Immunological aspects of asthma

H. E. AMOS
M.B., B.S., Ph.D.

Department of Pathology, University of Cambridge

PROFESSOR SCADDING's definition of asthma (Scadding, 1969) i.e. 'a condition characterized by variable dyspnoea with wheezing and prolonged expiration wholly or partially reversed by bronchodilators', is a clinical definition. It would be premature at this stage to attempt to define asthma in relation to its pathogenesis as this is still not understood. For the purpose of this symposium, however, I would like to present firstly asthma as an immunological disease and secondly, as a condition in which the intrinsic and extrinsic types have the same underlying abnormality.

Evidence for immunological involvement in asthma

The tissue damage seen in the lungs during a paroxysm of dyspnoea are shown at the microscopic level in Fig. 1. It can be seen that the lumen of the small 2-5 mm bronchus is filled with mucus and cell debris. The cellular infiltration consists mainly of eosinophils. Neutrophils are also present and these may be particularly dense if there is a concurrent infection. Goblet cells in the submucosa are increased in number and there are islands of epithelial regeneration. If the disease is long-standing the basement membrane becomes thickened and the smooth

muscle surrounding the bronchi increases in thickness. Oedema and vessel dilatation are also present. Thus there is suggestive evidence in the histopathology of an allergic element to the disease.

Other evidence in favour of an immunological involvement includes the relationship between the induction of an asthmatic attack and unusual environmental antigens like castor bean (Figley & Elrod, 1928), the close seasonal correlation with grass pollens and the evidence afforded by provocation test with aerosol extracts (Lowell & Schiller, 1948).

The hypersensitivity reaction in asthma

The incrimination of immunological mechanisms in asthma implies that in the first instance the patient must become sensitized to the allergen: this phase does not manifest as a clinical disease. Further contact with the allergen produces a hypersensitivity reaction which leads to tissue damage and clinical symptoms. Coombs & Gell (1963) classified the clinical results of hypersensitivity reactions into four types of allergic mechanism. These are illustrated in Fig. 2. Historically asthma has been linked with Type 1. In this reaction a specialized class of antibody is produced which has affinity for certain target cells

FIG. 1. Histology section of the lung from patient dying in status asthmaticus.

FIG. 2. Types of allergic mechanisms underlying hypersensitivity tissue damage. (Reproduced with permission, from *Clinical Aspects of Immunology*, edited by P. G. N. Gell & R. R. A. Coombs, Blackwell Scientific Publications, Oxford.)

The antibodies are termed reagins. When antigen/antibody combination takes place on the surface of the passively sensitized cell, a biochemical sequence is started which leads eventually to the release of histamine and other mediators. Although substances such as histamine, 5-hydroxytryptamine (5-HT), slow reacting substance-A (SRS-A), kinins and prostaglandins can be shown in *in vitro* systems to be released by antigen/antibody interactions, conclusive evidence of their role in atopic diseases is lacking.

Perhaps the most significant advance in relation to Type 1 hypersensitivity is the identification of the reaginic antibody. A serum protein was isolated from the sera of atopic patients and shown to carry reaginic activity (Ishizaka, Ishizaka & Hornbrook, 1966). It was later shown to be an immunoglobulin distinct from the already known classes and designated IgE (Ishizaka, Ishizaka & Terry, 1967). The finding of a myeloma protein (Johansson & Bennich, 1967) which cross-reacted with IgE greatly accelerated the work on its structure and properties. The

molecule was shown to be susceptible to cleavage by the enzymes papain and pepsin and thus to consist of two light and two heavy polypeptide chains (Bennich & Johansson, 1967). Physicochemically IgE has a molecular weight of about 200,000 and a sedimentation coefficient of 8·2S. Metabolic studies by Waldman & Terry (1970) indicate that the antibody has a half-life of 2 days. This would be compatible with the continuous production of antibody which probably occurs in allergic conditions. The serum concentration of IgE in normal individuals is very low. The range has been reported as 0·1–0·7 $\mu\text{g/ml}$ (Johansson, Bennich & Wide, 1968). A recent survey by Rowe & Woods (1970) in which IgE serum levels were measured in asthmatic and normal children did not arrive at a definite correlation between raised IgE levels and the disease state. Many atopic patients had levels of antibody well within the normal range. However, plasma cells producing IgE have been demonstrated in the upper and lower respiratory tract (Ishizaka & Newcomb, 1970) which suggests that the local production of IgE might be a factor in the pathogenesis of allergic hay fever and asthma.

One of the properties of γE antibodies is that they can sensitize homologous species which is a reflection of the affinity of the IgE molecules for the specialized target cells. Such passive sensitization can be blocked by non-antibody γE (Ishizaka, Ishizaka & Borsos, 1961) and by E myeloma proteins (Stanworth *et al.*, 1967). The Fc fragment of the molecule was shown to be responsible for this effect (Stanworth *et al.*, 1968) which means that the structures necessary for skin fixation reside in the Fc piece of the antibody. *In vitro* experiments using an isolated monkey-lung preparation passively sensitized with antibody, showed that anti- γE and its F(ab')_2 dimer brought about the release of histamine and SRS-A. The monomer fragment Fab' did not (Ishizaka *et al.*, 1970). The conclusion drawn from these experiments was that complement is not essential for the reaction, as F(ab')_2 has no complement-fixing activity and that γE antibody is needed to bridge two IgE molecules on the target cells for the induction of the reaction. In other words IgE is divalent. A further important finding which may be very relevant in asthma is that circulating basophils from atopic subjects have IgE on their membranes (Ishizaka, Tomioka & Ishizaka, 1970). The role of basophils in asthma is not clear but it is conceivable that a continuous supply of the cells from the circulation migrating into the local site of action, could potentiate and prolong the atopic symptoms.

Until recently, delayed hypersensitivity was believed to play no part in atopic disease. Reference to Fig. 2 shows that delayed hypersensitivity does not involve serum antibodies. Instead, the tissue damage

is caused by specifically allergized cells reacting with antigen. The usual way to demonstrate the state of delayed hypersensitivity is by a reaction induced in the skin to an intradermal challenge of the antigen. The reaction has a characteristic time-course and well-defined histological features (Boughton & Spector, 1963). Intradermal injection of the antigen in atopic individuals produces the very different wheal and flair which is seen almost immediately upon injection. Thus it appeared that delayed and immediate hypersensitivities could not co-exist to the same allergen in the same individual. The development of *in vitro* techniques for cell-mediated hypersensitivity has led to a reappraisal of this interrelationship. Brostoff & Roitt (1969) using the lymphocyte-transformation test (Oppenheim, Wootstencroft & Gell, 1967) and macrophage-migration inhibition (David Al-Askari & Lawrence, 1964) were able to demonstrate the immunologically specific allergized cells which mediate delayed hypersensitivity in patients with summer hay fever. Furthermore they were able to reproduce a Type 4 skin reaction by injecting the allergen along with an antihistamine. The existence in hay fever and asthma of cells capable of producing Type 4 tissue damage is not reflected in the pathological findings. Histologically the features shown in Fig. 1 do not resemble the granulomatous reaction associated with the delayed hypersensitivity. Brostoff & Roitt (1969) therefore interpreted the presence of the allergized cells in the light of the current concept of cell-cooperation. The lymphocytes involved in delayed hypersensitivity and the lymphocytes involved in antibody production both arise from a common bone-marrow precursor cell but they can be immunologically separated. The former develop an antigenic marker by passage through the thymus and are called T lymphocytes (Reif & Allen, 1964). The B lymphocytes which eventually produce antibody do not pass through the thymus. There is evidence to suggest that in certain circumstances before the B lymphocytes can produce antibody, cooperation from the T lymphocytes is necessary (Miller & Mitchell, 1968). Thus the presence of T lymphocytes in conditions mediated by IgE is not mutually exclusive. Much of the work on cell cooperation is still to be confirmed, but nevertheless it seems that in atopic diseases more than one allergic mechanism is probably involved.

In order to keep a perspective I would like now to broaden my brief slightly and consider asthma as a pattern of bronchial hyperreactivity which can be triggered by a wide range of stimuli. The known findings which need an explanation are the following:

(a) the pathology and physiology of bronchial constriction and the hyperreactivity of the bronchial tissue in asthmatic subjects to the action of histamine,

(b) immunologically why a specialized class of antibody is produced,

(c) eosinophilia and the concept of the 'shock organ',

(d) the close association of asthmatic attacks with respiratory infection,

(e) adrenalin tolerance and the effectiveness of bronchodilator drugs.

The anaphylactic guinea pig upon which the symptomatology of asthma was previously interpreted does not explain many of the above points and is therefore not a good experimental model. A better one is that proposed by Szentivanyi, Fishel & Talmage (1963) i.e. the response in animals to the infection with *Bordetella pertussis*. It has been shown that in such animals the tissues are hyperreactive to histamine (Kind, 1958) and that the hyperreactivity extends to less specific stimuli like temperature (Munoz & Schuchardt, 1957) and respiratory irritants (Fairchild, Bobb & Thompson, 1966). Immunologically, *Bordetella pertussis* has a marked adjuvant effect (Munoz, 1964) and the antibody response includes antibodies of the reaginic type (Mota, 1958). There is also an increase in circulating eosinophils (Tjabbes & De Wied, 1962). In contrast to the hyperreactivity to pharmacological mediators, the animals showed reduced susceptibility to catecholamines (Szentivanyi *et al.*, 1963). It was claimed (Szentivanyi *et al.*, 1963) that the pharmacological hyperreactivity is due to an imbalance of the two adrenergic receptor systems. They showed that if the uptake of peripheral glucose is inhibited by deprivation of normal β -adrenergic activity, then the tissues are more reactive to histamine. On the evidence afforded by the *Bordetella pertussis* mouse, Szentivanyi (1968) proposed that a similar adrenergic imbalance might account for the clinical manifestations of asthma. The main tenets of his hypothesis are that histamine and other mediators, if considered in their physiological role, are the natural chemical organizers of autonomic action. Consequently, non-immunological triggers of asthma would probably still act by utilizing the same mediators. Adjustment to their action requires activation of their natural antagonists—the catecholamines—and the balanced expression of the amines through the two adrenergic effector systems. If as Szentivanyi proposes, a genetic or an acquired block exists on the β side, then α stimulation would be unopposed. In the context of asthma therefore, the bronchial tissue deprived of β -adrenergic stimulation would respond to unopposed α activity by constricting. Fig. 3 shows diagrammatically the major pathways postulated. Current thinking on the β receptor associates it with an enzyme adenylyl cyclase (Szentivanyi, 1968). In the presence of magnesium ions adenylyl cyclase is activated by the catecholamines and catalyses the formation of 3'5'AMP and pyro-

FIG. 3. Scheme outlining the β -adrenergic block hypothesis of the atopic abnormality. The jagged line represents the site of postulated blockage.

phosphate from ATP (Sutherland Robison, 1966; Belleau, 1966). The cyclic nucleotide then functions as an intracellular organizer of amine action. The inactivation of 3'5'AMP is brought about by a second enzyme phosphodiesterase, which can be inhibited by the methylxanthines. Thus these drugs exert their beneficial effect in asthma, by inducing adrenergic action distal to the hypothetical blockage. Time does not permit a more full analysis, but all the points listed earlier are explicable wholly or partially in terms of β -adrenergic blockade. There is also experimental evidence to show that the immunological trigger, that is IgE/antigen interaction producing the release of histamine, works through the accumulation of intracellular cyclic AMP. Lichtenstein & Margolis, 1968 demonstrated that the release of histamine from sensitized leucocytes could be prevented by the catecholamines and indeed by 3'5'AMP itself (Ishizaka & Ishizaka, 1970).

In conclusion therefore it is possible that both the intrinsic and extrinsic types of asthma have the same basic atopic abnormality. By differing in respect to their triggering mechanisms it appears clinically that each has a distinct aetiology.

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