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Studies on so-called protective ferments VIII. On the mechanism of anaphylaxis and antianaphylaxis.

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As we have reported a little over a year ago,[1] the interaction between an immune serum and its corresponding substratum is followed by a formation of toxic split products. We found that the toxic material originated not from the substratum or antigen, but from the serum itself.[2] These findings threw light on some of the unsettled questions in the theory of anaphylaxis and antianaphylaxis. Experiments conducted with the view of correlating our findings with the accepted views on this subject, suggested a following hypothesis about the nature and mechanism of anaphylaxis.

Blood serum contains normal proteolytic ferments which require special conditions of the medium in order to exhibit their activity. Normally the degree of concentration of colloids in the serum offers an obstacle to the activity of these ferments. In the experiments in vitro it is possible to change the degree of concentration of colloids in the serum, thus diminishing its antitryptic inhibiting power and setting free the ferments.[3]

This activation of normal serum can be accomplished by mechanical adsorption, as in experiments of Plant, Peiper and others, or by the dissolution of some of the serum colloids, as in the experiments of Jobling.[4] In either case the degree of dispersion of remaining colloidal particles is increased and thus ferments are allowed to act.

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[1] Bronfenbrenner, *Pennsylvania State Journal*, 1914, October, p. 20.

[2] Bronfenbrenner, PROC. SOC. EXP. BIOL. AND MED., 1914, XII, p. 7–8; also *Journ. Exp. Med.*, 1915, Vol. XXI, No. 5, p. 480.

[3] Bronfenbrenner, *Journ. Exp. Med.*, 1915, XXI, No. 3, p. 221.

[4] Jobling and Peterson, *Journ. Exp. Med.*, 1914, Vol. XIX, p. 239. Though the authors find it necessary to remove the lipoid in order to activate the enzyme, our own experiments show that the removal of lipoid is not necessary. Mere bubbling of ether vapor through the serum accomplishes the activation.

Our experiments have shown that also the physico-chemical changes following the specific interaction between the antigen and antibody influence the colloidal conditions of the medium in the same manner.[1] Our records show that both stalagmometer and refractometer register the increase of dispersion in the immune serum following the addition of the specific antigen and parallel with it the actual measurements of the antitryptic titer of the serum show a steady diminution of the power of this serum to check the activity of its own proteolytic ferments.[2]

In anaphylaxis the latter process takes place, namely, if a suitable amount of antigen is injected into a sensitized animal, the interaction between the specific antibodies and the antigen produce a physico-chemical change in the serum, followed by a diminution of its antitryptic activity. Once the balance between the tryptic and antitryptic powers of the serum is destroyed, the proteolytic ferments may attack the protein of the serum with the production of toxic split products, and anaphylactic shock follows.[3]

That the mechanism of anaphylaxis rests on the disruption of balance between the tryptic and antitryptic properties of the serum is especially evident from our experiments in which we succeeded in preventing anaphylactic shock in experimental animals by increasing the antitryptic power of their serum at will before subjecting them to shock.[4] In doing so we found that practically any substance which caused the rise in antitryptic titer of the serum of experimental animals, protected them also from the subsequent anaphylactic shock. We found also that all such substances are toxic by themselves if injected in sufficient quantity. The mechanism of this protection seems to be as follows.

The introduction of poisons in quantities not sufficiently large to kill the animal outright is followed by the death of the tissues immediately affected by the poison. With the death of the tissues

[1] Bronfenbrenner, PROC. SOC. EXP. BIOL. AND MED., 1914, XII, p. 4.

[2] Bronfenbrenner, Mitchell and Titus, *Biochemical Bulletin.*

[3] Bronfenbrenner, *Penna. State Med. Journ.*, October, 1914; also *Journ. Exp. Med.*, 1915, Vol. XXI, p. 480. In a current number of the *Journ. of Exp. Med.*, this view of anaphylaxis is corroborated by Jobling, Peterson and Eggstein.

[4] Bronfenbrenner and Schlesinger.

the intra cellular ferments are set free.[1] These ferments possibly with the collaboration of the ferments thrown out from the surrounding fixed cells as well as from blood serum and leucocytes proceed to dispose of the dead material. Some of these split products of protein constituents of digested tissue cells, together with some non-protein constituents (lipoids?) of these cells, exert antagonistic antitryptic action, and retard or stop the activity of proteolytic ferments.

Since, as it was suggested before by us,[2] the specific anaphylactic shock is due to the intoxication of the animal following the liberation of proteolytic enzyme in its blood, it is possible that the preliminary injection of a suitable amount of poison causes the increase of the amount of protein split products in the circulation of the animal and the resulting change in the degree of colloidal dispersion paralyzes the activity of proteolytic ferments which are liberated upon the subsequent introduction of a lethal dose of antigen into a sensitized animal.

The effect of the vaccinating injection of a sublethal dose of antigen into sensitized animals, or of the vaccinating injection of a sublethal dose of anaphylatoxin into normal animals, is evidently due to the same mechanism of partial proteolysis followed by the output of split products acting as antitrypsin and not to the exhaustion of antibody.

Usually the anaphylactic state is taken to be the opposite to the state of immunity. The above theory makes both the active immunity and anaphylaxis a part of the same process. The difference between the two reactions being only in the rapidity and extent of proteolysis induced by the specific combination of antigen with its antibody in vivo.

[1] In the experiments which are to follow we will show the actual changes in the blood and urine following the liberation of ferments during the specific anaphylactic shock, as well as during nonspecific proteolysis due to poisoning.

[2] Bronfenbrenner, *Bioch. Bull.*, March, 1915, p. 87.