

CROONIAN LECTURE.—*The Biological Significance of Anaphylaxis.*

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(Abstract.)

Anaphylaxis was regarded by Richet, who first clearly recognised the phenomenon, as the opposite of immunity or "phylaxis." At an interval of some weeks, after a first dose of any one of a group of poisonous proteins, the animal was found to be apparently much more susceptible to the action of the poison in question. Further investigation has shown that this susceptibility is not connected with the naturally poisonous properties of the substance used, but can be developed in relation to perfectly harmless protein substances, provided they are obtained from a different species and introduced into the system without hydrolytic cleavage. The sensitiveness is highly specific. It discriminates between corresponding substances from different species, between materials from different organs from the same species, and between individual proteins from the same organ. It can be transferred to a normal animal by blood or serum from an anaphylactic animal. In the nature of the substances producing it, in the limits of its specificity, and in the possibility of its transfer by serum from a treated animal, it shows a very suggestive correspondence with the type of immunity associated with "precipitin" formation. A highly precipitating serum from an immunised animal confers anaphylaxis on a normal animal more readily, *i.e.*, in smaller dose, than serum from an animal itself anaphylactic. Nevertheless, the serum from an anaphylactic animal forms no visible precipitate with the antigen, and an animal whose serum has this obvious precipitating quality is not anaphylactic, but immune. Anaphylaxis is not so much the direct opposite of immunity as an anomalous concomitant of a certain phase in its development. An animal rendered anaphylactic to a naturally poisonous protein is immune to the natural poisonous action, but has acquired a new sensitiveness to it as a protein.

The symptoms following injection of the sensitising antigen into an anaphylactic animal are characteristic, not of the substance but of the species exhibiting the reaction. In the guinea-pig the most conspicuous feature is an intense tonus of the plain muscle, which by causing a valve-like closure of the bronchioles produces rapid asphyxiation. In the dog the central feature is a poisoning of the endothelial wall of the capillary blood vessels, especially in the liver, causing a shock-like collapse of the blood-pressure and hæmorrhages into mucous membranes. In the rabbit the heart muscle seems to be

primarily affected. They resemble closely the characteristic types of action, on these same species, of a large class of naturally poisonous proteins, protein cleavage products, and organ extracts, and of the organic base amino-ethyl-glyoxaline (histamine). Blood in clotting acquires toxic properties of a similar type. The complex can be analysed into an action mainly on two tissues—stimulation of plain muscle and poisoning of the vascular endothelium. These two effects appear with different relative prominence in the different species.

Several theories have been put forward to explain the anaphylactic phenomena. It is agreed by all that anaphylaxis is due to the presence of a specific antibody of the precipitin type.

1. It is supposed that the formation of the complex of antigen and antibody in the blood leads to a rapid digestive hydrolysis, with the liberation of poisonous cleavage products.

2. It is supposed that the union of antigen and antibody produces a disturbance in the equilibrium of the blood colloids, initiating pre-coagulation changes and rendering the blood toxic to the tissues.

3. It is supposed that the difference between anaphylaxis and immunity is due to the different distribution of antibody between the cells of the tissues and the blood-plasma. The occurrence of the reaction between antigen and antibody in the tissue cells is regarded as the cause of the anaphylactic symptoms. Evidence in favour of the last hypothesis is afforded by the reaction of isolated plain muscle from (actively or passively) anaphylactic and immune guinea-pigs.

The meaning of the "specificity" of anaphylaxis and immunity is discussed, in the light of the recent work by Dakin and Dudley, which gives the first hint of the difference in molecular pattern between corresponding proteins from different species.

There has been a general tendency to interpret the anaphylactic reaction in terms of the action of poisonous cleavage products of proteins, explaining the symptoms by assuming the formation of the products having this type of action. It is suggested that the true order of interpretation may be in the inverse direction; that more is known of the nature of the change in the cells which results in the anaphylactic shock than of the mode of action of the substances which produce analogous symptoms in the normal animal.

Further study of the anaphylactic reaction may throw light on the action of naturally poisonous protein-derivatives and drugs, and on the intimate physiology of plain muscle fibres and other cells.

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