

EFFECTS OF DISODIUM CROMOGLYCATE AND BECLOMETHASONE DIPROPIONATE ON ASTHMATIC REACTIONS TO BRONCHIAL PROVOCATION TESTS

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Analysis of the patterns of asthmatic reactions, their mechanisms and the effects upon them of therapeutic agents such as disodium cromoglycate (Intal, Lomudal, cromolyn sodium), and corticosteroids given systemically or by inhalation in the form of beclomethasone dipropionate (Becotide), is made possible by bronchial provocation tests carried out under controlled conditions. The main patterns of asthmatic reaction so elicited are "immediate" reactions, "late" reactions, and dual reactions, in which both immediate and late reactions occur. The features of these reactions are shown in Table 1 (9). The immediate reaction to the inhalation of aqueous aerosols and common allergens, such as grass pollen, *Dermaphagoides* spp. extracts and house dust, or to ingested allergens, such as alcoholic beverages, is compatible with and corresponds well with Type I, IgE-mediated allergic reactions. The "late" asthmatic reaction to these and other allergens, such as avian serum proteins, is compatible with and corresponds well with Type III, immune-complex reactions. Dual asthmatic reactions to such allergens are compatible with the presence together of Type I, IgE-mediated and Type III reactions. However, adequate supporting information is not available on the apparently identical patterns of reaction elicited by chemical dusts, vapours and fumes tested by occupational-type exposures to the actual materials involved. Because of this and the more recent questioning of the mech-

TABLE 1

Overall Features of Asthmatic Reactions in Bronchial Provocation Tests.

Immediate reactions	Late reactions	
Acute, sharp, rapid fall in FEV ₁	Slowly developing, progressively severe	
Clinically readily evident, subjectively and objectively	Often not obvious clinically except on exertion, until fully developed when	
Tightness of chest, dyspnoea and wheezing	dyspnoea and wheezing appear	
<i>Onset of reaction</i>		
10-20 min	(A) Approx. 4-8 hr (B) Approx. 1-2 hr	
<i>Maximum fall in FEV₁</i>		
10-20 min	(A) 8 hr	(B) 3-4 hr
<i>Duration</i>		
1-2 hr	(A) Approx. 24-96 hr (B) 3-4 hr	
<i>Systemic reactions</i>		
Usually none	Malaise, myalgia, fever may be present	
<i>WBC</i>		
Little or no change	Leucocytosis often present especially with systemic reactions	
<i>Eosinophilia</i>		
Blood 0 to + or ++	May be increased 0 to + or ++	
<i>Reversibility by isoprenaline inhalation</i>		
Readily and completely or almost completely reversible	Usually poorly or only temporarily reversible	
<i>Reaction inhibited by</i>		
Inhalation pre-test of: sodium cromoglycate isoprenaline	Systemic or inhaled corticosteroids	
No inhibition by systemic or inhaled corticosteroids	Inhalation of sodium cromoglycate	

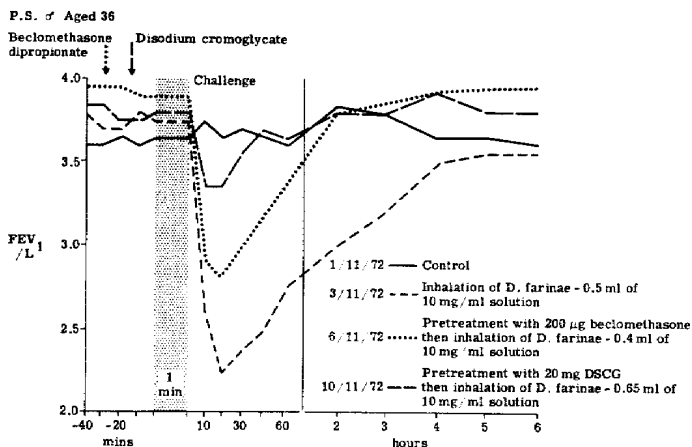


Fig. 1.

Immediate asthmatic reaction to *D. farinae* extract. Inhibited by disodium cromoglycate and not by beclomethasone dipropionate.

anisms of late reactions to common allergens (5), it is in general preferable to describe the asthmatic reactions according to their clinical characteristics, with the addition of the appropriate immunopathological description where appropriate.

Immediate Asthmatic Reactions

Fig. 1 shows the typical immediate asthmatic reaction to a *D. farinae* extract in a house-dust sensitive subject giving immediate wealing reactions on skin testing. The reaction is inhibited by pre-treatment with Lomudal but not by beclomethasone dipropionate (10).

Fig. 2 shows that Lomudal inhibits the immediate reaction to the ingestion of a white wine to which the subject was sensitive, whereas beclomethasone dipropionate had no effect.

Fig. 3 shows that the asthmatic reaction to another white wine in another patient was also inhibited by Lomudal and

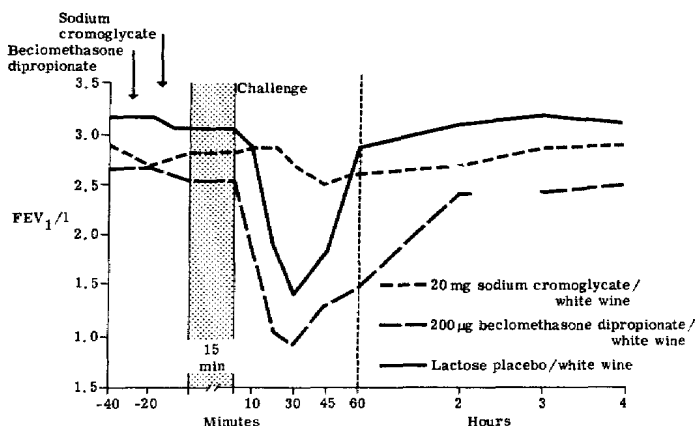


Fig. 2.

Immediate asthmatic reaction. Ingestion of 95 ml of white wine. Effect of pre-treatment with 20 mg disodium cromoglycate and 200 µg beclomethasone dipropionate. --- 20 mg disodium cromoglycate/white wine; — 200 µg beclomethasone dipropionate white wine; — lactose placebo/white wine; stippled area, challenge.

that the reaction was not due to the ethyl alcohol content of the wine (1).

Fig. 4 shows the typical immediate asthmatic reaction following occupational-type exposure to a complex salt of platinum to which the subject was sensitive and which gave immediate wealing reactions on prick testing in very low concentrations. The immediate reaction, like those to the common allergens, was inhibited by Lomudal (13).

Fig. 5 shows a typical immediate asthmatic reaction following occupational-type exposure to tolylene di-isocyanate, which was inhibited by Lomudal (15).

Thus, the immediate reactions to these various and very different agents had the same characteristics and were inhibited in a similar fashion by Lomudal, and not, where so tested, by beclomethasone dipropionate.

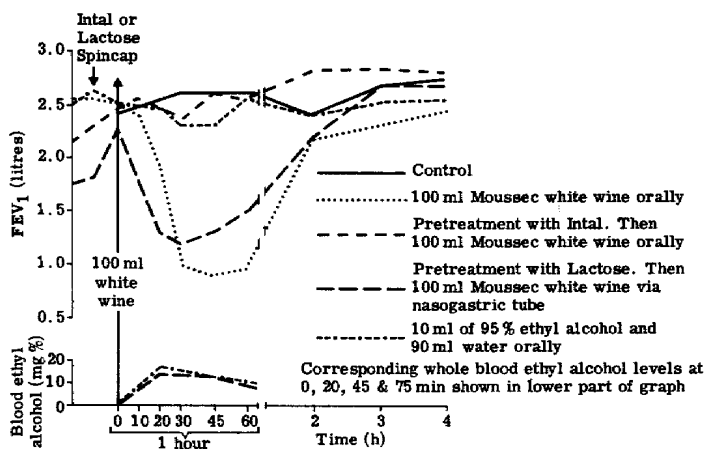


Fig. 3.

Oral challenge with white wine with and without pre-treatment with Lomudal and challenge via nasogastric tube with white wine following pre-treatment with lactose spincap. Oral challenge with ethyl alcohol-water mixture also shown. Corresponding whole blood ethyl alcohol levels at 0, 20, 45 and 75 min shown in lower part of graph.

"Late" Asthmatic Reactions

Fig. 6 shows a late asthmatic reaction in a non-atopic subject with precipitins, but no evidence of Type I, IgE allergy to an extract of *A. clavatus*. It is noteworthy that the late reaction was only temporarily reversed by inhalation of isoprenaline.

Fig. 7 shows a late asthmatic reaction in a non-atopic bird fancier with precipitins but no Type I, IgE sensitivity to pigeon serum proteins. The late reaction is inhibited by Lomudal (11).

Fig. 8 shows a late asthmatic reaction to occupational-type exposure to piperazine dihydrochloride in a subject engaged in its manufacture. In this case Lomudal had to be given before the challenge and 4 hours afterwards in order for it to exert an inhibitory effect (14).

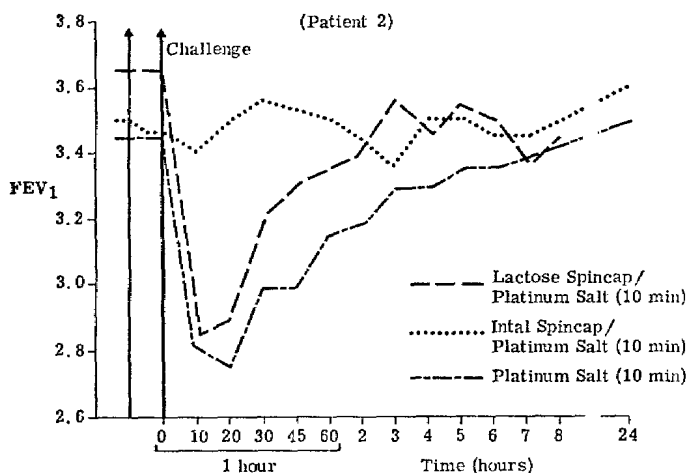


Fig. 4.

"Inhalation" tests with ammonium hexachlorplatinat with and without pretreatment with Lomudal and placebo (lactose).

Patient L.E.

OCCUPATIONAL EXPOSURE TO ISOCYANATE

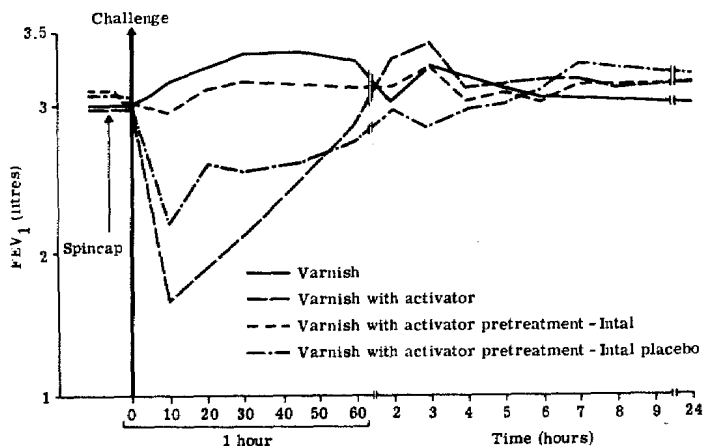


Fig. 5.

Reproducible immediate asthmatic reactions to varnish and "TDI activator" and inhibition by Lomudal.

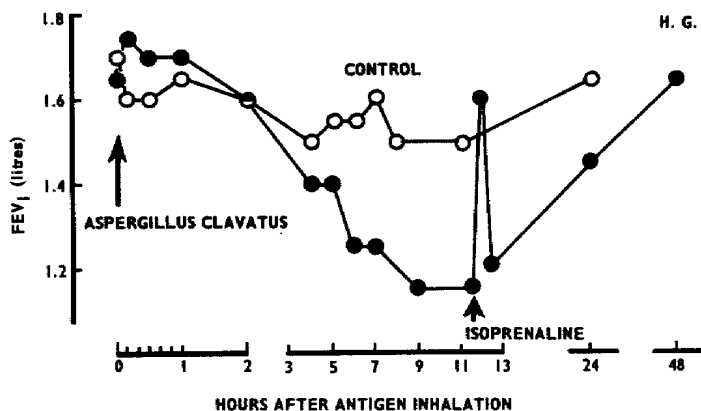


Fig. 6.

Late asthmatic reaction to inhalation of an aerosol of an extract of *Aspergillus clavatus* in a brewer working with barley and malt.

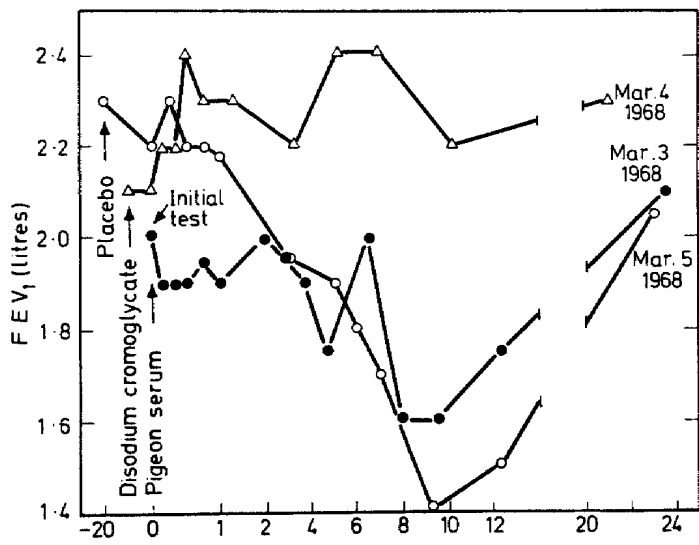


Fig. 7.

Extrinsic non-atopic asthma. Type III, "late" asthmatic reaction to pigeon serum. Inhibition of reaction by disodium cromoglycate but not by lactose placebo.

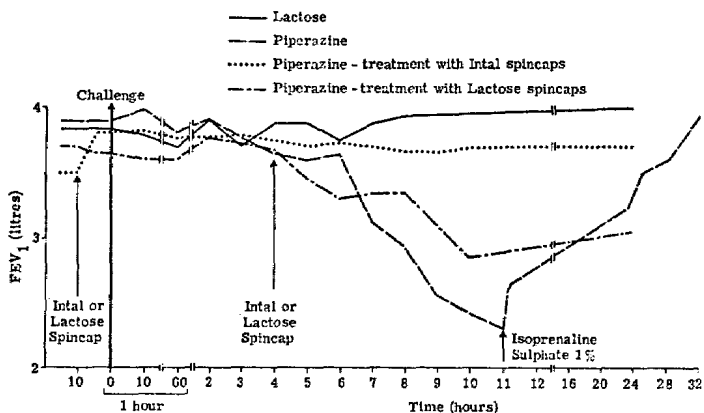


Fig. 8.

"Inhalation" tests with piperazine dihydrochloride; with and without treatment with Lomudal and lactose (placebo). Note: No reaction to lactose control. "Late" reaction to piperazine/lactose mixture and similar reaction to the same test preceded by inhalation from a spincap of lactose placebo. Inhibition of reaction by pre-treatment with Lomudal.

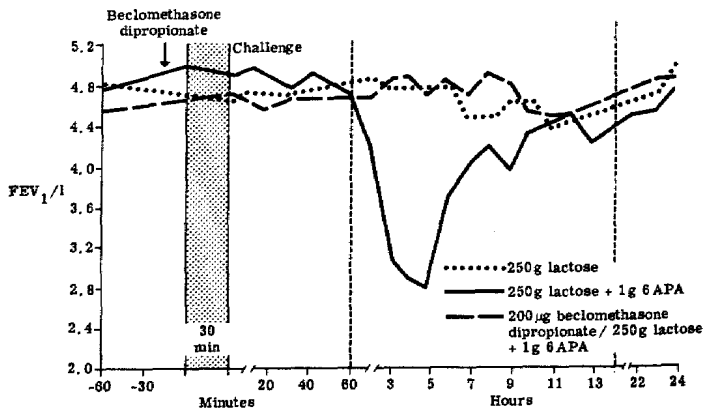


Fig. 9.

Late asthmatic reaction to occupational-type exposure to 6 amino-penicillanic acid, showing inhibition by inhaled beclomethasone dipropionate.

E.F. ♂ Aged 60. Nov. 1972.

TDI EXPOSURE

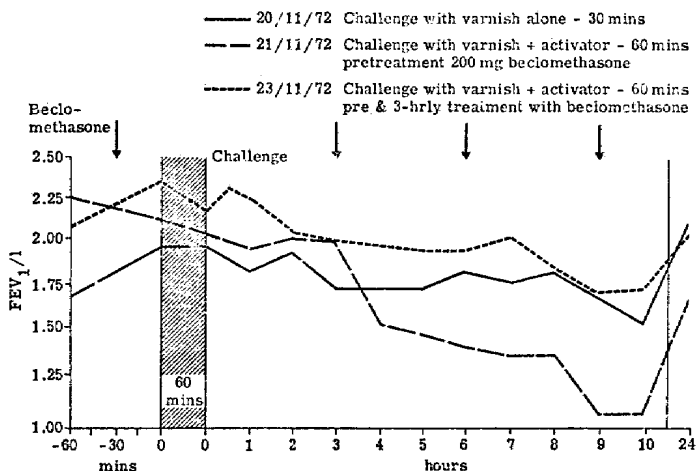


Fig. 10.

Late asthmatic reaction to tolylene di-isocyanate. Not inhibited by pre-treatment with beclomethasone dipropionate; inhibited by pre-treatment with it followed by 3-hourly administration.

Fig. 9 shows a late asthmatic reaction to occupational-type exposure to the powder of 6-amino-penicillanic acid in a worker engaged in the manufacture of ampicillin, to which he gave an identical late asthmatic reaction. The reaction was inhibited by the inhalation of beclomethasone dipropionate. When he was given ampicillin orally, the same late reaction was also elicited (4).

Fig. 10 shows a late asthmatic reaction to tolylene di-isocyanate. This reaction was not inhibited by pre-treatment with beclomethasone or Lomudal. Inhibition of the reaction was produced when either of these drugs was given at 3-hour intervals after the challenge. This illustrates the need to try more frequent administration of both drugs than the conventional four doses per day, before deciding that they are not likely to be effective. Indeed, König & Godfrey (6) have

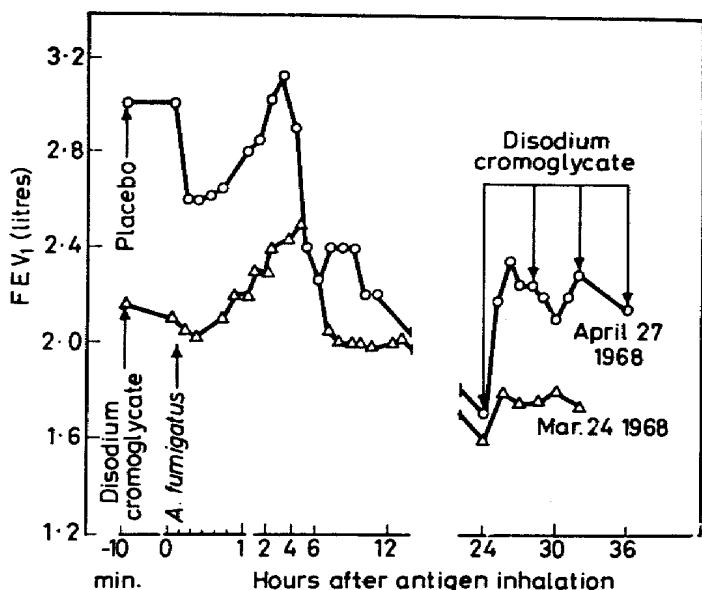


Fig. 11.

Dual, Type I plus Type III, asthmatic reaction to *A. fumigatus*. Inhibition of immediate reaction and partial inhibition of late reaction by disodium cromoglycate. No inhibition by lactose placebo. Note partial inhibition of late reaction by disodium cromoglycate given during the late reaction.

shown that Lomudal can be effective if given more frequently in children in whom the four times daily administration was ineffective. We have made similar observations with inhaled beclomethasone dipropionate in relation to late asthmatic reactions to provocation tests.

Late reactions may be accompanied by fever and leucocytosis. A greater tendency to peripheral blood eosinophilia has been found in the subjects giving late reactions as compared with those giving immediate reactions (Pepys & Hutchcroft, in preparation).

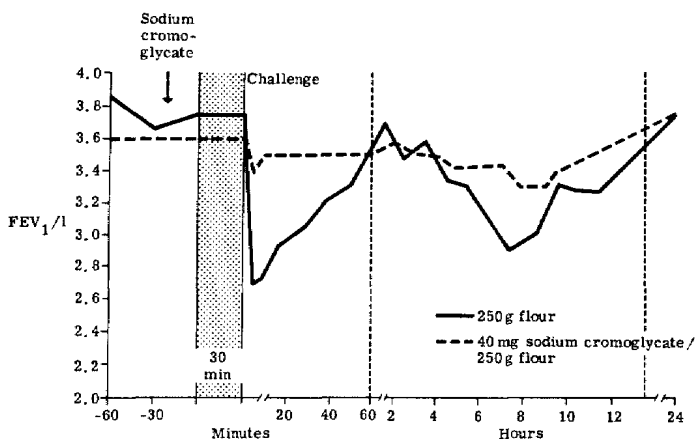


Fig. 12.

Dual asthmatic reaction. — Inhalation challenge with 250 g wheat flour;
 --- Effect of pre-treatment with 40 mg disodium cromoglycate/250 g flour.

Dual Asthmatic Reactions

The classical example of combined immediate, followed by late asthmatic, reactions in subjects with IgE antibody and precipitins is allergic broncho-pulmonary aspergillosis. *Fig. 11* shows a dual reaction in a patient with allergic broncho-pulmonary aspergillosis, in which both reactions are inhibited by Lomudal (11).

In such patients on corticosteroid treatment only immediate reactions were elicited and the Type III skin test reaction was also inhibited, whereas the Type I skin reaction was unmodified. These patients illustrate a further important feature. The immediate reactions showed complete reversibility on inhalation of isoprenaline, whereas the late reactions showed only a 73 per cent reversibility (7, 9). Late reactions respond only poorly or temporarily to inhaled isoprenaline.

Figs. 12 and 13 show a dual asthmatic reaction to occupational-type exposure to wheat flour in a flour-sensitive baker. Both of the reactions were inhibited by Lomudal given before

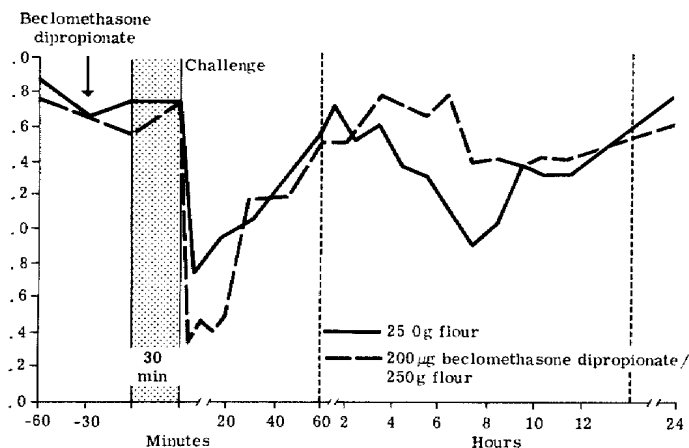


Fig. 13.

Dual asthmatic reaction. — Inhalation challenge with 250 g wheat flour.
 - - Effect of pre-treatment with 200 µg beclomethasone dipropionate/250 g flour;
 stippled area, challenge.

the challenge, whereas the beclomethasone dipropionate inhibited the late asthmatic reaction and had no effect on the immediate reaction (10).

Analysis of Bronchial Reactions to 256 Challenge Tests

Table 2 shows the patterns of asthmatic reaction to different types of allergen challenge (9). The only group to show systemic reactions, such as fever and leucocytosis, were those challenged with aqueous aerosols of common allergens, mainly of avian and thermoactinomycete origin. These subjects resembled patients with allergic broncho-pulmonary aspergillosis who gave dual reactions to *A. fumigatus* extracts, accompanied by fever and leucocytosis in most cases.

The absence of such reactions in late reactors to chemical agents may be due to differences in the mechanisms responsible for the reactions, or even simply to the dosage of the challenge. For example, none of the patients giving late asth-

TABLE 2
Patterns of Asthmatic Reactions in Bronchial Provocation Tests.

		Immediate	Late	Dual
Total tests	256			
No. positive	95	42	34	19
No. of patients	71	36	25	13

matic reactions to amino-ethyl-ethanolamine present in the fumes of aluminium soldering flux (12) had systemic reactions, whereas patients challenged more intensively with this material by Sterling (16) had prolonged febrile reactions.

Conclusions

The above examples illustrate the value of carefully conducted bronchial provocation tests in making a direct aetiological diagnosis in circumstances where other evidence may not be obtainable at present. The similarities of the patterns of reaction suggest that they may be produced by similar or related immunopathological mechanisms. The challenge procedure we employ is calculated to elicit only a positive reaction, so that the challenge is seldom of sufficient strength to elicit reactions requiring reversal by bronchodilators or corticosteroids. In actual clinical experience the exposure is much greater and the severity and nature of the clinical reactions may therefore have features in addition to those shown by our tests.

The different effects of Lomudal and corticosteroids help to clarify some of the problems of asthma. The inhibition of immediate reactions by Lomudal is probably responsible for the inhibition of the late reaction where both are present together. The importance of an immediate reaction for the subsequent development of a Type III reaction has been shown in experimental animals by Cochrane (3) and in man by Pepys (8). In the case of subjects giving late reactions, without evidence of an immediate reaction as measured by the FEV₁,

the possibility of an immediate reaction being present, but not sufficient to produce a change in ventilatory function measurable by the FEV_{11} , has been considered, and indeed, flow-volume measurements have shown this to be the case in some of the subjects giving late asthmatic reactions to extracts of Western Red Cedar (2). Inhibition of such a reaction by Lomudal could be responsible for the inhibition of the late reaction.

The inhibitory effect of inhaled beclomethasone dipropionate and of systemic corticosteroids on the late, but not the immediate, reaction raises the question of the role of the immediate reaction in clinical asthma. It may be that its more important role is to serve as an introductory mechanism for Type III reactions.

The production of dual asthmatic reactions to a single exposure to the relevant agent is also of clinical importance, particularly as the immediate reaction responds well to inhaled isoprenaline whereas the late reaction does not. In clinical asthma, therefore, isoprenaline may be effective at one time during the day and far less effective some hours later. The loss of effect is usually attributed to excessive use but may, in light of the above findings, be explicable by the different patterns of asthmatic reaction.

The assessment of the effects of anti-asthmatic agents must take into account the different patterns of asthmatic reaction which can occur. The agents discussed here have contributed greatly to the recognition of these patterns. This recognition is likely to improve the understanding and management of clinical asthma.

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DISCUSSION

N. Svanborg: Could you explain what you mean by inhibition of the bronchial reactions? We find that Lomudal reduces bronchial sensitivity in the Type I allergic reaction, but does not give total inhibition. On the other hand, we find that steroids give a slight reduction in bronchial sensitivity to a Type I reaction induced by specific antigens, though this protection is less marked than that from Lomudal.

J. Pepys: I think the word inhibition must be interpreted in its full sense—there can be either a partial or a complete inhibition. The method of testing is very important in this context. Our aim in testing is to produce an unequivocal reaction. With our method, which uses a rebreathing bag, we very rarely have to use drugs to terminate the reaction. It is difficult for those workers who induce reactions of such severity that they have to be terminated to know exactly what is going on and what the true nature of the reaction is. With regard to the completeness of the inhibition with Lomudal, 16 out of 19 patients we studied had almost complete inhibition of the immediate reaction. With corticosteroids, the inhibition of the immediate reaction is very limited and it must be remembered that the method of testing gives small variations anyway.

F. Lange-Nielsen: One could draw the conclusion from your remarks that if corticosteroids are effective then one is not dealing with a Type I reaction. But in practice one finds that in the most typical seasonal Type I reactions in young people, a single long-acting intramuscular injection can be very effective.

J. Pepys: This is a common example, but I would stress that it is not possible to produce prolonged nasal obstruction by a simple Type I reaction.

In hay fever, the initial bouts of sneezing tend to terminate and then complete obstruction with sneezing occurs. This can

be produced by nasal challenge. If you give a nasal challenge to a patient with allergic aspergillosis, you get an immediate obstruction which resolves and a complete obstruction some hours later which lasts for a day or more. My feeling is that hay fever is not purely an IgE-mediated disease. Taylor in Manchester has challenged untreated pollen-sensitive subjects in the skin and in the nose and produced dual reactions in both. He has been unable to correlate complement-fixing antibodies with the reaction, but he has been able to correlate it with another immunoglobulin, which is not complement-fixing and which is not IgE. I think we have to get away from the idea that these diseases are only IgE-mediated. When steroids control symptoms clinically, it may not be the IgE-mediated part that is modified.

B. Kjellman: It seems to me that the reactions that many of your patients had to inorganic chemicals emphasise the fact that not all clinically immediate reactions are the same as reagin-mediated reactions.

J. Pepys: I do not know that I agree with you. I think the inorganic chemicals may well form a complete allergen on entry into the body, acting as a hapten, and that these immediate reactions probably are IgE-mediated.

B. Kjellman: Do you believe in non-specific immediate reactions and bronchial obstruction which is not reagin-mediated?

J. Pepys: There is definite evidence for the existence of non-immunological bronchial reactions, such as that to acetylcholine. In our cases it must be remembered that they were sensitive to extremely small doses and that they were a few sensitive individuals from the large number of workers who were exposed. Both these factors point to a hypersensitivity reaction, and there is already some immunological evidence in favour of this.

B. Simonsson: There will probably be an individual variation in bronchial reactivity to these salts, as for any constricting stimulus, allergic or non-allergic. Do you know what the mediators of the late reaction are—are complement and

SRS-A involved? As bronchodilators give some relief, I assume the reaction must involve broncho-constriction.

J. Pepys: In the immediate reaction, mediators are released from mast cells and presumably that group of mast cells does not discharge a further supply of mediators. In the immune complex reaction, the situation is quite different. First of all, anaphylatoxin is split off from complement quite quickly and probably has a considerable effect. Then you have other factors such as lysosomal release and platelet thrombosis. It is a complicated situation. A bronchodilator may relax smooth muscle, but the immunopathological changes continue. The effect of steroids may be related to their stabilizing effect on lysosomal membranes. There is very little known, however, about mediators and mediator release in this context.

H. Colldahl: Do you think that the bronchial changes in the late reaction are the same as those in the immediate reaction? Could the constriction of the airways take place at a different part of the bronchial tree? My second question concerns some experimental studies I once made with guinea-pigs. If a sensitized animal was exposed in a closed system for 2–3 hours, moderate to severe asthma of long duration resulted. Is that an immediate or late reaction? Similarly, a house dust-sensitive patient is exposed to the antigen all night in bed—is the reaction to that situation immediate or late?

J. Pepys: At present I do not think there is any information as to whether the late reaction has a different mechanism in the tissues to the immediate. We are all tempted to think it may involve the smaller bronchi, but it is much too early to say. With regard to your second question, I think that in your guinea-pig experiment you were seeing the late reaction—it is difficult to talk about an immediate reaction when the animal has been exposed for 2 hours. In the clinical situation, it is very difficult to assess what happens when you do not know the exact details of the exposure. That is the main reason we use single challenge studies—at least we know what is happening. We have not studied the effect of repeated challenge, where there may be an overlapping of reactions.

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