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Edited by Jonathan Brostoff

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The workshop was organized by Professor T. E. Oppé and Professor J. Pepys

Editorial

Any meeting that helps to clarify two central questions in allergy has performed a useful service. First, what defect(s) lead a subject to become atopic; and second, what factors may allow such a child to grow out of this allergic state? Although neither question can be answered fully at the present time, much information is now available that relates pertinently to these topics.

The last question that generated much heat concerned the definition of the word 'atopy'. At an operational level it was agreed that sensitization by natural exposure to allergen, positive immediate skin tests, relevant symptoms and a family history of allergy were the hallmarks of an atopic. But what of the patient with subacute bacterial endocarditis who with treatment gives a single positive skin test to penicillin or the elderly baker with a positive skin test to flour? If one takes a skin test as the sole criterion (and some do), then these patients are indeed atopic. However, most would agree that this was not the classical picture of the atopic state. And again, is atopic eczema, eczema in an atopic or a separate clinical entity? Until the basic underlying abnormality in atopic states which could be a mucosal permeability abnormality or β adrenergic blockade is completely understood, these questions cannot be answered. It is to be hoped that the time will not be far off before they are.

As Editor, my path was smoothed by Mrs A. Moorhouse and Dr C. A. C. Pickering was most helpful in translating the tapes of the discussion onto paper. To both of them my thanks.

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Types of allergic reaction

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Introduction

The term 'allergy' (von Pirquet, 1906) can be summarized as the 'acquired, specific, altered capacity to react'. Each component of the definition has not only immunological, but also well-defined clinical implications. 'Acquired' means that there must have been prior adequate antigenic or allergenic exposure for immunological stimulation. In practice, this means that unnecessary exposure should be minimized to prevent hypersensitivity, in contrast where appropriate, to deliberate exposure for the production of immunity. The most effective applications of the concept of 'allergy' as defined above and of its 'acquired' nature depend upon full knowledge of potential environmental allergens and how these can be avoided or modified, and upon the use of all available methods for the study of their immunological and clinical effects. Identification of the population most at risk requires better understanding of the genetics of allergic sensitization, of how the allergic state arises and the qualitities of allergenic agents.

'Specificity' of allergic reactions describes the physico-chemical relationship between allergenic determinants and the corresponding antibodies. The presence of identical and in some instances of similar determinants in apparently different materials is the basis for cross-reactivity. 'Altered capacity to react' describes the different response elicited by an agent after antibodies have been produced against it. This reaction may be decreased, as for example, to a toxin or infective agent, described as 'immunity' or it may be of an increased nature, described as hypersensitivity. The essential qualities of this altered capacity to react are its accelerated and amplified nature and the smallness of immunological dosage capable of eliciting it. We shall be dealing mainly in this workshop with problems of hypersensitivity.

The form of the altered capacity to react, that is the type of allergic reaction, is determined by the nature of the immunoglobulin antibody or cell-mediated hypersensitivity which is produced. Consequently, different antigens acting through the same class of immunoglobulin produce similar pathological manifestations and depending upon the organ involved, similar clinical manifestations. In the induction of hypersensitivity, however, it is usual for more than one type of allergy to be produced,

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the reaction on re-exposure being influenced by a variety of factors, though tending to show a predominance of one or other type of allergy. These have their particular well-defined characteristics and may not only be present together, but may also be interdependent for their expression. As immunological knowledge advances, continuous re-appraisal and re-assessment is necessary of even the most generally accepted microscopic, histological or clinical forms of allergic reaction.

Types of allergic reaction

The four main types of allergic tissue reaction are classified by Gell & Coombs (1968) as follows: type 1, immediate anaphylactic allergy, mediated by reaginic antibody; type 2 cytotoxic allergy, in which the antibodies are directed against antigens on cells or tissues, or antigens formed there by combination with another antigen or hapten; type 3, Arthus, allergy due to toxic, soluble, complement-fixing complexes of antigen and precipitating antibody; and type 4, delayed allergy of the tuberculin type mediated by sensitized lymphocytes. This classification is useful for its simplification of terminology and avoidance of solecisms, such as the description as 'immediate', both of the rapidly developing wealing, anaphylactic allergy which appears within minutes and is mediated by reaginic, IgE, antibody, and the more slowly developing, Arthus allergy which appears after several hours and is mediated by precipitating antibodies.

Modifications of this classification are now becoming necessary. For example, it is now known that immediate skin test reactions in man can be mediated by an IgG antibody (Parish, 1970) as well as by IgE antibody. In the case of precipitating antibodies it is also now known that in addition to the acute inflammatory reactions caused by soluble immune-complexes, formed in moderate antigen excess, the insoluble complexes, formed in equivalence, which do not fix complement, cause the appearance of epithelioid cell granulomata (Spector & Heesom, 1969). Further reasons for care in the interpretation of reactions are the effects of agents which may act through final common pathways to those of antigen-antibody reactions. For example, type 1 reactions may be mimicked by the effects on mast cells of histamine liberators such as 48/80 and alkaloids, and also by the effects in aspirin sensitive subjects of aspirin, indomethacin, and phenylbutazone. These latter agents inhibit prostaglandin synthesis (Vane, 1971b). It has been shown in tests on sensitized human lung that indomethacin decreases the liberation on challenge of prostaglandins with an accompanying increase in the release of slow-reacting substance which is a potent bronchoconstrictor in man. It is suggested that this may be the mechanism for aspirin induced asthma (Piper & Walker, 1973; Walker, 1973). Agents which activate C3 and perhaps other components of complement by alternate pathways, bypassing the classical C142 sequence, may mimic type 3 reactions. Tissue eosinophilia, a feature of type 1, IgE, reactions and attributable to a small molecular eosinotactic factor liberated in reaginic antibody reactions, may also be produced by a large molecular factor which attracts both eosinophil and neutrophil cells and is liberated in immune-complex reactions (Kay & Austen, 1971).

Types 1 *and* 3 *allergic reactions and their clinical manifestations*

The skin and respiratory tract responses to types 1 and 3 allergic reactions provide readily accessible and reproducible models for their study and may throw light on their effects in other less accessible organs. The latter will be dealt with by other con-

tributions to this workshop, for example, on allergic reactions in the eye by Rice (1973), the nose by Taylor (1973), and the gut by Freier (1973).

Type 1 reactions can be described as 'immediate' and type 3 reactions as 'late'. Where immunological proof of their mechanisms is lacking or has not yet been sought, the descriptions 'immediate' and 'late' are to be preferred. The effects upon these reactions of sodium cromoglycate, corticosteroids and isoprenaline, all important therapeutic agents for respiratory allergic reactions will be discussed and their use as analytical research tools illustrated.

Type 1, *immediate allergy*

As defined by Gell & Coombs (1968) this is 'initiated by allergen or antigen reacting with tissue cells passively sensitized (allergized) by antibody produced elsewhere, leading to the release of pharmacologically active substances', the latter to be discussed by Orange (1973). It is now known that in man, as in experimental animals, there is more than one class of immunoglobulin capable of mediating immediate mast and basophil cell and skin test reactions and which need to be taken into account in interpreting type 1 immediate reactions.

Type 1, *IgE allergy*

The immunoglobulin, IgE, identified by Ishizaka, Ishizaka & Hornbrook (1966) is the heat-labile antibody giving prolonged sensitization and described by Coca & Grove (1925) as atopic reaginic antibody. It is suggested that the term reagin should be reserved for IgE antibody, the ready production of which is a feature of atopic subjects. It is further described as long-term or long-latency homocytotropic antibody and it owes its biological and clinical importance to its affinity for basophil and mast cells to which it becomes firmly attached by its Fc, footpiece, portion for periods of weeks. It is present in minute amounts in the serum. Serological methods for estimating total and specific IgE antibody will be discussed by Wide (1973).

There are about 30–40,000 IgE molecules per basophil cell with a maximum of 100,000 (Ishizaka & Ishizaka, 1973). IgE antibody is now known to be divalent (Ishizaka & Ishizaka, 1973) and it is the bridging of two antibody molecules on the surface of the basophil or mast cell which triggers the rapid release of histamine and other tissue mediators. These are responsible for the immediate and amplified nature of the reaction elicited. Blockade of the beta-adrenergic 'receptors' on the cells potentiates this reaction and it is thought that this may also be a feature of atopic subjects (Szentivanyi, 1971). Conversely, stimulation of the β-receptors with adrenergic drugs results in increased adenyl-cyclase activity and an increase of cyclic-AMP in the cell, which blocks the liberation of histamine (Lichtenstein & Bourne, 1971). Theophylline derivatives have a similar effect attributed to inhibition of phosphodiesterase which breaks down cyclic AMP. Sodium cromoglycate permits the allergen/IgE reaction to take place on the mast cell surface but inhibits the release of the tissue mediators. Its mode of action is unknown.

Production of IgE antibody

The lymphoid tissues in which IgE is produced lie mainly in the mucosal membranes of the respiratory and gastro-intestinal tract, which are the portals of entry for the common allergens encountered in ordinary life. IgE does not cross the placenta and is

present in small amounts in the newborn. *In vitro* synthesis of IgE by tissues from an 11-week-old foetus is reported by Miller, Hirvonen & Gitlin (1973). Specific IgE antibody has been reported in neonates against penicillin (Levin, Attman & Sela, 1970), and against allergens different from those to which the mother was sensitive (Kaufman, 1971). Evidence of an immune response gene in the HLA7 locus for the production of IgE antibody has been reported by Goodfriend, Laskoff & Marsh (1973) and will be discussed further by Levine (1973).

The production of reaginic antibody in already sensitized animals can be potentiated by parasitic infestations (Jarrett & Stewart, 1972) and by injection of *B. pertussis* (Reed *et al.*, 1972).

Atopy and IgE antibody production

The classification of subjects according to atopic status has important immunological and clinical implications. The concept of atopy, for which a common usage is desirable, had its origins in the report by Cooke & Vander Veer (1916) on 'human protein hypersensitiveness'. They distinguished the subjects with often multiple 'natural' hypersensitivity from those sensitized 'artificially' by injection. Their large series of patients had hay fever and asthma, commonly associated with infantile eczema which was regarded separately, and there was a common family history of similar disorders which they calculated would affect about 10% of the population. The term 'atopy' was introduced by Coca (1923) to describe these patients with hay fever and asthma. The criteria he suggested for atopy were; that it could be caused by non-precipitinogenic as well as precipitinogenic substances; that it could be benefitted by desensitization; and that it was confined to man and was different from anaphylaxis. It is seldom appreciated that yet another of his criteria was that atopy could not be passively transferred by the serum of affected subjects. In 1925, however, Coca & Grove reported that atopic (heat-labile) reagins were present in sensitive subjects, which could passively transfer the specific sensitivity, but they did not regard these as antibodies. They claimed that there was no evidence that they resulted from immunological stimulation, hence their description as reagins, by analogy with the Wasserman reagin. These findings did not however lead Coca to amend his original criteria for atopy until later.

Differences in usage of the term have arisen because some workers following Coca use it to describe the clinical features of rhinitis and asthma, whether or not atopic hypersensitivity is demonstrable; others use it to describe the immunological status of subjects who produce reaginic (IgE) antibody readily, and yet others use it for a combination of both clinical and immunological features. The presence of long lasting production of reaginic antibody and of genetic factors responsible for this in experimental animals (Levine, 1973) means that the immunological responses of atopy are not confined to man. Anaphylaxis in man is also mediated by this antibody. The main remaining criteria for atopy according to Coca (1923) are therefore the clinical manifestations of hay fever and asthma, but asthma and rhinitis often occur without any demonstrable evidence of the production of reaginic antibody. On the other hand, IgE antibody may be present without obvious clinical manifestations. It is for these reasons that it is suggested that the term 'reagin' should be confined to IgE antibody, and that the capacity to produce this antibody readily should be taken as the criterion for 'atopy'. This immunological description does not carry clinical implications. It serves to identify the polar group in the population who develop IgE antibody in response to the limited exposures to otherwise innocuous allergens in the environment.

Factors influencing the development of atopic sensitivity

Atopic subjects develop type 1 allergy more readily than non-atopic subjects in response to intranasal administration of polysaccharide and protein substances whereas both groups respond similarly to their injection (Leskowitz, Salvaggio & Schwartz, 1972). Among the explanations proposed for these differences are increased permeability of the mucosal membranes in the atopics, the portal of entry of environmental allergens. Absence or deficiency of secretory IgA in atopic subjects, which will be discussed later may be responsible or a contributory factor (Taylor, 1973; Salvaggio *et al.*, 1973). Little is known about chemical or other features of allergens which might favour IgE

Table 1. Distribution of 1000 asthmatic patients including ages of presentation at hospital and atopic status estimated by Prick Tests with twenty-one common allergens and classified into reactors to 0, 1, 2, or 3 or more

Age of presentation	Atopic status				Total
	0	1	2	3 or more reactions	
0–9	20 (12%)	22 (13%)	19 (12%)	97 (63%)	158
10–19	16 (8%)	23 (11%)	33 (16%)	136 (65%)	208
20–29	32 (13%)	35 (15%)	35 (15%)	138 (56%)	240
30–39	38 (24%)	18 (11%)	19 (12%)	83 (52%)	158
40–49	42 (34%)	24 (20%)	14 (12%)	41 (33%)	121
50–59	47 (59%)	11 (16%)	6 (8%)	11 (16%)	75
60+	28 (70%)	3 (7%)	0 (0%)	9 (23%)	40
TOTAL	223	136	126	515	1000

Males and Females. Percentages to be read horizontally.

antibody production, though Berrens (1971) suggests that a common feature is the presence of lysine-sugar determinants. It would seem that minor components, usually present in small amounts in antigenic mixtures, are important. It is probable that differing associations of these and other factors all play a part in inducing IgE antibody production.

Atopic status

The atopic immunological status can be assessed by the reactions to prick tests with a battery of common allergens relevant to the subject's environment. There is a good correlation between the immediate, wealing reactions and the presence of specific IgE antibodies in the serum (Stenius *et al.*, 1971). The levels of total and specific IgE antibodies have shown no correlation with the age of onset, severity or duration of the clinical manifestations (Stenius *et al.*, 1972), suggesting that IgE antibody alone, however important it may be in determining these manifestations, is not the sole mechanism responsible. The possible, though limited, participation of IgG antibodies (Parish, 1970) in the production of the skin test reactions has now also to be considered.

Table 1 shows that the higher the atopic status, the earlier the age of presentation at hospital. Table 2 shows that the earlier the age of onset of asthma the greater the incidence of multiple skin reactions. The proportion of negative reactors, that is of

'non-atopic' subjects, increases with increasing age of onset of the asthma. Table 3 shows that the higher the atopic status, the more common the presence of hay fever, perennial rhinitis and infantile eczema in the subjects. Infantile eczema is associated with the highest proportion of multiple reactions and is a 'stigma' of subjects with a high or potentially high atopic status, even though there is no evidence that IgE antibody plays a part in the production of this obscure skin disorder.

The familial incidence of the disorders associated with atopy is controversial.

Table 2. Distribution of 978 asthmatics: age of onset in relation to atopic status estimated by Prick Tests with twenty-one common allergens and classified into reactors to 0, 1, 2, or 3 or more

Age of onset	Atopic status				Total
	0	1	2	3 or more reactions	
0–9	36 (8%)	51 (11%)	63 (13%)	319 (68%)	469
10–19	15 (10%)	20 (14%)	23 (16%)	88 (60%)	146
20–29	41 (30%)	29 (22%)	11 (8%)	54 (40%)	135
30–39	48 (44%)	16 (14%)	15 (13%)	33 (29%)	112
40–49	36 (57%)	13 (21%)	6 (10%)	8 (13%)	63
50–59	26 (66%)	5 (13%)	3 (8%)	5 (13%)	39
60+	11 (79%)	2 (14%)	— —	1 (7%)	14

Percentages to be read horizontally.

Table 4 shows that if the families are taken as units there is no significant correlation of the presence in them of asthma, hay fever or infantile eczema with the subjects grouped according to atopic status. Table 5 shows, however, that highly significant correlations are present if the total numbers of first degree relatives are examined in relation to the groups of subjects classified according to atopic status. The higher the atopic status of the group, the higher the incidence of hay fever and infantile eczema in the first degree relatives. These correlations are evident when the subjects are

Table 3. The incidence and distribution of hay fever, perennial rhinitis and eczema in 1000 asthmatics according to their atopic status, estimated by Prick Tests with twenty-one common allergens and classified into reactors to 0, 1, 2, or 3 or more

	Atopic status			
	0	1	2	3 or more reactions
Asthma	223	136	126	515
Hay fever	18 (7·7%)	39 (30%)	43 (34%)	284 (55%)
Perennial rhinitis	108 (48%)	110 (78%)	92 (73%)	434 (85%)
Eczema	17 (7·3%)	24 (17%)	19 (15%)	174 (34%)

Percentages to be read vertically.

Table 4. Incidence of allergic disorders in families as units. Total number of families with positive family history of asthma or hay fever or infantile eczema according to the atopic status of the patients estimated by Prick Tests with twenty-one common allergens and classified into reactors to 0, 1, 2, or 3 or more. Regression trends in terms of atopic status 0, 1, 2, or 3 or more reactions within each age group

	χ^2	P
0–9	1·428	n.s.
10–19	0·945	n.s.
20–29	2·664	0·1
30–39	2·606	0·1
40–49	0·631	n.s.
50–59	0·030	n.s.
60+	numbers too small	

n.s., not significant.

examined in terms of age of onset and atopic status, the most significant correlations being shown in the subjects with the earlier ages of onset. When the incidence of asthma in the first degree relatives was examined in relation to age of onset and atopic status of the subject, no significant correlations were found, suggesting that the asthma is not inherited in exactly the same way as hay fever and infantile eczema which have more obvious relationships to the atopic state.

Table 5. Incidence of allergic disorders in parents and 1st degree sibs according to the atopic status of the patients estimated by prick tests with twenty-one common allergens and classified into reactors to 0, 1, 2, or 3 or more. Regression trends in terms of atopic status 0, 1, 2, 3, or more reactions within each age group and finally for total of groups—all ages

	Probability of χ^2-test of trend (1 d.f.)			
Patients	Parents etc. with a positive history of asthma, hay fever or infantile eczema	History of asthma	History of hay fever	History of eczema
Age of onset				
0–9	n.s.	n.s.	0·009	0·027
10–19	0·0003	0·048	0·023	0·022
20–29	0·0003	n.s.	0·015	0·023
30–39	n.s.	n.s.	n.s.	n.s.
40–49	0·021	n.s.	0·0095	0·083
50–59*	n.s.	n.s.	n.s.	n.s.
All ages	>0·0001	>0·0001	>0·0001	>0·0001

* Age group 60–69 not tested for significance as numbers too small.

A highly significant correlation was however found between the presence of asthma in all of the subjects put together and classified according to atopic status and its presence in the total of all of their first-degree relatives. This suggests that the asthma tendency is inherited in its own right, but is more frequently manifest the higher the atopic status of the subject. These findings correspond with the conclusions of Schwartz (1952.)

Immediate allergic reactions

Immediate allergic reactions are mediated predominantly in man by reaginic IgE antibodies. The reaction develops rapidly, is maximal at about 10–15 min and lasts for

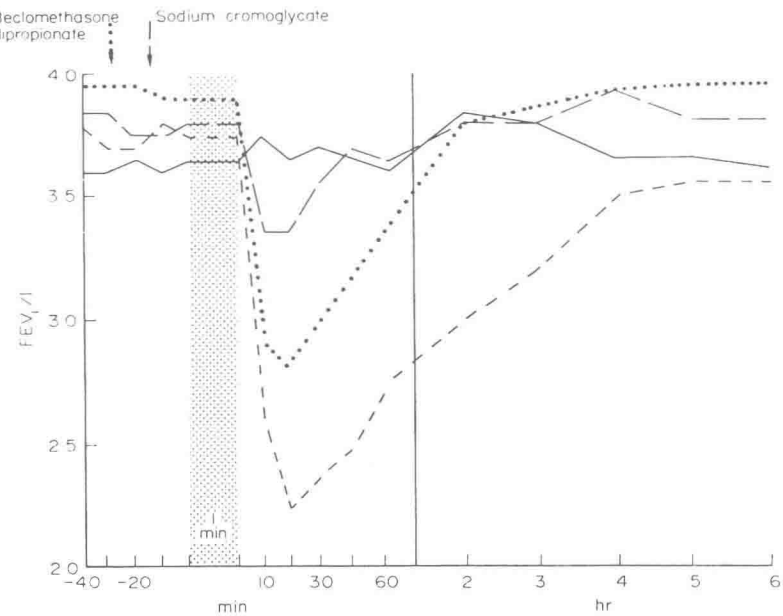

Fig. 2. Type 1 immediate asthmatic reaction to inhalation test with extract of *D. farinae*, showing inhibition of reaction by inhalation of sodium cromoglycate and absence of inhibition by beclomethasone dipropionate. ——, control. Carbol saline inhalation showing no reaction; – – –. Inhalation of *D. farinae* extract showing immediate reaction; · · · ·. Pretreatment with 200 μg beclomethasone followed by inhalation of *D. farinae* extract; —— ——. Pretreatment with 20 mg sodium cromoglycate followed by inhalation of *D. farinae* extract. Stippled area = challenge.

about 1½–2 hr. The skin reaction (Fig. 1) consists of itching, erythema and wealing, and is accompanied by a local eosinophil cell infiltration. It is inhibited partially or completely by antihistamine drugs but is little, if at all, affected by corticosteroid drugs. Nasal, conjunctival and bronchial reactions to clinical exposure or provocation tests are analogous to the skin test reaction in speed of appearance and duration. Figure 2 illustrates the typical immediate paroxysmal asthmatic reaction to provocation test with an inhaled allergen, an extract of *Dermatophagoides farinae* and Fig. 3 to an ingested allergen, an alcoholic beverage to which the subject was sensitive. These reactions were inhibited by the inhalation of sodium cromoglycate prior to the challenge. This agent permits the combination of allergen and IgE antibody on the surface of the mast cell, but blocks the release of histamine and other tissue mediators, and therefore the tissue and clinical reactions. Corticosteroids given systemically or, as shown in Figs. 2 and 3, by inhalation do not inhibit the immediate asthmatic reactions.

A wide variety of inhaled chemical dusts, vapours and fumes can also provoke immediate asthmatic reactions which are inhibited by sodium cromoglycate but not by corticosteroids (Pepys, 1973). The similarities of these reactions to the type 1, IgE mediated asthmatic reactions to common allergens suggest that the chemical agents may be producing their effects in the same way. Until the immunological mechanisms have been demonstrated, it is preferable however, to describe the asthmatic reaction as 'immediate' without any commitment as to mechanism.

Immediate nasal reactions to provocation tests can also be inhibited by pre-treatment with sodium cromoglycate (Orie *et al.*, 1970; Taylor & Shivalkar, 1972), as may conjunctival tests. Pre-treatment with sodium cromoglycate inhibits the immediate asthmatic reaction to exercise particularly in atopic subjects (Silverman & Turner-Warwick, 1972), whilst corticosteroids do not. Sodium cromoglycate also inhibits the immediate asthmatic reaction to cold (Breslin & Pepys, in preparation).

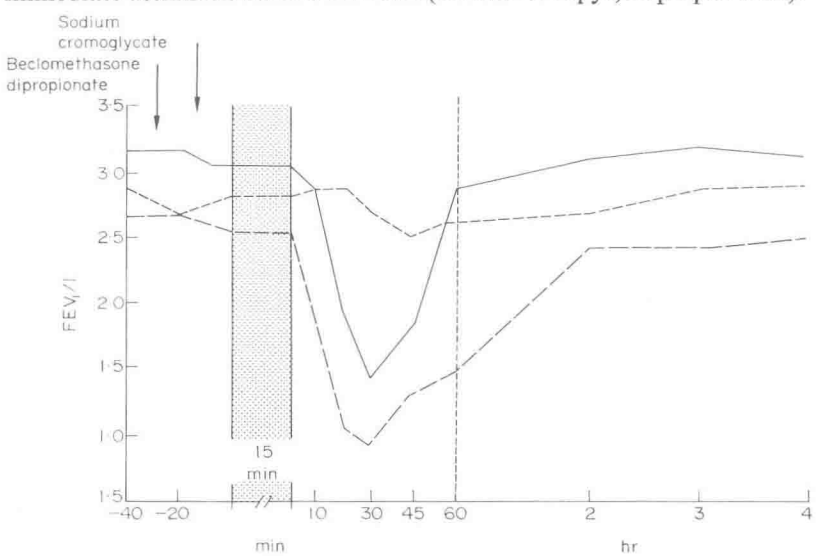

Fig. 3. Type 1 immediate asthmatic reaction to ingestion of white wine, showing inhibition of reaction by sodium cromoglycate and absence of inhibition by inhalation of beclomethasone dipropionate. —, pretreatment c̄ lactose then oral ingestion 95 ml white wine; – – –, pretreatment c̄ 20 mg sodium cromoglycate then oral ingestion 95 ml white wine; — —, pretreatment c̄ beclomethasone then oral ingestion 180 ml white wine. Stippled area = challenge. (Pepys *et al.*, 1974).

The question is whether non-specific factors are responsible in themselves for clinical reactions or whether their effects are enhanced by immunological priming of mast cells. Evidence in favour of the latter is shown by the correlation between the sizes of the weals produced by skin tests with 48/80 and the levels of total IgE (Stenius *et al.*, 1971) and by the observations that sensitized guinea-pig and human lung liberate more tissue mediators in response to non-specific stimuli than non-sensitized lung (Vane, 1971a; Piper & Walker, 1973; Walker, 1973). Sodium cromoglycate can however also inhibit the effects of non-specific agents on mast cells (Cox, 1970; Marshall; 1972).

Immediate, type 1, *IgG mediated reactions*

The presence in experimental animals of short-term, heat-stable, homocytotropic antibody as well as long-term, heat-labile, homocytotropic antibody has been known for some time. Sodium cromoglycate inhibits the release of tissue mediators from

mast-cell reactions mediated by both types of antibody (Orr, Gwilliam & Cox, 1971). The amount of histamine liberated by short-term antibody reactions is far less than by long-term antibody reactions. It is likely, therefore, to be less effective in provoking acute immediate reactions. It is not known to what sub-class or classes of IgG it belongs, nor what immunopathological role it is playing. It may, like IgE antibody, provide the introductory, immediate, reaction, which precedes the development of type 3 reactions. Its possible presence has to be considered in assessing immediate skin test reactions, particularly in subjects regarded as non-atopic. It has also been found together with IgE antibody in some atopic subjects (Parish & Pepys, personal communication).

Type 3, *Arthus immune-complex reactions*

Precipitating antibodies are common in man, providing immunological evidence of exposure to the particular allergen. Their immunopathological role is determined by the relative amounts of antigen and antibody. In moderate antigen excess soluble, toxic, immune-complexes are formed which fix and activate C3 component of complement. These attract and are ingested by neutrophil polymorphonuclear cells which are destroyed, liberating their lysosomes into the extracellular tissues. Skin biopsies of type 3 reactions show perivascular particles, presumably immune-complex aggregates, which stain for the presence of IgG, IgM and IgA immunoglobulins and for beta-1-C component of complement (Fig. 5). They are present in the vascular endothelium and lie freely in the perivascular tissues, and are also present in mononuclear cells, which are a characteristic of type 3 reactions (Pepys *et al.*, 1968). In severe reactions fibrinoid vascular necrosis may be present. Corticosteroids have a protective effect on the lysosomes (Weissman & Thomas, 1962), which may be one of the mechanisms whereby they exert their potent inhibitory effect on type 3 reactions.

The type 3 skin test reaction (Fig. 4) develops after several hours and is usually preceded by an immediate reaction which resolves within about 2 hr. This introductory immediate reaction is important in the vascular deposition of immune complexes (Cochrane, 1971), and in the production of type 3 reactions in experimental animals (Bier *et al.*, 1968) and in man (Pepys, 1973). The late slowly developing, type 3 reaction is maximal at about 5–7 hr and lasts for about 24–36 hr. It is large, oedematous, poorly defined, pale or erythematous and may have a small area of central induration, being evidence of tissue destruction.

In atopic subjects giving type 3 reactions, the presence of IgE antibody provides the introductory immediate reaction. Bronchial tests in such subjects elicit dual asthmatic reactions consisting of the typical, immediate, paroxysmal asthmatic reaction lasting for about 2 hr, followed by a late reaction coming on after several hours. The late reaction develops slowly, becoming gradually more severe and is maximal usually at about 5–7 hr and resolves within 24–36 hr (Fig. 6). The late asthmatic reaction may be accompanied by fever, myalgia and malaise and by a polymorphonuclear neutrophil leucocytosis. The two forms of asthma differ in their presentation. The immediate reaction is accompanied by the rapid appearance of tightness of the chest and wheezing, whereas in the late reaction even larger falls in the FEV_1 may not be accompanied by these features and the patient may become aware of the bronchial reaction only when it has become severe. Inhaled bronchodilators usually reverse the immediate reaction completely, whereas the late reaction is reversed only partially or temporarily. As the bronchial tests simulate ordinary clinical exposure, it is possible that following