CRITICAL REVIEW

ASTHMA AND ANAPHYLAXIS.

By CHARLES McNEIL, M.A., M.D., F.R.C.P., Edinburgh.

THERE has been a definite advance in our knowledge of asthma in the last decade, and this advance has been chiefly due to the recognition of a basis of anaphylaxis in at least half the cases of asthma. The association of anaphylaxis with asthma is proved by the positive cutaneous protein reactions obtained in those cases. In this review it is proposed to give a brief account of recent work on experimental anaphylaxis and of the cutaneous tests as applied to asthma, and also to discuss briefly the constitutional factor in asthma.

Experimental Anaphylaxis.—Anaphylaxis is a much abused term at the present time, and has been carelessly used to describe almost any reaction of living tissues to irritation. Before dealing with the relation of anaphylaxis to the clinical condition of asthma, it will be well to examine this peculiar reaction as shown in the exact conditions of animal experiment. Most of our knowledge of anaphylaxis is derived from a study of the guinea-pig sensitised to horse-serum, and to a lesser extent of the dog, cat, and rabbit. But the original classical experiment by C. Richet,[1] who was the first to describe the condition in 1902 and to give it its name, was on the dog by the subcutaneous injection of *congestin*, a highly irritant poison extracted from the tentacles of certain sea-anemones. Most of the later experimental work on the condition has been done on guinea-pigs, dogs and rabbits, with inert animal sera, and especially horse-serum.

In the guinea-pig, the intravenous reinjection of horse-serum, a definite number of days after the primary injection, is followed by immediate severe symptoms and by death in a few seconds, and death has been shown to be due to acute constriction of the bronchial muscles and suffocation. It is a condition of acutely fatal asthma. This experiment is known as the Theobald Smith[2] phenomenon.

Another important experiment was made by Arthus[3] on the rabbit, in which after repeated subcutaneous injections of horse-serum great swelling and even sloughing appeared at the site of reinjection. This is really a positive cutaneous reaction, and is known as the Arthus phenomenon.

These two experiments are very important, for it seems probable that they present the two essential features of the anaphylactic reaction, whether in clinical conditions or in an animal experiment. The first is a tonus or constriction of unstriped muscle; the second is a depressor and vasodilator action on capillary endothelium. Dale[4] brings this out very clearly in his recent Herter lectures, emphasising

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this twofold reaction of living tissues in anaphylaxis. But he also shows that the relative degree of the two reactions is not the same in different animals; that in the guinea-pig the tonus of plain muscle is intense and predominant, especially in the bronchial muscle, while the depressor effect on capillary endothelium is present only in minor degree; while in the dog a general capillary engorgement is the outstanding feature of the anaphylactic reaction, and that a constrictor action upon plain muscle is relatively trivial.

Now in man we have in serum-disease—the symptoms occurring after a second injection of antitoxic sera—conditions approximating to those of the above animal experiments. And it is noteworthy that the phenomena of serum-disease, urticaria, arthritis and fever, indicate rather a toxic action upon capillary endothelium than a constrictor action upon plain muscle. Goodall's[5] observations upon 200 cases of serum-disease confirm this, for he does not mention asthma as one of the symptoms. Further, in that intense type of serum-disease, known as "immediate reaction," there is very severe and general vasomotor depression, shown in the cyanosis, coma, collapse, high fever, and rapid appearance of the rash, and asthma is either not present or is entirely masked by the intense vascular depression. So that in serum-disease—the form of human anaphylaxis most closely resembling that of animal experiments—the reaction in man is more akin to that in the dog, where death takes place from general arterial depletion, than to that in the guinea-pig, where death is due to acute asthma and suffocation.

Clinical Anaphylaxis and Asthma.—If asthma does not occur in man in the definite and limited conditions of experimental anaphylaxis, we have still to give proof of the association of anaphylaxis with asthma as occurring clinically in man, for example in hay-fever, in the various animal asthmas, and in the large group of spasmodic asthmas and bronchial asthmas. In the first two groups, proof is given by the positive cutaneous reactions obtained by applying pollen and the various animal substances to a small skin abrasion. By this procedure, the specific substance is brought into contact with capillary endothelium, and produces in a few minutes a wheal. A positive skin test is in fact the demonstration of the Arthus phenomenon in a mild degree. And in the third group of spasmodic and bronchial asthmas, positive skin reactions to one or more of a great variety of substances have been obtained in at least one-half of the cases. In these various clinical types of asthma, anaphylaxis must be induced under quite different conditions from those in animal experiments: and it is through the mucous membranes of the respiratory and alimentary tracts that the foreign protein substance must enter the body, and produce first sensitisation, and later the anaphylactic reaction.

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Asthma and Anaphylaxis

In a large number of cases of asthma, the clinical history alone will suggest the exciting cause, *e.g.*, incidence of attacks in the hay season, proximity to animals, horses, cats, etc., some special occupation, the onset of symptoms after eating particular foods. If this suggestion is confirmed by a positive cutaneous test with the corresponding substance, the cause of the asthma and its anaphylactic nature have been demonstrated, and an opportunity of specific and radical treatment given.

There now exists a considerable body of published work on cases of asthma investigated and treated by these new methods. The pioneer clinical work was done by Noon [6] and Freeman [7] on hay-fever. In 1916, Cooke and Vander Veer,[8] published a large series of 621 cases of sensitisation, nearly all being cases of hay-fever. More recent papers are those of Goodale,[9] Walker,[10] and Coke.[11] A brief account may be given of Walker's 400 cases of bronchial asthma. Of this number, 191, or almost 50 per cent., gave positive cutaneous reactions; 78 to one or more animal hairs; 68 to food proteins; 33 to bacterial toxins; and 92 to pollens. A good many patients reacted to more than one protein. This frequency of multiple sensitisation in one individual is also shown in Cooke and Vander Veer's paper, where it was present in 42 per cent. of their large series; and it has also been emphasised by Freeman,[12] and Coke. A positive skin reaction is defined by Walker as a wheal not less than 5 millimetres in diameter, developing in from ten to thirty minutes, with a typically irregular periphery; but Freeman points out that the reaction may be delayed, and especially in the bacterial tests. Walker gives special attention to the age of onset, showing that the percentage of positive reactions is much higher under fifteen years than at later ages, and also that the younger the age of incidence, the more likely is the asthma to be a food-protein anaphylaxis.

As to results, Freeman [13] reported, in 1914, on 84 cases of hay-fever treated by specific vaccination, a complete cure or great improvement in 64 per cent. Goodale gives much the same percentage in 123 cases of hay-fever, observed for a period of two years or more, and emphasises the superiority of prophylactic over phylactic treatment. Walker also gives results of specific treatment in 48 cases of horse-asthma, the symptoms being "relieved" in 63 per cent.: while in 34 cases with positive reactions to certain cereal foods, the condition was "relieved" by omission of the offending foods.

There remains that large group (50 per cent.) of cases of asthma where no positive cutaneous reactions are obtained even with a large number of protein test substances. This figure, given by Walker, is accepted by Coke and others. Are these cases of asthma also to be accepted as cases of anaphylaxis, the exciting protein cause being unknown? Coke is inclined to this, as a hypothesis. But Hurst [14]

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in a recent paper has pointed out other possible causes, a reflex stimulation of the bronchial centre in the medulla from irritants and lesions of the nose, bronchi, stomach, and bowels, and even a purely hysterical and emotional condition. In the meantime, it is safer to leave unexplained this large group of asthmas with negative cutaneous reactions.

It is clear, however, that the use of the cutaneous tests, and our interpretation of them as phenomena of anaphylaxis, mark a great advance in our knowledge of asthma, especially in accuracy of diagnosis, but also in efficacy of treatment.

The Constitutional Factor in Asthma.—The modern doctrine of asthma as an anaphylactic reaction has not cleared away all the obscurities of the subject. There is the mysterious influence of heredity, which, in asthma, is an important factor. Cooke and Vander Veer found in their series of 504 cases a positive history of some sensitisation in an ancestor either direct or collateral in 482: and the same thing is shown by Freeman in the family history diagrams published in his last paper.[13] Most authorities are agreed that what is transmitted from parent to child, is not a specific anaphylaxis, but a tendency to develop anaphylaxis to any form of protein. The child acquires an anaphylaxis much more readily than do other children. The age-incidence of asthma is also in favour of the view that there is some constitutional factor at work. John Thomson[15] in an analysis of 100 cases of asthma found the onset in 71 to be in the first five years of life. This constitutional tendency is too difficult and obscure to elucidate in our present knowledge; but the age-incidence and the strong hereditary tendency in asthma make its existence a reasonable conjecture and give it a place with anaphylaxis in the conditions that produce asthma. Auld's[16] successful treatment of asthmatics by peptone—a treatment which is non-specific, but which seems to reduce the constitutional liability to anaphylaxis—seems to point in the same direction of a constitutional factor in asthma.

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