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This Week's Citation Classic®

Altounyan R E C. Inhibition of experimental asthma by a new compound—disodium cromoglycate "INTAL." *Acta Allergol.* 22:487, 1967.
[Fisons Pharmaceuticals Ltd., Holmes Chapel, Cheshire, England]

This short report described the protective effect of pretreatment with sodium cromoglycate (INTAL) against allergen-induced bronchoconstriction in an allergic asthmatic subject. The degree and duration of protection were dependent on dose and the time interval between inhalation of drug and inhalation of antigen. Little or no protection was observed when the drug was given after challenge. [The *SCI*® indicates that this paper has been cited in more than 260 publications.]

INTAL and Asthma Prophylaxis

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The story starts with the secondment of a physician who suffered from asthma (Roger Altounyan) to work with two chemists (Colin Fitzmaurice and Brian Lee) and a pharmacologist (Phil Sheard) who were already embarked on a project to discover and develop a new bronchodilator agent based on khellin, a plant extract with known smooth muscle relaxant properties. At that time (mid-1950s), the principal pharmacological screen for bronchodilator activity was reversal of acute bronchoconstriction induced in the sensitised guinea pig. However, Altounyan knew from personal experience that drug effects demonstrated in animal models of allergy and asthma were not reliable predictors of clinical activity in man, so he volunteered to screen new compounds using himself as the test system. He observed that some derivatives of khellin had no effect on histamine-induced bronchoconstriction, but weakly attenuated the response to antigen; and he preceived the potential clinical value in developing a drug with protective properties in allergic asthma as distinct from one that provided acute relief of symptoms.

The success of INTAL as a treatment for asthma prompted a wide search for other sodium cromoglycate-like drugs. The perceived mode of action of sodium cromoglycate was inhibition of mediator release from mast cells,[1] and, although a number of mast cell stabilisers were developed, none showed efficacy in therapeutic studies. Throughout the 1970s, Altounyan continued to study drug actions on asthma using a battery of bronchial challenge tests. He was particularly interested in the effect of drugs on the allergen-induced late asthmatic reaction since this is accompanied by a persistent increase in nonspecific bronchial hyperreactivity—a classic feature of day-to-day asthma. Work done in the 1970s[2,3] showed that sodium cromoglycate blocked the development of this late phase response and reduced long-term hyperreactivity. There were conflicting views on the mechanism of bronchial hyperreactivity, but in the 1980s attention focused on bronchial inflammation as the underlying factor.[4,5]

It is ironic that in 1964 Altounyan commented that "curative therapy will reduce the abnormally high level of airway irritability which is observed in patients with chronic bronchitis and asthma" and that, early in the clinical investigation of sodium cromoglycate, he reported that sputum eosinophilia was predictive of a good response to INTAL therapy irrespective of the atopic status of the patients. He thus anticipated the airway inflammation/airway reactivity concept of the mechanism of asthma by some 20 years. Altounyan was awarded the Prix Galien for sodium cromoglycate in 1971 and the DM from the University of Southampton for his contributions to respiratory medicine.

1. **Cox J S G, Beach J E, Blair A M J N, Clarke A J, King J, Lee T B, Loveday D E E, Moss G F, Orr T S C, Ritchie J T & Sheard P.** Disodium cromoglycate (Intal). *Advan. Drug Res.* 5:115-96, 1970. (Cited 245 times.)
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3. **Cockcroft D W, Ruffin R E, Dolovich J & Hargreave F E.** Allergen-induced increase in nonallergic bronchial reactivity. *Clin. Allergy* 7:503-13, 1977. (Cited 365 times.)
4. **Kay A B, Durham S R, Gin W, Mogbel R, MacDonald A J, Walsh G M, Shaw R J, Cromwell O, Mackay J & Carroll M.** Inflammatory cells in early, late-phase and chronic asthma. *Prog. Respir. Res.* 19:211-23, 1985. (Cited 10 times.)
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