitized cells return to normal, they will again be sensitized with the antibodies which still remain, and again the state of anaphylaxis may set in.

In conclusion, I am of the same opinion as Besredka, Friedberger, Weil, Coca, etc. with respect to the cause of antianaphylaxis produced by the abolishment or diminuation of anaphylactic antibodies, these being neutralized by the combination with antigens. But I have another view as regards the interpretation of desensitization.

抗過敏症ノ研究

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被動性過敏症ノ働性感作＝及ボス影響，試験注射＝反復＝ヨリテ生ジタル抗過敏症，抗過敏症ノ特殊性，遊離抗體ノ過敏症狀發現＝及ボス障害，試験管内及動物體内＝於ケル過敏症抗體ノ中和，抗過敏症もるもっコ＝同種及異種動物免疫血清ヲ以テセル被働性感作，甲抗原＝對シ抗過敏性ナルもるもっコ＝乙抗原ヲ以テ免疫セルもるもっコ血清ヲ以テセル被働性感作及もるもっコ＝於ケル母體ヨリ仔體へノ過敏症抗體ノ移行＝就テ試験シ抗過敏症ノ性質ヲ説明セリ（専詳細＝歯薬調査所研究報告第7號＝於ケ報告スベラ）（自抄）