Antigen-antibody Reactions in Broncho-pulmonary Disease

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The 1966 International Congress of Internal Medicine adopted as its theme 'The Integration of Internal Medicine', which set me thinking about whether there exists any quality or activity that can be regarded as the unifying feature of internal medicine. I concluded that the essential feature common to all branches of internal medicine is that they are integrative activities centred on the diverse problems of individual patients. The physician must keep himself aware of current work in all fields of science relevant to clinical problems, perceive and investigate possible practical implications of new additions to knowledge, and integrate them with existing knowledge and with each other to increase his understanding of the phenomena he observes in his patients; for such understanding is the basis both for the cure or alleviation of disease in the individual patient and for the prevention of disease in the community, which are the ends to which his work must be directed.

This integrative activity is strikingly exemplified by certain recent developments in the application of immunology to respiratory diseases. Advances in immunology, both basic and applied, have been correlated with information derived from the standard clinical procedures, radiology, and from clinically applicable tests of pulmonary function that have become available in the past twenty years. Among the results have been the recognition of a pattern of lung disease determined by antigen-antibody reactions in the peripheral gas-exchanging part of the lung and exemplified by 'farmer's lung'; advances towards the understanding of the mechanisms underlying the diverse types of lung disease associated with the common mould *Aspergillus*, which may, like 'farmer's lung', prove to be the type-example of a reaction pattern; and tentative approaches to the role of altered reactivity to tissue components of the body itself in some lung diseases of uncertain cause, and in modifying reactions to inhaled inorganic dusts. In relation to asthma, no spectacular advance has been made recently, but perhaps the way has been made clear for such an advance by the recognition that the disease can best be defined primarily in terms of a disorder of function. This has removed the obstacle

created by attempts to define asthma primarily in immunological terms, which led in some quarters to the unjustified belief that the assumed immunological basis must be present in all cases even though no evidence could be found for it, and in others to unjustified neglect of immunological investigation because in many cases the presumed immunological basis could not be demonstrated.

The first task is to clear the ground by reminding you of the patterns of respiratory dysfunction and of the types of hypersensitivity reaction.

PATTERNS OF RESPIRATORY INSUFFICIENCY

For most clinical purposes, respiratory insufficiency can be analysed into components, which may occur singly or in several recognisable combinations (Scadding, 1966):

Ventilatory Defects
Obstructive: airways obstruction
Non-obstructive: restrictive
hypodynamic

Defects in Gas Transfer or Exchange
Of these, hypodynamic ventilatory defects due to neuro-muscular disease are not relevant to the present discussion, and will not be considered further.

Airways obstruction can usually be detected by clinical methods and confirmed and quantified by spirometry. Widely, variable airways obstruction is the defining characteristic of asthma. A definition of asthma in these terms leaves the way clear for a partial classification in terms of types of antigen-antibody reaction: how far such a classification can be taken will be considered later.

Restrictive ventilatory defects can sometimes be suspected clinically, but usually require spirometry for unequivocal demonstration and measurement. They may be due to such diverse causes as surgical removal or destruction by disease of large amounts of lung, restriction of thoracic movement by a thick pleura, and occupation of space within the thorax by tumours, effusions or gas, but their relevance in the present context is that a restrictive ventilatory defect is part of the pattern of functional disturbance caused by widespread involvement of the peripheral air spaces of the lung in various disease processes. Disease of the latter sort is also characterised by serious disturbance of gas-exchange. The presence of such a disturbance can be suspected in a patient who is dyspnoeic without evidence of airways obstruction, though there may be a restrictive ventilatory defect, who may be observed to have a

high minute ventilation at rest, and certainly on exercise, whose arterial or mixed venous pCO_2 is normal or low, and whose arterial pO_2 is below normal, falling on exercise. More refined laboratory methods are required for detailed analysis and measurement of a gas transfer defect.

TYPES OF HYPERSENSITIVITY REACTION

Antigen-antibody reactions of importance in human disease have been classed into four types (Gell and Coombs, 1963).

Type I. In this type, antibodies present in the blood attach to the surface of tissue cells and react with antigen, causing release of various pharmacologically active substances (histamine, SRS-A, 5HT, acetylcholine, heparin, bradykinin). The skin reacts to minute amounts of the antigen in prick or intradermal tests, with an immediate 'weal and flare' reaction.

Type II, as far as is at present known, is irrelevant to the present discussion. This type, in which antibodies in the blood react with an antigenic component of cells or an antigen or hapten attached to cells, usually in the presence of complement, are of importance in certain haemolytic anaemias, transfusion reactions, and in some drug reactions.

Type III is mediated by precipitating antibody in the blood. Reactions to antigen introduced locally are caused by antigen-antibody precipitates in and around small vessels, leading to reactions of the Arthus type, characterised by vascular changes (oedema, thrombosis, and haemorrhage) and cellular infiltration. Skin test reactions characteristically appear several hours after the test and consist of ill-defined oedematous swelling, contrasting with the immediate 'weal and flare' Type I reaction. Serum sickness is an example of a generalised reaction mediated by precipitating antibody when an excess of antigen combines immediately with antibody as it develops.

Type IV is the well-known tuberculin-type reaction, in which the antibody is carried by lymphocytes and is not demonstrable in the blood serum; skin test reactions consist of localised indurations, maximal at 48 to 72 hours.

ASTHMA

Type I hypersensitivity may be induced by contact with certain organic antigens, and about 10 per cent of people are particularly liable to develop such sensitisation. When these 'atopic' subjects develop asthma, it is generally possible to demonstrate an association with exposure to one or more of the common inhalant allergens, to which prick tests produce immediate 'weal and flare' reactions. Asthma in such subjects tends to appear in childhood or at least in early adult life, to be associated with seasonal allergic rhinitis, and sometimes to follow infantile eczema. Family histories of these illnesses are

often obtainable. Many asthmatics fail to show evidence of this sort of hypersensitivity. In them, the disease develops later in life, perhaps in middle age or later, often with no previous history of the possibly related disorders already mentioned. They often have an eosinophilia in blood and sputum, but the absence of evidence of hypersensitivity, either in skin tests or in bronchial challenge tests, to a wide range of the common inhalant allergens is so striking that it may be regarded almost as a positive feature. This important group of asthmatics is recognisable by both clinical and immunological features. They are often referred to as intrinsic asthmatics, to distinguish them from the extrinsic asthmatics in whom it is known or believed, on good grounds, that Type I hypersensitivity to inhalant allergens is the cause of their paroxysmal increases in airways resistance. That antigen-antibody reactions are concerned in the intrinsic asthmatic is very probable, but their nature remains unknown; they are almost certainly different from those involved in the extrinsic asthmatic. Among patients with polyarteritis nodosa, a small number (e.g. 12 of the 111 reported by Rose and Spencer (1957)) present with asthma as the first manifestation; in these cases the asthma has all the characteristics of the intrinsic type.

EOSINOPHILIC INFILTRATIONS OF THE LUNG

It is becoming increasingly recognised that hypersensitivity to the common mould *Aspergillus*, nearly always the species *fumigatus*, is an important cause of transient pulmonary infiltrations with blood eosinophilia (Hinson *et al.*, 1952). With few exceptions the patient is an asthmatic or is evidently an 'atopic' subject, often with a family history of asthma or hay fever, or a history of hay fever himself. A common story is that he has started to have recurrent episodes of increased wheezing, cough and sputum, sometimes with fever or pleuritic pain; he may have noticed small firm 'plugs' in his sputum; in these episodes rather irregular mottling, generally in one, occasionally in more than one, pulmonary segment may be observed radiographically, different segments being involved in successive episodes. In these cases, blood eosinophil counts of the order of 1000–2000/mm^3 are usual; the 'plugs' consist mainly of inspissated mucus with many eosinophils and a small amount of mycelium, often demonstrable only after special staining; the skin shows an immediate 'weal and flare' reaction to *Aspergillus* antigens, and occasionally a late oedematous reaction; bronchial challenge produces an immediate narrowing of airways with increased wheezy dyspnoea, and in some cases a more prolonged reaction after a delay of six or more hours; precipitins are discoverable by double diffusion in agar gel in about 70 per cent of cases (Pepys *et al.*, 1959; Longbottom and Pepys, 1964); and the infiltrations usually resolve promptly under

corticosteroid suppression. Occasionally, tomograms during an episode will show the 'plugs' *in situ*, generally in the proximal part of a segmental bronchus, and bronchograms after a number of episodes will often show irregular dilatation of segmental bronchi at the sites where these 'plugs' have presumably been lodged. This bronchiectasis has the unusual feature that the part of the bronchial tree peripheral to it shows a normal bronchiolar pattern, in contrast to most sorts of bronchiectasis, in which the dilated bronchi end blindly, their bronchioles having been obliterated, and if the alveoli of the affected part of the lung remain aerated it is through collateral communications at alveolar level with adjacent parts supplied by unaffected bronchi (Scadding, 1967). It seems possible that damage by a Type III reaction at the site of lodgement of the 'plug' containing the source of the antigen is responsible for this bronchiectasis. The consolidation in the obstructed segment is probably an eosinophilic pneumonia. In one of my patients there was histological evidence post mortem to support this view. The exact roles of reaginic and of precipitating antibodies in the causation of this eosinophilic pneumonia remain uncertain.

Eosinophilic infiltrations of similar character may possibly be precipitated in extrinsic asthmatics by some other inhaled antigenic particles, but up to the present the evidence is convincing only for *Aspergillus*. Similar infiltrations may also occur in intrinsic asthmatics. It is hardly surprising that their immunological basis in these patients remains quite obscure; it may be significant that the intrinsic asthma, which is a prodrome to polyarteritis nodosa, is frequently accompanied by eosinophilic infiltrations in the lungs.

HYPERSENSITIVITY REACTIONS IN THE PERIPHERAL GAS-EXCHANGING PART OF THE LUNG

'Farmer's lung' was the first of the syndromes of reaction to particulate antigens in the peripheral gas-exchanging part of the lung to be subjected to correlated immunological and physiological study. Characteristically, affected individuals develop malaise, headache and a feeling of tightness in the chest, but no wheezing, several hours after exposure to dust from mouldy hay. Examination during an episode of this sort may show crepitations at the bases of the lungs, but no rhonchi, and some fever. Fine mottling may be found in a chest radiograph. Histologically, the reaction is a granulomatous one, with a tendency to fibrosis (Dickie and Rankin, 1958). As would be expected from its situation, it interferes with gas exchange and diminishes compliance of the lung, leading to a restrictive ventilatory defect, without airways obstruction (Bishop *et al.*, 1963; Williams, 1963). Mild attacks appear to be self-terminating, but repeated and severe attacks may lead to permanent lung damage. The first clue to the nature of the hypersensitivity reaction was the demon-

stration of precipitins to mouldy hay extracts (Pepys *et al.*, 1962; Koboyashi *et al.*, 1962). Further work has shown that the antigens are derived from certain thermophilic *Actinomycetes* (Pepys *et al.*, 1963; Pepys and Jenkins, 1965). These *Actinomycetes* are the commonest moulds in hay that has overheated in going mouldy, and their spores are about 1 μ in diameter, small enough for them to reach and be deposited in the peripheral part of the broncho-pulmonary tree.

It is now clear that reactions resembling that of 'farmer's lung', in involving principally the gas-exchanging part of the lung and being associated with precipitating antibodies to the relevant antigens, may follow the inhalation of a variety of finely particulate organic matter. Groups who have been shown to be liable to such reactions include pigeon-breeders (Barboriak *et al.*, 1965; Reed *et al.*, 1965; Hargreave *et al.*, 1966), budgerigar fanciers (Hargreave *et al.*, 1966), and patients taking pituitary snuff for diabetes insipidus (Pepys *et al.*, 1966). Certain differences are evident between these groups, both clinically and immunologically. Whereas the farmers generally show no reaginic hypersensitivity, some among the other groups show both immediate Type I and Type III reactions to skin tests with the relevant antigens. While pigeon-fanciers, who tend to be exposed occasionally to high concentrations of dust containing the relevant antigen, often have an episodic clinical history, like the farmers, the budgerigar fanciers tend to develop symptoms insidiously, presumably because they are exposed persistently to small concentrations of antigen, and often present with established lung fibrosis.

The resemblance of the histological pictures of cases of these types, as well as their clinical and radiological aspects, to those of 'cryptogenetic' fibrosing alveolitis (Scadding and Hinson, 1967) must be noted. These include cellular thickening of alveolar walls, large mononuclear and other cells within the alveoli, and variable degrees of lymphoid follicle hyperplasia. On the other hand, the granulomatous element, already noted in the 'farmer's lung' pattern, is not seen in cryptogenetic fibrosing alveolitis. The relationship of the various elements in the histological pattern of 'farmer's lung' to specific antigen-antibody reactions remains a subject for discussion. It is a plausible hypothesis that the features that resemble those of cryptogenetic fibrosing alveolitis may be due to antigen-antibody complexes causing Type III reactions, while the granulomatous reaction may be a modified foreign-body reaction to insoluble particulate matter. Emanuel *et al.* (1966) have reported that in 'maple-bark' disease, associated with inhalation of the spores of *Cryptostroma corticale* and with the presence of precipitins of this mould in the blood, the granulomatous element is prominent, and many spores are demonstrable in the lung.

Finally, I wish to draw your attention to an analogy, which, like all analogies, must not be carried too far, but may be a useful indication of fruitful lines of research. In several respects, cryptogenetic fibrosing alveolitis stands in similar relation to the 'farmer's lung' group of diseases, as do eosinophilic infiltrations in intrinsic asthmatics to those associated with *Aspergillus* hypersensitivity in extrinsic asthmatics. In 'farmer's lung' and in the *Aspergillus* eosinophilic infiltrations of extrinsic asthmatics, we have syndromes of lung disease that can be related to demonstrable types of antigen-antibody reaction, the antigen being contained in inhaled particulate matter. Cryptogenetic fibrosing alveolitis has important similarities to the 'farmer's lung' syndrome in symptomatology, effects on lung function, and even pathology; and eosinophilic infiltrations in intrinsic asthmatics are distinguishable with certainty from the *Aspergillus* type only by the recognition of the asthma as of the intrinsic rather than the extrinsic type and by the absence of specific *Aspergillus* hypersensitivity. In cryptogenetic fibrosing alveolitis and in eosinophilic infiltrations in intrinsic asthmatics we thus find evident resemblances to diseases known to be reactions to external agents to which specific hypersensitivities can be demonstrated. This leads to a strong suspicion that in these two diseases of as yet unknown cause, antigen-antibody reactions of some sort are important. Certain other features of these diseases are compatible with this view, e.g. changes in serum proteins and the suppressive effect of corticosteroids on their active phases. The search for evidence of antigen-antibody reactions and the elucidation of their nature seems the most promising approach to the difficult problem of the aetiology of these diseases.

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