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The discovery of cromolyn sodium and its effect on research and practice in allergy and immunology

Roger Altounyan had his first attack of asthma one night when he was a medical student at the Middlesex Hospital in London from 1949 through 1952. His description—"I woke up gasping for breath and thought I would die"—illustrates his understanding of the severity of the disease. After a more severe attack the following night, he consulted the student's medical officer only to be told "you've only got asthma" and that the most important cause was "the old psyche." He was given a prescription for phenobarbital and ephedrine, which reflects the current thinking at that time: treatment was to allay anxiety and to reverse bronchoconstriction.

He joined the research group at Benger's Research Laboratories, a small British pharmaceutical company, in 1956 and was able to pursue his interest in asthma by treating patients at nearby Monsall Hospital in Manchester. The research group at that time was attempting to improve the bronchodilating properties of the furanochromone, khellin, by means of chemical synthesis.¹ To test the different chemical compounds, the research group used guinea pigs sensitized to egg albumin and then challenged with an aerosol of egg albumin to induce bronchoconstriction. They had already shown that some chromones could delay the onset of distress induced by bronchial antigen challenge in guinea pigs. However, Altounyan recorded the following:

I became sceptical of the relevance of their results especially when I was told that anti-histamines were very effective in protecting guinea-pigs challenged with antigen—I knew from bitter experience that such drugs are useless in controlling clinical asthma.

The research project therefore changed direction, and this marked Altounyan's first major contribution

to our understanding of allergy and allergic asthma, which eventually led to the discovery of cromolyn sodium: the need to investigate human asthma and drugs that might modify it in human subjects because there is probably no animal model that exactly reflects human disease.

Altounyan embarked on a program in which he used bronchial challenge in a human subject (himself) to investigate the ability of drugs to prevent the bronchoconstriction induced by the inhalation of antigen. Although other workers² had been investigating bronchial antigen challenge in asthmatic patients, Altounyan was the first to introduce standards to produce a consistent reaction and also to use it to evaluate the potential of a particular drug as a treatment of asthma. Fig 1 illustrates a series of challenge experiments performed by Altounyan in the early 1960s with a chromone designated BLA 8. His control challenges with either 100% antigen or 10% antigen alone resulted in maximum decreases in FEV₁ of 53% and 22%, respectively.

A 0.5% aerosol of BLA 8 reduced the maximum decrease to 22% with 100% antigen and 5% with 10% antigen. Altounyan would describe these results in terms of percentage protection. BLA 8 provided 78% protection against 10% antigen and 61% protection against 100% antigen. Percentage protection against challenge became a very important and essential measurement in screening new chemical compounds, and Altounyan established that for a new drug to be potentially useful in allergic asthma, it would need to provide at least 50% protection for at least 6 hours in challenge experiments in human subjects. To be confident in his outcomes, he also needed to standardize the control challenge and to monitor his underlying bronchial reactivity. When he initially produced a batch of antigen for challenge purposes, he would dilute it until it would produce a consistent decrease in his FEV₁ of 30% to 35%. He describes how he established a routine to provide consistent results. Every Monday and Thursday, he would perform a single antigen challenge at 4 p.m. On Tuesdays, he would inhale histamine or carbachol at regular intervals to measure bronchial reactivity. These principles established an entirely new approach to both the use of bronchial antigen challenge and to drug development that remained valid up to and after the discovery of cromolyn sodium. It allowed Altounyan to write "eureka" on his spirogram when he first tried cromolyn sodium in a single antigen challenge test on January 21, 1965.

Altounyan and his coworkers recognized as early as 1960 that they were on the track of something entirely novel in the treatment of asthma. In addition to the human challenges, they were screening all compounds for their ability to inhibit the release of histamine and SRS-A (later to become the leukotrienes) from sensitized, chopped guinea pig lung. However, when

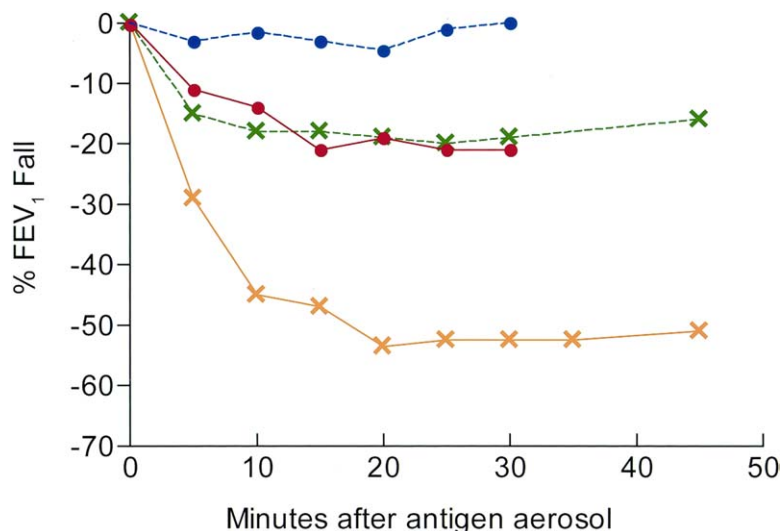


FIG 1. Effect of the chromone BLA 8 on reduction of FEV₁ induced by 2 different concentrations of inhaled antigen in a single individual. *Circles with dashed line*, 0.5% BLA 8 inhaled 10 minutes before 10% antigen; *x with dashed line*, 10% antigen; *circles with solid line*, 0.5% BLA 8 inhaled 10 minutes before 100% antigen; *x with solid line*, 100% antigen.

the project was officially stopped in 1961, screening continued in secret by using only bronchial challenge in Altounyan until the discovery of cromolyn sodium in 1965. Altounyan was able to show within a few months that although a dose of 1.0 mg provided 70% protection if administered 10 minutes before antigen, to obtain adequate protection against antigen challenge for at least 6 hours, a 20-mg dose was required.³ A new delivery method was required to deliver this to the lung, and a modification of a dry powder inhaler invented and developed by Altounyan in the late 1950s, the Spinhaler, was used for this purpose. This was to introduce a whole new class of inhaled delivery systems for the treatment of lung disease. A further requirement established by Altounyan was the need to add a small amount of a short-acting bronchodilator to the cromolyn sodium powder. This was to counteract the bronchoconstriction that some patients experienced when they first inhaled the powder. The bronchoconstriction was thought to be caused by the inhalation of the powder itself, but a more likely explanation is that cromolyn, being a sodium salt, does cause momentary bronchoconstriction. The first product to be launched in the United Kingdom in 1968 was a combination of 20 mg of sodium cromoglycate and 0.1 mg of isoproterenol.

It was after Altounyan had completed the challenge work on himself and established the first product that he and the pharmacologic team, at what was now Fisons Research Laboratories, returned to research the likely mode of action of cromolyn. A series of experiments conducted and published at this time established that the likely mode of action was the inhibition of the antigen-induced release of bronchoconstrictive spasmogens within the lung. Orr and Cox, in 1969,⁴ showed that the drug inhibited degranulation

of mast cells and the release of histamine. Sheard and Blair, in 1970,⁵ showed that it inhibited contraction of passively sensitized human lung strips when challenged with antigen, and it also inhibited the release of histamine and SRS-A from sensitized, chopped human lung when challenged with antigen. Interestingly, in the experiments with human bronchial strips, they showed that the antihistamine mepyramine had no effect on the size of the contraction and that the amount of histamine released did not itself cause contraction of human bronchial muscle. They concluded that the contraction induced by antigen was most likely due to SRS-A and that the effect of cromolyn on the response of a bronchial strip to antigen challenge was mainly caused by a reduction in the SRS-A released. In retrospect, it is a pity that this aspect of the activity of cromolyn was not followed because subsequent experiments concentrated mainly on the effect of the chromones on histamine release from mast cells rather than SRS-A. This probably was due to the fact that the measurement of SRS-A at the time required a biologic assay with guinea pig ileum.

Although Altounyan was not directly involved in these experiments, there is no doubt that he recognized the importance of the findings. A letter written to a pediatrician at Great Ormond Street Hospital dated April 15, 1958, included the following: "It appears that SRS-A is concerned in human anaphylaxis and it is possible to protect humans in acute anaphylactic shock by a combination of anti-histamine and anti-SRS-A drugs." At that time, the chromones they were using in antigen challenge experiments did have anti-SRS-A activity. It was a later chromone, FPL 55712, used initially by Altounyan in challenge experiments, that helped the Swedish workers to separate SRS-A into its different leukotriene components.

The discovery of cromolyn sodium opened up a whole new science on the mechanisms involved in asthma and eventually other allergic diseases. Altounyan was able to influence the direction and standardization of future bronchial antigen challenge experiments that led to the recognition of the immediate and late asthmatic reactions, the importance of the influx of eosinophils in allergic disease, and the central role played by the mast cell in allergic inflammation. In extending the experiments to examine the protection provided by cromolyn on the immediate and late bronchial reactions, the groups led by Pepys in London⁶ and Orie in Groningen, The Netherlands⁷ followed the protocol established by Altounyan in earlier years.

Inhaled cromolyn sodium was first launched in the United Kingdom in 1969 and was followed in the main countries of the world in the early 1970s. It did transform the treatment of asthma in both children and adults because up to that time, the only treatments available were oral and inhaled bronchodilators and oral corticosteroids. In addition to the improvement in the symptomatic control and the lives of asthmatic patients, perhaps the most important characteristic was the oral steroid-sparing effect demonstrated.

It was not long before other investigators began to investigate the efficacy of cromolyn in other bronchial challenges and in other organs affected by allergy. At the launch symposium held at the Royal Society of Medicine in London on March 5, 1969, there were the first reports by Davies of the effectiveness against exercise-induced asthma and by Pelikan from Orie's group of the effectiveness of nasal application against antigen challenge in the nose. These led to the development of nasal powders and nasal solutions for the treatment of seasonal and perennial allergic rhinitis and the establishment of the inhaled form to prevent exercise-induced asthma both in children and in athletes and sportsmen.

In the early 1970s came the first reports of topical solutions of cromolyn being used in eye diseases⁸ and early trials of what was to become one of its most important uses, the treatment of vernal keratoconjunctivitis. Until then, topical steroids were the only treatment available, with all the attendant long-term problems, and cromolyn eye drops have a steroid-sparing effect, as well as being efficacious in this distressing condition. The eye drops were also shown to be effective in seasonal allergic conjunctivitis and are widely used in this common condition, as exemplified by the allergic conjunctivitis caused by cedar tree pollen in Japan.

In the early 1970s, inhaled solutions began to be administered to younger children and infants with powered nebulizers. Cromolyn began to be used in the treatment of wheezing diseases in infancy. Although not always effective, probably because of an inadequate

dose being delivered, because of its proved safety, it did provide a new approach to the management of this younger age group.

The next organ to which cromolyn was administered was the gastrointestinal tract. Trials were undertaken in a range of conditions from aphthous stomatitis to allergic proctitis. Studies in inflammatory bowel disease did not provide consistent results, and studies in conditions of food allergy were controversial. The inconsistency in the results probably reflected the difficulties in providing an adequate dose at the likely site of action, the upper part of the jejunum. The most consistent results have been in the diarrheal form of irritable bowel syndrome with evidence of an IgE food-related cause.⁹ However, use of the oral form of the drug in 2 difficult and severe conditions should be mentioned: systemic mastocytosis¹⁰ and eosinophilic gastroenteritis.¹¹

The only organ exposed to external antigen in which no cromolyn product yet exists is the skin. There have been a number of published trials demonstrating the efficacy of topical application of cromolyn to the skin for the treatment of atopic dermatitis. Sometimes patients are ahead of physicians and the pharmaceutical industry. The support Web site for parents and children with systemic mastocytosis, www.mastokids.org, gives a formula for a topical lotion of cromolyn to treat the itching associated with this distressing condition: Magic-Masto-Lotion or MML. Altounyan would have been fascinated and delighted by this because he suffered very severely from eczema as a child. A new skin formulation named after Altounyan, Altoderm (Thornton & Ross Ltd, Huddersfield, United Kingdom), has recently been developed and shown in a double-blind, placebo-controlled trial to be both effective and to provide a steroid-sparing effect in atopic dermatitis in children.¹² This latest development takes the story of this drug full circle, from the lung to the skin through the nose, eye, and gut, providing treatment of all diseases resulting from the exposure of these body surfaces to external allergens.

It is fitting that patients should have the last word; Magic-Masto-Lotion, developed by a patient, summarizes both the primary mode of action of this remarkable drug, inhibition of the release of chemical mediators of allergic inflammation from mast cells, and its qualities in a range of conditions in which the mast cell is involved, all of which resulted from the dedicated work of one man.

Alan M. Edwards, MB
The David Hide Asthma and Allergy Research Centre
St Mary's Hospital
Newport
Isle of Wight
United Kingdom

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