

DEVELOPMENTS IN THE TREATMENT OF ASTHMA WITH DISODIUM CROMOGLYCATE (LOMUDAL)

R. E. C. ALTOUNYAN, M.D.

While there is controversy over the basic mechanisms of asthma, there is at least agreement that there are many causes of the disease which we know as asthma. Whatever the cause, the target organ remains the lung and my purpose is to discuss the effect of Lomudal on the target organ. I hope to show how the drug can modify the responsiveness of the lung in various situations.

The several physiological controls of bronchial muscle are shown diagrammatically in Fig. 1. The bronchus is under autonomic control, with some degree of psychological involvement, but there are other determinants of the tone of bronchial smooth muscle. Some of these are immunological, others are not. Their effects may be mediated directly, through the mast cell or through leucocytes. An effect may be a direct action on smooth muscle or an indirect action through the triggering of a reflex. It should be remembered that the mast cell can influence the polymorphonuclear leucocyte and the picture is complicated still further by the positive feed-back mechanism, whereby released mediators can increase the receptiveness of the mast cell or similar cells. For example, Dr Orr has shown that β -blockade of mast cells renders them more fragile and liable to disruption by mediators such as histamine, which normally have no effect (15). Possibly Szentivanyi's β -blockade theory of asthma can explain the hyperreactivity not only of smooth muscle but also of cells involved in mediator release (17).

I would like to consider first the autonomic innervation of

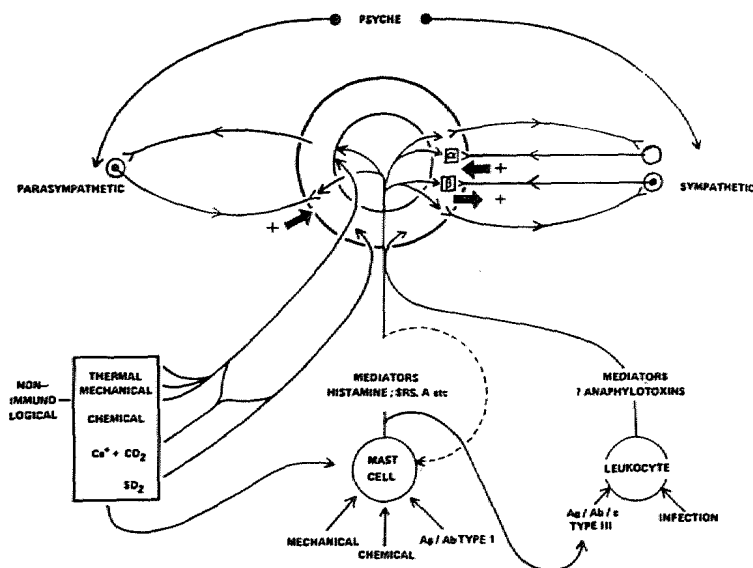


Fig. 1.

Factors controlling bronchial muscle tone.

bronchial muscle—the α - and β -receptors and the parasympathetic side (Fig. 2). There is currently considerable interest in the parasympathetic, particularly as a result of the work of Simonsson in Sweden (16) and Gold in America (19). They have postulated that it is a very important factor in the causation of asthma and in recent studies have shown that atropine can give almost total inhibition of the response to antigen. I feel that they have exaggerated the importance of this aspect and I have been unable to show such a marked atropine effect in my experiments, in which I probably use much larger challenge doses. Fig. 3 summarizes some work I carried out in the 1950's, which shows that atropine protects well against carbachol challenge but has only a small effect against histamine and practically none against antigen (1). In a study of a num-

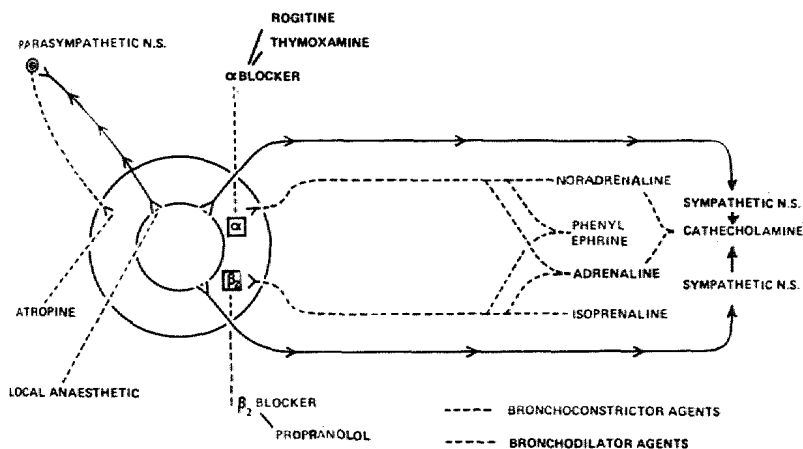


Fig. 2.

Pharmacologically active agents concerned with bronchial muscle tone.

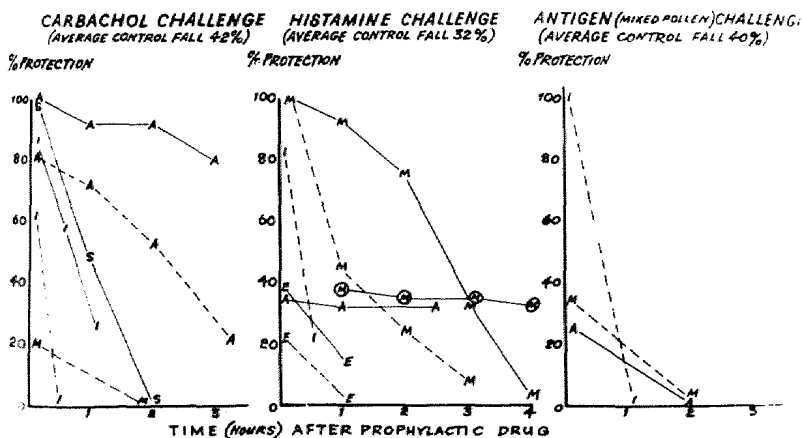


Fig. 3.

Protective effect of atropine against carbachol, histamine or antigen challenge.

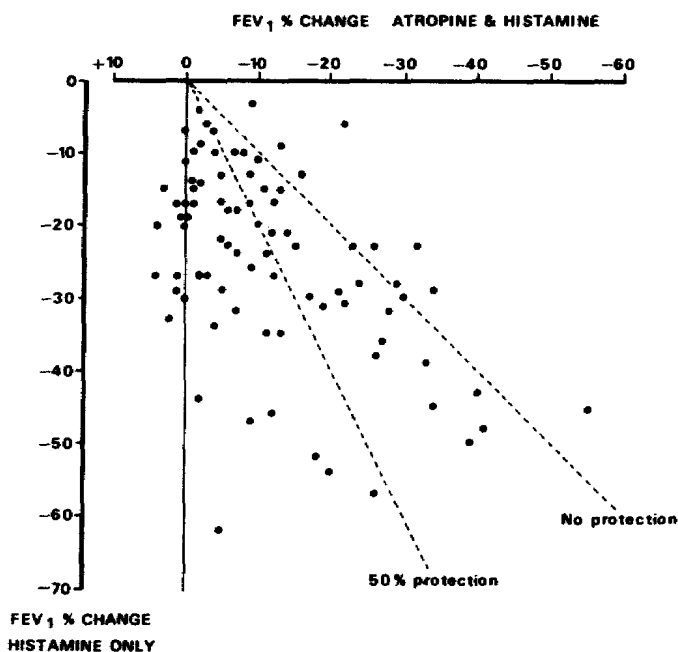


Fig. 4.

Protective effect of atropine against histamine challenge in a number of patients.

ber of patients, atropine did not protect against histamine challenge in all cases (Fig. 4) and the atropine response of each patient varied widely at different stages of the disease. Dickson has shown that atropine can protect some children against exercise-induced bronchospasm (9), but I suspect that if these patients were tested again at different times the same variability would be seen.

The bronchodilator effect of atropine also varies with time. Patients may show little response to atropine and a good response to β -stimulants, or *vice versa*, and an individual may change from one pattern of reaction to another. For instance, the data in Fig. 5 relate to a patient of mine who had no re-

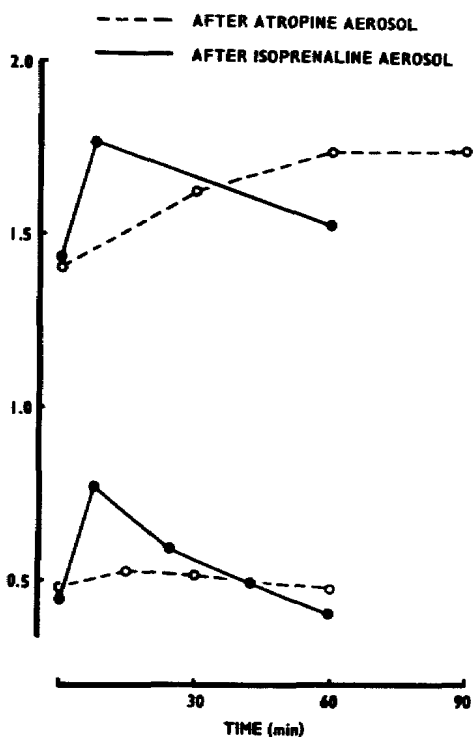


Fig. 5.

Atropine response in one patient before and after steroid treatment.

sponse to atropine when he was very ill, but a reasonable response, comparable to that of β -stimulants, after 5 days of steroid treatment (2). In most patients, Lomudal has a marked effect on the atropine response (defined as the ratio of the atropine-induced increase in FEV_1 to the isoprenaline-induced increase in $FEV_1 \times 100$). An average of 3 weeks' Lomudal treatment produced a significant increase in the atropine response from a pre-treatment mean of around 50 per cent (Fig. 6). Not all patients responded (3). A simi-

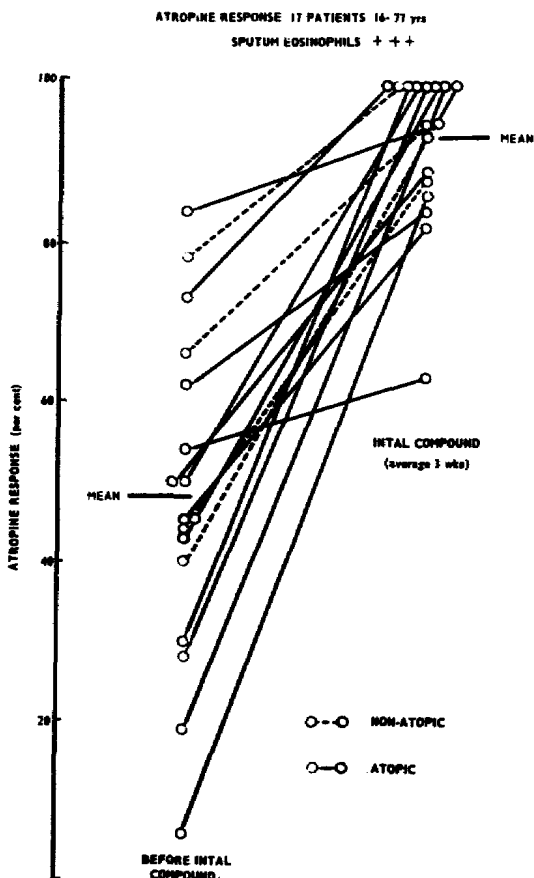


Fig. 6.

Effect of Lomudal treatment on atropine response in 17 asthmatics.

lar effect has been noted with steroids. From these observations it would appear that Lomudal, while itself having no effect on the parasympathetic nervous system, is able to modify in some way the tissue response to atropine.

Moving on to consider the other side of the autonomic

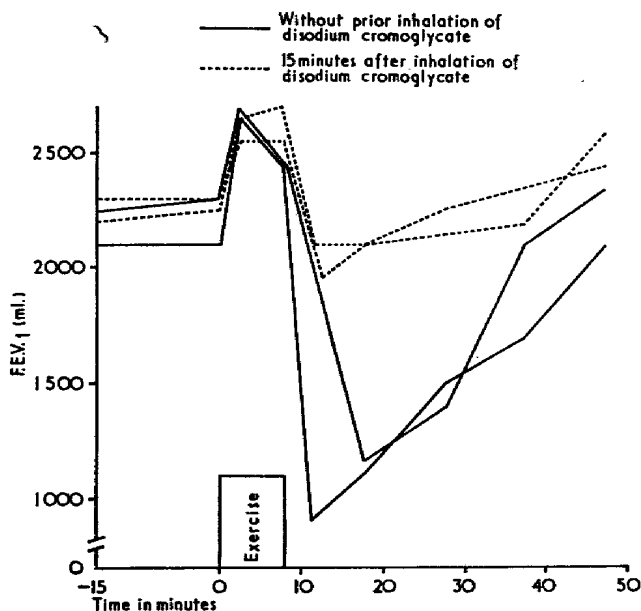


Fig. 7.

Inhibition by Lomudal of exercise-induced asthma (7).

nervous system, we have been unable to demonstrate any sympathomimetic effect of Lomudal. The drug is certainly not acting as a stimulator of the β -receptor. In very high doses in animal studies it is possible to show some phosphodiesterase inhibition, but we think this bears no relation to the effect of the drug at clinical dose levels. Professor Simonsson's demonstration of the α -receptor in patients has been followed by work by Marcelle in Belgium (13) and de Kock in South Africa (8). They have shown that Lomudal apparently acts as an α -blocker. Adrenaline is both α - and β -stimulant, but in patients pre-treated with the β -blocker propranolol it acts as a broncho-constrictor. If phenoxybenzamine, an α -blocker, is also used for pre-treatment, adrenaline now acts as a broncho-

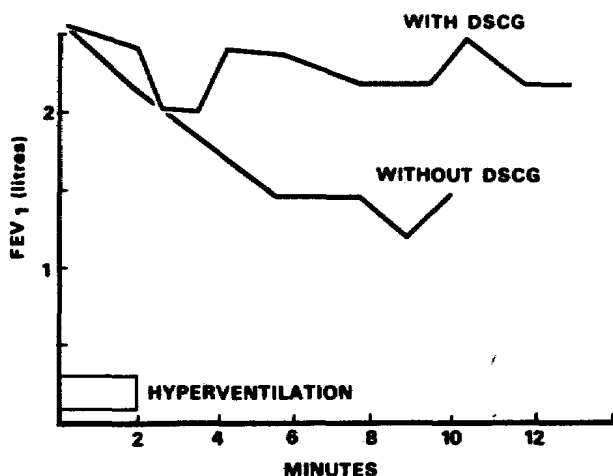


Fig. 8.

Inhibition by Lomudal of hyperventilation-induced asthma (5).

dilator. Lomudal can be substituted for phenoxybenzamine and can prevent the broncho-constrictor effect of adrenaline in β -blocked patients. I visited de Kock recently and he has repeated his experiments with more patients; there is thus some evidence for the involvement of Lomudal with sympathetic transmission, perhaps indirectly as an α -blocker. I myself have been unable to show any α -receptor effect of the drug on intact human bronchial muscle.

Continuing our survey of the way in which Lomudal can modify the determinants of asthma, let us consider some non-immunological triggers of the asthmatic attack. Probably the best known of these is exercise. As Dr Godfrey has already discussed this topic, I will merely draw your attention to the initial observations by Davies (7), that pre-treatment with Lomudal prevents the exercise-induced fall in FEV₁ (Fig. 7). The effect of Lomudal in asthma provoked by hyperventilation is less well known. Clarke in Australia (5), showed the drug to have a very definite protective effect (Fig. 8). The

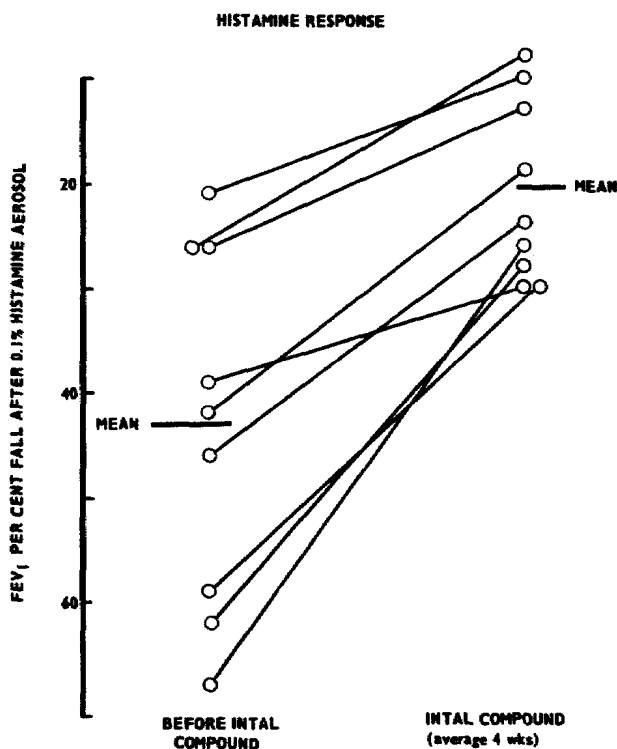


Fig. 9.

Effect of Lomudal treatment on histamine response.

work of Dr Orr on the protective effect of Lomudal on hyper-reactive β -blocked mast cells may be relevant to these studies (15). One can imagine a stabilizing effect of Lomudal on hyperfragile mast cells in exercise and hyperventilation-induced asthma.

Another non-immunological asthmagenic stimulus is the inhalation of an aerosol solution of histamine. I investigated the effect of Lomudal treatment on histamine responsiveness in a group of asthmatics who benefitted from the drug clinic-

INHALATION TEST WITH HOUSE DUST-EXTRACT

Male (15 y)

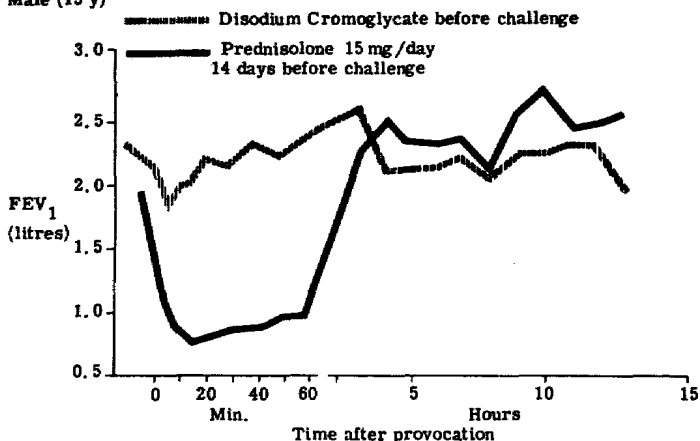


Fig. 10.

Effect of Lomudal on immediate and late reactions to house dust extract (14).

ally (3). After 4 weeks' treatment the histamine response decreased from a 42 per cent fall in FEV₁ to a 21 per cent fall (Fig. 9). This is not a very marked effect, and other workers, such as Townley, have failed to observe it (18). Townley's patients, however, were not tested during their asthma season as mine were. Inoue has claimed that in some of his patients a single acute administration of Lomudal reduced the histamine response (10). From my experience, all I would claim is that continuous use of Lomudal over a period of several weeks will modify the histamine response to a moderate extent.

We have not yet considered the protective effect of Lomudal in situations where the trigger of the asthmatic attack is immunological. I would like to deal first with immediate and late reactions to inhalation of antigen. You will all be familiar with the work of Professor Orie in this field (14). He has shown that Lomudal given before challenge with house dust

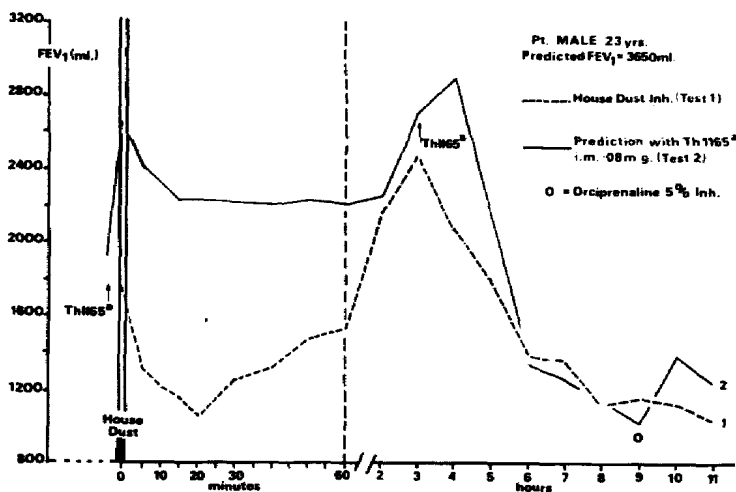


Fig. 11.

Effect of a β -stimulant (fenoterol) on immediate and late reactions to house dust extract (14).

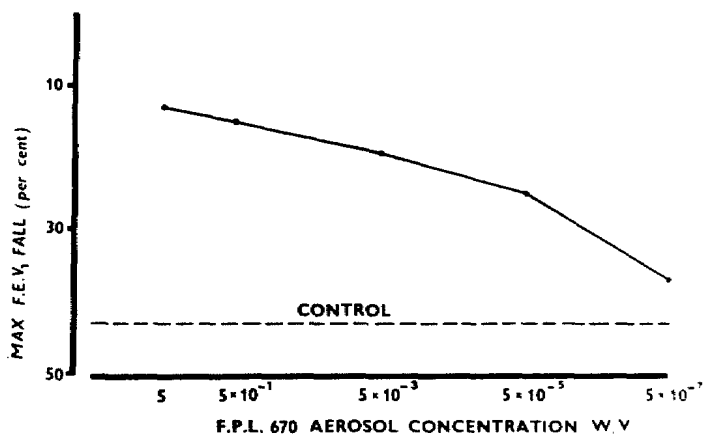


Fig. 12.

The relationship between aerosol concentration of Lomudal and the protective effect against antigen challenge.

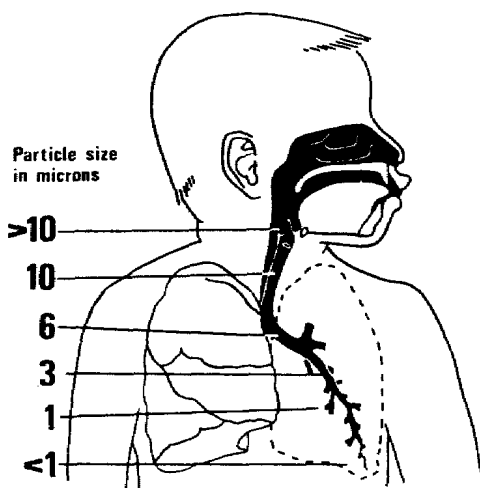
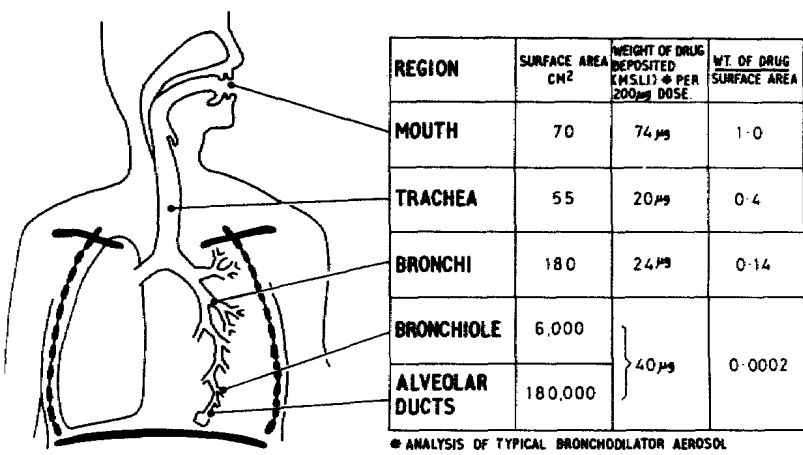


Fig. 13.

Theoretical distribution of inhaled particles within the respiratory tract.

prevents both the immediate and late reaction, whereas steroids prevent only the late reaction (Fig. 10). He has also studied the effect of β -stimulants, with interesting results (4). Lichtenstein & Margolis (12), and several others have shown experimentally that β -stimulants can inhibit mediator release from sensitized cells. Orie found that β -stimulants such as fenoterol completely inhibited the immediate reaction (14) but had no effect at all on the late reaction (Fig. 11). Some early work of mine showed a similar effect, with isoprenaline protecting against the immediate reaction but failing to prevent a subsequent decline in lung function (6). I think this failure to protect against the late reaction is important and clearly differentiates the sympathomimetics from Lomudal.

There seem to be two types of response to Lomudal: firstly, those in which there is a rapid response, the immediate and late allergic reaction in exercise-induced asthma and the effect on α -stimulation; and secondly those responses which



* ANALYSIS OF TYPICAL BRONCHODILATOR AEROSOL
J.H. BELL, K. BROWN & J. GLASBY (IN PRESS)

Fig. 14.

Relative concentrations of inhaled drug within the respiratory tract.

are seen only after several weeks treatment, such as changes in atropine and histamine response. The rapid responses are perhaps the more easily understood. We have an explanation for the activity of the drug in immunological situations in terms of mast cell stabilization, and it is possible to imagine a similar explanation for the effect in exercise-induced asthma. Similarly, the protective effect of Lomudal against α -stimulation may also be related to the mast cell since the work of Kaliner and others suggests that α - and β -receptors are also present on mast cells (11).

The long-term effects of the drug are less easy to explain. I believe that the drug, taken over a long period, may be able to reduce the intrinsic hyperreactivity of the muscle itself. It is relevant that repeated antigen challenge in an unprotected sensitive individual leads to a hyperreactive state. I can illustrate this by reference to a patient of mine whose histamine sensitivity I studied for several years (2). He was sensitive to grass pollen and during the season his histamine sensitivity

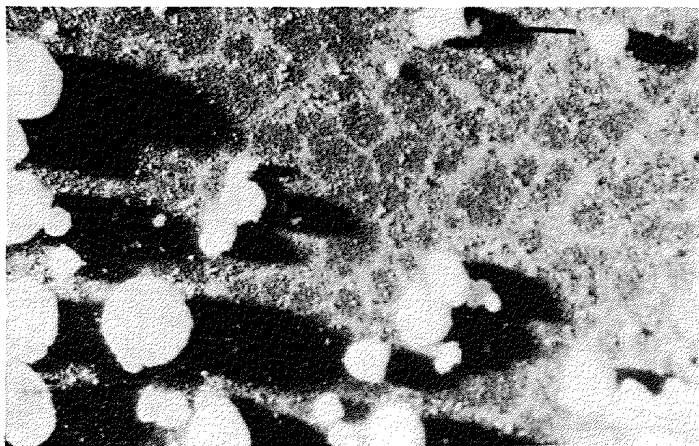


Fig. 15.

Large particles of lactose and DSCG before inhalation through the Spinhaler.

was greatly increased. In 1965 I tried him first on lactose placebo with no effect and then on Lomudal. There was no immediate effect, but after two weeks' treatment his sensitivity was markedly reduced. Presumably Lomudal inhibited the antigen-induced liberation of mediators and this allowed a gradual recovery from the hyperreactive state. Possibly one could use a similar argument for the increased atropine response on Lomudal therapy; the response to atropine normally decreases during a period of repeated antigen challenge, and Lomudal prevents this decline of the atropine response by inhibiting the allergic reactions.

I would like to turn now to some practical aspects of treatment with Lomudal. The first problem is which patients to select for treatment. I have always maintained that sputum eosinophilia is a good indication that the patient will respond. As Professor Pepys mentioned this morning, eosinophil aggregates are associated with anaphylotoxins as well as with the Type I reaction. In my experience with the drug, I have never seen a response in a patient who did not have sputum eosino-

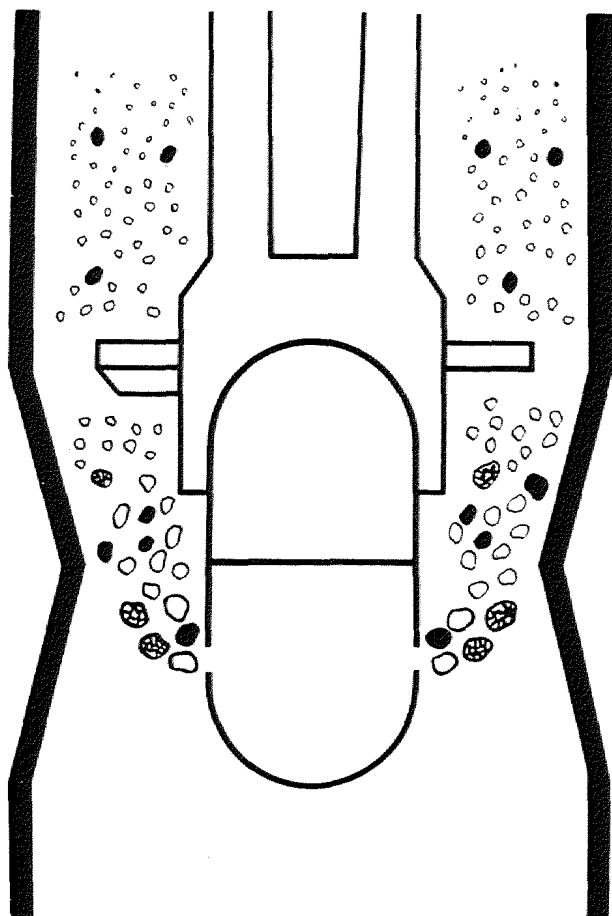


Fig. 16.

Dispersion of aggregates within the Spinhaler.

philia. Hence the absence of eosinophilia from the sputum makes it very unlikely that a response will be seen in that patient.

There are several points I would like to make concerning

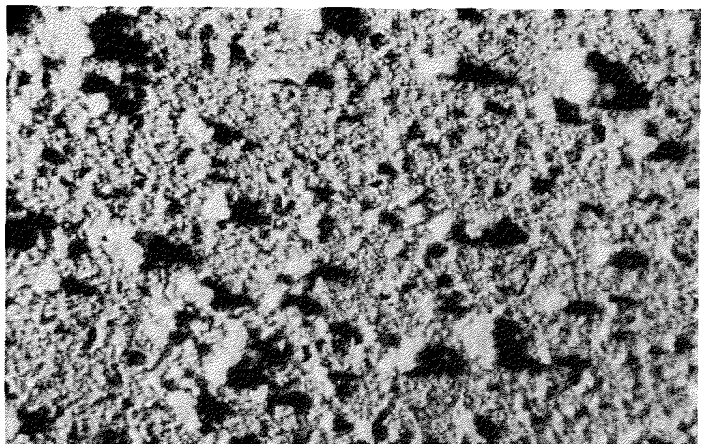


Fig. 17.

Fine dispersion of lactose and DSCG particles after inhalation through the Spinhaler.

the administration of the drug. I would remind you first that Lomudal is a very active drug—concentrations of 10^{-7} (w/v) in aerosol form give protection in antigen challenge studies (Fig. 12). In man there is no evidence of the bell-shaped dose response curve that Dr Orr finds in animals. It is quite possible to administer Lomudal by aerosol, but high concentrations and frequent doses are necessary to give significant protection. A 5 per cent solution of the drug gives protection for 2 hours or more, but it would be very difficult to give enough of the drug by this route to ambulant, non-hospitalized patients. We were therefore forced to develop an alternative drug delivery system and the Spinhaler was the result. The original version was assembled by me from pieces of glass and plastic, using a razor-blade—rather surprisingly it worked. The final version as now produced is a much more sophisticated apparatus which has two functions, to dispense the drug from its gelatine capsule and also to disperse the drug by

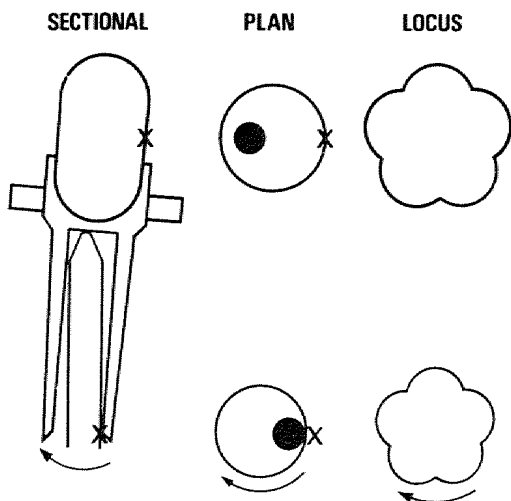


Fig. 18.

Rotation of Spinhaler propeller shaft on the pivot.

breaking up aggregates of powder into particles of the required size.

This disaggregation is an important function and I would like to remind you of the way in which particles are deposited in the lung. Particles of $10\text{ }\mu\text{m}$ and over do not get much beyond the epiglottis and do not reach the smaller airways. To reach this region, which may be the problem area in asthma, we need particles of $1\text{--}2\text{ }\mu\text{m}$ (Fig. 13). Using cascade impactors and other techniques, it can be shown that for any inhaled drug, the concentration deposited on a unit surface area gets progressively less as we go deeper in the lung. The concentration can decrease from an arbitrary value of 1 in the mouth to 2×10^{-4} in the bronchioles (Fig. 14). It follows that to achieve an effective concentration of drug by aerosol in the small airways there must inevitably be a gross overdose administered to the upper airways. In my opinion, this inevita-

ble overdosage in the larger airways is a real objection to the long-term use of aerosol steroids.

The disaggregation function of the Spinhaler is necessary because of the lactose which is added to the fine Lomudal powder to make it fluid. The lactose particles are 60–100 μm but particles of Lomudal adhere to them, giving a final size of perhaps 200 μm (Fig. 15). These large particles pass through the venturi of the Spinhaler during inhalation (Fig. 16) and are only broken up to give the fine particles of Lomudal necessary to achieve deep penetration of the lungs at inspiratory rates of over 100 litres/min. The patient must therefore be trained to inhale as rapidly as possible through the Spinhaler (Fig. 17).

The way in which the Spinhaler disperses powder is also of interest. The dispersion occurs because of the unusual way in which the propeller shaft of the Spinhaler rotates on its spindle. The base of the propeller shaft fits loosely on the pivot where there is rolling friction during rotation whereas at the tip of the pivot the shaft rotates on a point where there is sliding friction (Fig. 18). This combined rolling and sliding friction can be shown to impart a peculiar vibratory movement to the capsule during rotation. This causes the powder to move up the side of the capsule and out of the pierced holes.

It is essential to train each patient on the correct use of the Spinhaler. He must also be urged to maintain it properly since he cannot benefit from the drug if it is deposited in large lumps in the oro-pharynx.

REFERENCES

1. Altounyan, R. E. C. (1964): Variations of drug action on airway obstruction in man. *Thorax* 19, 406.
2. Altounyan, R. E. C. (1969): Changes in histamine and atropine responsiveness as a guide to diagnosis and evaluation of therapy in obstructive airways disease. In *Proc. Symp. Roy. Soc. Med.*, March 1969, London.
3. Altounyan, R. E. C. (1970): Disodium cromoglycate—clinical pharmacology in obstructive airway disease. In *Bronchitis, III, Proc. 3rd. Int. Symp. Bronchitis*, Sept. 1969, p. 346, Groningen, The Netherlands.

4. Assem, E. S. K. & Schild, H. O. (1969): Inhibition by sympathomimetic amines of histamine released by antigen in passively sensitised human lung. *Nature (Lond.)* 224, 1028.
5. Clarke, P. S. (1971): The effect of disodium cromoglycate on exacerbations of asthma produced by hyperventilation. *Brit. med. J.* 1, 317-319.
6. Cox, J. S. G. & Altounyan, R. E. C. (1970): Nature and modes of action of disodium cromoglycate (Lomudal). *Respiration* 27, Suppl., 292-309.
7. Davies, S. E. (1968): Effect of disodium cromoglycate on exercise-induced asthma. *Brit. med. J.* 3, 593-594.
8. De Kock, M. A. (1970): Discussion on disodium cromoglycate. In *Bronchitis, III, Proc. 3rd. Int. Symp. Bronchitis*, pp. 354-358, Sept. 1969, Groningen, The Netherlands.
9. Dickson, W. (1969): A one year trial with Intal Compound in 24 children with severe asthma. In *Roy. Soc. Med. Symp.*, March 1969, London. Butterworths, London.
10. Inoue, S. (1970): Effects of disodium cromoglycate on airway histamine hypersensitivity and daily pulmonary function in asthmatic children. 7th Int. Cong. Allerg., (Special sectional meeting), October 1970, Florence.
11. Kaliner, M., Orange, R. P. & Austen, K. F. (1972): The immunological release of histamine and SRS-A from human lung. IV. Enhancement by cholinergic stimulation. *J. Exp. Med.* 136, 556.
12. Lichtenstein, L. M. & Margolis, S. (1968): Histamine release *in vitro*. Inhibition by catecholamines and methylxanthines. *Science* 161, 902.
13. Marcelle, R. (1970): Activité du DSCG sur la bronchomotricité de l'homme *in vitro* (Activity of DSCG in human bronchial tone *in vitro*). *Respiration* 27, Suppl., 369-371.
14. Orie, N. G. M., Van Lookeren Campagne, J. G., Knol, K., Booij-Noord, H. & De Vries, K. (1973): Late reactions in bronchial asthma. 8th Int. Cong. Allerg., Special sectional meeting, October 1973, Tokyo.
15. Orr, T. S. C. (1972): Personal communication.
16. Simonsson, B. G., Anderson, R., Bergh, N. P., Skoogh, B. E. & Svedmyr, N. (1970): *In vivo* and *in vitro* studies of pharmacological effects on different receptors regulating bronchial tone in man. In *Bronchitis III, Proc. 3rd. Int. Symp. Bronchitis*, p. 334, Sept. 1969, Groningen, The Netherlands.
17. Szentivanyi, A. (1968): The beta adrenergic theory of the atopic abnormality in bronchial asthma. *J. Allergy* 42, 203.
18. Townley, R. G., Kang, B., Lee, C. K. & Kolotkin, B. (1973): Effects of disodium cromoglycate on the intravenous infusion of histamine in asthmatics (abst.). *J. Allergy Clin. Immunol.* 51, 121-122.
19. Yu, D. Y. C., Galant, S. P. & Gold, W. M. (1972): Inhibition of antigen-induced bronchoconstriction by atropine in asthmatic patients. *J. Appl. Physiol.* 32, 823.

DISCUSSION

B. Uvnäs: How much of the inhaled dose of Lomudal is excreted in the urine?

R. Altounyan: Between 2 and 5 per cent. About half of the absorbed material is excreted in the urine and half in bile.

J. Kiviloog: I should like to speculate about the possible mechanism of the long-term benefit from Lomudal. I think it is reasonable to assume that over a long period repeated asthmatic attacks affect bronchial muscle tone and that there is probably some muscle hypertrophy. When this hypertrophic muscle is irritated, a marked contraction might result. Thus a given irritant stimulus could give a severe asthmatic attack. Possibly Lomudal inhibits the development of bronchial muscle work hypertrophy and prevents a further deterioration of the disease. This hypothesis is particularly interesting in exercise-induced asthma. I have found that marked bronchial irritability is a feature of this condition—this can be measured as methacholine sensitivity. These hyperreactive patients with high sensitivity and frequent asthma attacks have a particular need for prophylactic medication.

R. Altounyan: A study has been made by Dr Dickson in Bolton of a group of children. He measured their histamine and exercise hyperreactivity at frequent intervals for 4 years, and found at least two patterns of response. In one class of patients there were no changes in histamine or exercise reactivity throughout the whole period of study and in another class there was a slight decrease in histamine reactivity but none in exercise reactivity. There were definitely two types of response, but the reason is unknown. I do not agree, however, that histamine hyperreactivity correlates with exercise. I remember trying to persuade Dr Godfrey to do histamine tests in children and he had great difficulty in detecting any response, even at high doses. In Dr Dickson's series, there was

very little correlation between histamine and exercise hyper-reactivity.

N. Svanborg: I think it has been shown with steroids that there is passive uptake into pneumocytes and active excretion, so that it takes some time for an effective concentration to build up in the cells. Does this have any relevance to the work with small particles of Lomudal?

R. Altounyan: I think not, because if Lomudal is given immediately before antigen or exercise challenge, there is maximum protection. There appears to be no time lag for the drug to reach its receptor, whatever and wherever that is.

N. Svanborg: Do you not want the Lomudal particles in the upper airways?

R. Altounyan: I do not know where the allergic reaction is going on. I know you can get allergic reactions in the nose, the soft palate, the larynx, the trachea. Ideally, I would like my patients to be relieved of both upper and lower airway symptoms. As you know, naturally occurring antigens cover a vast range of particle sizes and presumably the ideal therapy will cover the whole mucosal tract from the nose to the alveolus.

B. Simonsson: I hope nobody really believes that we think atropine can block any kind of challenge. I think it is likely that with many types of challenge there is a reflex component to the observed response and it is this component that can be affected by atropine. I would like to ask if atropine has any other pharmacological effect, such as inhibition of mediator release or β -sympathomimetic activity. I think acetylcholine has been shown to release prostaglandins, so could there be a link between acetylcholine production by the vagal reflex and prostaglandin release?

R. Altounyan: I was making the point that you were one of the original workers who demonstrated the importance of atropine. In America, however, there is currently a great over-emphasis on the importance of atropine, acetylcholine and the parasympathetic, even in antigen challenge. It is claimed, for example, that atropine can completely prevent the effect of

antigen challenge, whereas I think it can give only a partial protection. Atropine does inhibit mediator release as Kaliner, Orange & Austen have shown with primate lung. Acetylcholine will increase mediator release and atropine prevents this. Theoretically, there might be a dual effect of atropine, on both mediator release and reflex effects, but I have been unable to demonstrate this clinically.

B. Uvnäs: It is difficult to understand how acetylcholine could be involved in the allergic reaction, because it is destroyed so easily and so rapidly. It has to be released in very close connection with the larger cell. My view is that the effects of atropine and acetylcholine *in vitro* have very little clinical significance.

This document is a scanned copy of a printed document. No warranty is given about the accuracy of the copy. Users should refer to the original published version of the material.