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From khellin to sodium cromoglycate – a tribute to the work of Dr. R. E. C. Altounyan (1922–1987)

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Sodium cromoglycate, which was launched in 1968 by the British company Fisons for the treatment of allergies and asthma, was an absolute novelty in chemical, pharmacological as well as therapeutic respects. The khellin derivative meanwhile did not owe its discovery to the usual strategies for finding drugs. On the contrary, the protective effect of the substance was discovered in a self trial through systematic antigen-induced provocation tests of the medicinal doctor and allergic Roger Ernest Collingwood Altounyan (1922–1987). The only subsequently formed hypothesis of a mast cell stabilising effect of Sodium cromoglcycate did not prove to be valid for the search for similar or more effective substances. A further development of this drug class could not take place because of the lack of suitable pharmacological models.

"This is the very stuff of modern mythology. It is also true."
T. S. C. Orr (1989) [1]

1. Introduction

An investigation into the development, production and marketing phase of antiallergic drugs, which lasted about 100 years, included the drug sodium cromoglycate [2]. Unlike all other medications investigated, the unwavering dedication of one individual resarcher, Roger Altounyan (1922–1987), was solely responsible for the development of this drug.

2. Roger Altounyan – life and work

"I am not a scientist but an asthmatic who happens to be a Doctor".
Roger Altounyan (1976) [3]

Roger Ernest Collingwood Altounyan was born in 1922 in Syria, the only son of Dora Collingwood who was English. His father, Ernest Haik Riddel Altounyan (1889–1962) was of Scottish, Northern Irish and Armenian origin and worked as a doctor at the Altounyan Hospital in Aleppo (Syria). Ernest Altounyan, who was a friend of the pro-Arabic British Agent Lawrence of Arabia (1888–1935), served as a liaison officer between the British and Syrians and played an important role in the negotiations which ultimately brought about political independence for Syria [4].

Like his father Roger Altounyan graduated in medicine at Cambridge. During the Second World War he trained bomber pilots in night-time low flying, a risky activity, for which he was awarded the AFC [5] service medal. After the end of the war he continued his clinical training at the Middlesex Hospital (London) and then joined his grandfather's hospital in Aleppo [6]:

"I worked there for a frantic 5 years attempting to cope with Tuberculosis, Typhoid, Tetanus and Trauma of all kinds. It is an interesting fact that I only saw 3 cases of asthma – none of which was serious, even though we saw ... the chronic sick from a population of ½ million. One possible reason for this remarkably low incidence ... may have been the highly developed conservation system ... in that ancient city ... This system ensured that 100% of the population suffered from recurrent ascariasis" [7, 8].

With the Suez crisis in the foreground the political situation for British citizens in Syria became critical and the Altounyan family left the country. The hospital and property were seized and the family made their new home in Britain [9]. In 1956 Roger Altounyan gained employment at Bengers Research Laboratories (Holmes Chapel, Cheshire), part of the Fisons Group, which was mainly involved in the fertiliser business. There he was given the position of "Medical Liaison Officer", *"not because I knew anything about research, but because I ... had known the research director as a medical student"*, as he laconically noted in 1977 [10]. His duties included agreeing pre-clinical research between chemists and pharmacologists. Altounyan occupied himself with the development of an enzyme preparation based on DNAse and chymotrypsin. Used as a powder inhalant this mixture was supposed to reduce the viscosity of sputum in patients suffering from chronic bronchitis or asthma [11]. Altounyan developed a forerunner of the inhaler later known as the Spinhaler® for the powder application:

"So quite naturally I thought of a propeller ... quite naturally because I had spent my war years in the RAF sitting behind a propeller ... The solution seemed quite simple ... since asthmatics can breathe in almost normally, why not get them to inspire through a tube inside which a propeller would rotate somehow releasing the drug automatically" [12, 13].

Fig. 1: Roger Altounyan (1922–1987)

Although the inhaler proved a success, within a short time the enzyme preparation was shown not to be effective. A veterinary iron preparation also represented a further setback, as the anticipated weight gain in piglets with the medication was not achieved. Altounyan summed up as follows:

"My first steps in pharmaceutical research were interesting but in therapeutic terms my achievements were classed either as 'setbacks' or 'disastrous failures' depending upon who was actually talking" [14].

In addition to his duties at Bengers, Altounyan remained active as a hospital clinical assistant and offered "unofficial" consultations for asthmatics released from hospital three times a week in an empty ward at the Monsall Hospital in Manchester as he was always personally concerned about their welfare [15]. To diagnose and judge the effectiveness of the therapy Altounyan carried out bronchial provocation tests with and on his patients which was still by no means standard practice in the fifties.

As the consultations could only provide a momentary record which could prove misleading, he got the patients to keep a daily record of their symptoms between consultations. Altounyan himself was allergic to pollen and animal hair and suffered from asthma as well as eczema:

"I can claim to speak from experience for such patients since I have had at least one, usually three allergic conditions since I was four years old. Until the age of 10, my major disability was eczema ... Bouts of intensive itching led to scratching, and then bloody tears ran from every flexure ... My first really severe attack of asthma came out of the blue when I was a medical student ... One night I woke up gasping for breath, and thought I would die ..."

After suffering a further asthma attack the following night, Altounyan went to see the 'Student Medical Officer'. The reaction of the doctor was a terrible experience for him; *"'It's alright, my lad', he said with a laugh, 'you've only got asthma'"* [16]. The doctor questioned the young medical student about the causes and therapy for the condition and then to cap it all, *"'You haven't mentioned the most important cause.' He tapped his head and nodded knowingly at me. 'The old psyche, you know', he proclaimed."*

In accordance with his presumption about the psychogenic cause of the asthma he prescribed phenobarbitone in addition to ephedrine, patted Altounyan on the shoulder and advised him not to worry too much. Altounyan fought against this simplistic "psychosomatic" view of asthma all his life:

"Asthma still has a social stigma ... To tell some persons that they have asthma is to tell them that you think they're neurotic, or that they could recover if they really tried. You may think I exaggerate, but this attitude still persists in the minds of some doctors – at least in Europe."

Altounyan called on doctors to reassure the patient, *"that the asthma is not his fault, and that it's a treatable disease, just like diabetes"* [17]. The search for *the* cure for asthma, like a modern "wonder drug", ultimately became Altounyan's life's work until his death on 7th December 1987 from this same disease. His work was based on khellin which was a very revolutionary drug in many respects in the early fifties.

3. The *Ammi visgnaga* ingredient khellin

The fruit of the native bishofite plant to Egypt (*Ammi visnaga* L. Umbelliferae or Apiaceae) was first described in the Ebers papyrus (around 1550 BC) and the Arabic name of the plant was "khella". Traditional areas of application for the drug included urinary tract infections (including colic caused by lithiasis) and cramp [18]. Trials conducted at the University of Cairo in the 1930's confirmed the spasmolytic effect on smooth muscle and also discovered a further coronary dilatory effect. *Ammi visnaga* decoction and tincture were first officially registered as pharmaceutical preparations in Egypt in 1934. In 1938 Ernst Späth isolated the main active ingredient khellin in its pure form in Vienna and identified the structure as a furanochromone [19]. The synthetic composition of khellin was successfully undertaken in 1949, although this was irrelevant for the subsequent technical production of chromone. Khellin can be obtained from pulverised fruit via ether extraction and re-crystallisation with methanol.

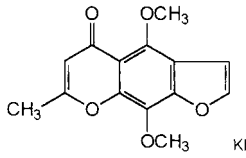
Since 1945 khellin has been used in angina pectoris therapy and in the 1950's it was in Germany widely prescribed for asthma. The advantages over adrenalin and ephedrin were the longer period of efficacy and the fact it did not raise blood pressure meant that it could also be used on hypertensive patients. In contrast to aminophylline (theophylline-ethylenediamine) which only has a limited benefit/toxicity ratio, furanochromone appears to be more practical for clinical use. In the 1950's a solution of *"Khellinum puriss., 'Moormann'"* was also on the market briefly in Germany under the name Khelfren® – Aerosol for inhalation with asthma and other respiratory diseases. The dose was *"20 mg Khellin = 4 ccm per aerosol treatment"* [20].

The substance was one of the first medicines whose effectiveness was critically tested in the double dummy trials introduced in 1946. *"By 1954 reports on the efficacy of khellin in the treatment of angina pectoris had disappeared from medical literature"* [21]. There is a negative monograph by Commission E of the former German Bundesgesundheitsamt on the ammeos visnagae fructus extract used in phytotherapy.

The poor water solubility of khellin (approx. 25 mg/100 ml) was always a problem giving rise to numerous attempts to change the molecular structure. One approach was:

"to split the two khellin methoxy groups and add two alkoxy groups ...", particularly as, *"dialkylaminoethyl groups offer additional pharmacological and therapeutic value in numerous substances, e.g. in antihistamines, local anaesthetics and spasmolytics as well as central analgesics."*

Even though the substances obtained were *"highly soluble in water"*, *"completely anti-spasmodic"*, suitable for intravenous application and between three and five times less toxic, they were not used in therapy [22]. Even the piperidinomethylkhellin synthesised by Benno Reichert (1906–1970) was not used, although the *"spasmolytic effect was twice that of khellin"* with his preparation [23]. Only the pharmacologically tested azaspirium chloride by Heinrich Hofmann (1909–1971) and Peter Marquardt (born 1910) was used in the compound Germakellin® [24]. This preparation was based on the Keldrin® model containing khellin and was also subjected to clinical trials by the renowned allergist Wilhelm Gronemeyer (born 1912) at the



Khellin

asthma clinic he ran at Bad Lippspringe [25]. Intravenous drip infusion of up to 20 ampoules/24 hours was apparently successful as *"a last resort"* for asthmatic cases. Germakellin® was advertised as the *"ultimate treatment for your asthma patients . . . without sympathomimetics or corticosteroids"* [26].

In addition to the problem of the structure of khellin, there were also discussions about the use of solvents. Theophylline derivatives, salicylates, hydroxycinnamic acid, tropic acid and other aromatic oxysulfonic acids as well as sodium dehydrocholate subsequently underwent testing. This gave rise to a dispute about whether the antispasmodic effects observed were not really caused by the solvents [27].

Other modifications to the khellin molecule resulted in benzaron and benziodaron. Benziodaron also produced uricosuria, in addition to the broncho-dilatory effect and is still available for therapeutic use today as Brom analogon benzbromaron (Narcaricin®).

Screening the phenol group in benziodaron produced amiodaron which was initially also used as a coronary dilator. Following cases of corneal deposits, skin discolorations and thyroid-related disorders the substance was discredited until 1974 when its usefulness was discovered in the treatment of cardiac disrhythmias otherwise known to be resistant to therapy (Cordarex®) [28].

Ultimately khellin also inspired the development of Nifedipin (Adalat®) in coronary therapy [29].

4. From khellin to sodium cromoglycate

"I decided to abandon my plans to teach you anything about discovery – so instead
I will tell you a story – the Intal story.
So, are you sitting comfortably?"
Roger Altounyan (1977) [30]

When Roger Altounyan joined Bengers Laboratories in 1956 the khellin product Benecardin® was already in circulation. Further a research project had also been launched to develop khellin derivatives which were more easily soluble. In 1957/58 they were initially successful with K 18 which was used on a small group of asthmatics. But, ultimately it was found to be insufficiently effective [31], particularly given the unpleasant taste and the fact that it acted as an irritant to the mucosa on inhalation [32].

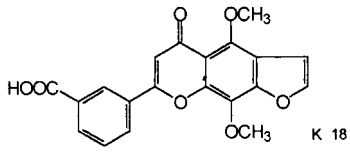
Moreover, it caused bilirubin serum levels in patients to rise which gave rise to concern about potential hepatoxic effects of the substance [33].

Altounyan described the general state of the research as follows:

"The compounds relaxed guinea-pig bronchial muscle and protected these animals from challenge with histamine or acetyl choline. One compound also delayed the onset of distress in sensitized guinea-pigs exposed to an aerosol of egg albumen."

However, Altounyan as an experienced clinician questioned the validity of the results:

"Knowing very little about such matters, I became sceptical of the relevance of their results, especially when I was told that antihistamines were very effective in protecting guinea-pigs challenged with antigen – I knew from bitter experience that such drugs are useless in controlling clinical asthma . . . I could see nothing in common between guinea-pigs and man except neither species wagged a tail" [34].



K 18

Altounyan was by no means alone in his scepticism about the guinea-pig model, although he alone was prepared to take the consequences which took an atopical constitution and willingness to put himself at risk:

"So, I decided to see whether I could duplicate these experiments using myself as a model for I knew I was sensitive to guinea-pigs, so . . . we cooked up some of their hair and cautiously I inhaled an aerosol of the soup – to my surprise I developed a sharp attack of asthma" [35, 36].

The first report on his self testing was dated 18th July 1957 [37]. After about one year he had established the following procedure: On Mondays and Thursdays Altounyan inhaled one of the standard antigen solutions to test the protective-anti allergic effect of the khellin derivatives. On Tuesdays he inhaled histamine or acetyl choline by aerosol a number of times at fixed intervals to determine any direct antihistamine-like or anticholine-like effects of the substances. The testing was conducted during his consultations at the Monsall Hospital.

Altounyan *"found it helpful to the morale of my discouraged patients to see their doctor coughing and spitting and wheezing just like they themselves."* It became clear in the self-tests that some of the khellin derivatives protected from antigen-induced broncho-constriction without developing any antagonism toward carbachol or histamine. *"In other words they appeared to be specifically anti-allergic."*

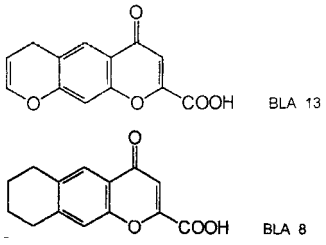
Although, the most active substance in the guinea-pig and all other pharmacological models proved to be completely inactive – it was only effective for a brief period, was completely ineffective as an oral preparation, it produced irritation to the mucosa on inhalation and tasted extremely bitter. The company management were very sceptical about the poor interim results of his research project. In 1977 Altounyan reported in retrospect:

"Their arguments ran something like this:
. . . Can we trust this Altounyan fellow? His record so far has not been very promising. I had already been involved in several disastrous projects and was largely responsible for proving them to be so – the bearer of unsavoury truth is never praised . . . Will his findings apply to other people? . . . All potent drugs have side-effects – or at least some pharmacological activity. These drugs have no spectrum of pharmacological activity – therefore it seems most unlikely they are going to be potent. Lastly, how can we support a research programme based on the human guinea-pig without animal screen?"

Altounyan concurred, *"I admit some of their arguments were valid."*

An externally appointed *"world expert"* advised the management to drop the project, but despite the *"gloomy dictate from on high"*, Altounyan was allowed to continue his work on *"very low priority. We played our little game of Molecular and Russian roulette. But at review meetings the old arguments would be repeated with deep sighs from the chair. We soon became adept of the limelight . . . We found it best not to mention the project and above all never to ask for money or equipment for it - these were all scrounged or somehow diverted from respectable, high priority projects"* [38].

Gradually the first structural-effect-relationships crystallised and the "hit rate" of synthetics rose. In 1961 he



summed up as follows about half-way through the sodium cromoglycate development:

"In the last two years it has taken up a major share of pharmacological working time ... It is, however, difficult to say how close we are to a product suitable for clinical trials in asthma ... Most of these active agents are confined to a narrow class of structurally related compounds ... Heaven only knows how much widespread activity of this sort is likely to be ...

But to plot a course through these uncharted seas requires great concentration, originality, intuition and good luck ... if we are to achieve success before someone else does so" [39].

After a management reshuffle at Bengers a report was to be submitted on the khellin project, Altounyan spoke out against the proposed sale of the results. He was removed from the research department and testing was halted. This occurred at a time when the first promising results had been obtained with BLA 8 and BLA 13 [40]. *"But by now our parental instincts had been fully developed – we were not going to stop for anybody."* The syntheses were continued in secret, after determining acute toxicity in animal experimentation, Altounyan continued to test the khellin derivatives as before via self-testing.

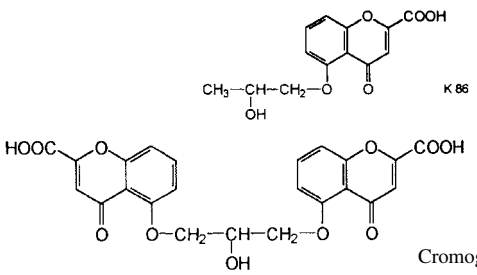
"In 1963 the first break came – one compound afforded nearly complete protection even at a concentration of 0.5% inhaled 2 hours before the antigen. That was what we had been waiting for ..."

But then there was an unexpected disappointment:

"A few days later the second batch was prepared and tested – but it proved no more active than other compounds. What had gone wrong? Was it my test? I had never had 'false' protection before" [41].

At this point the Bengers management were fired and the research department of Fisons were called upon *"to run the show ourselves until a new Research Director was chosen."* Altounyan returned to the Research Department. The chemist Brian Lee developed a theory that the exceptional activity of the trial could possibly be related to a Bis-chromone occurring during the synthesis.

The new Research Director supported the asthma project, *"more chemists were pressed into action."* On 19th January 1965 the chemist Colin Fitzmaurice who was in the project from the very beginning synthesised FPL 670, sodium cromoglycate. The substance represented the "bis compound" for K 86 [42].



Cromoglycic acid

"Two days later, on the basis of a single Ag test ... I felt sure we NOW had a drug" [43, 44].

By this point Altounyan had carried out 615 self tests using 206 different substances according to the reports available [45].

For the application of the sodium cromoglycate powder he optimised the aforementioned "Spinhaler®" in conjunction with an engineer.

"By late 1966 Fisons Laboratories ... were really beginning to hum ... It was a great experience for us all. Nothing seemed too much for anybody ... We all felt very excited ... DSCG was now everyone's child" [46, 47].

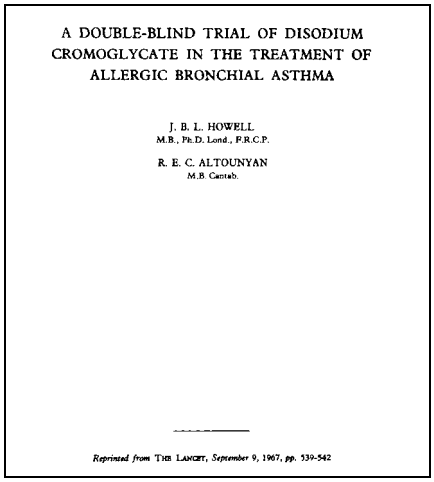
"Intal had reached the final stage of its development – had it now the stature to stand up in the clinical arena?" However three double-blind trials failed, because – by contrast to the procedure followed by Altounyan – no accurate documentation had been kept with patient diaries, etc. The Fisons management visited the testing centres to get an impression and ultimately were unable to resist the enthusiasm of Altounyan's friend, the chest specialist, Jack Howell (born 1926):

"They had no free choice since no-one, not even they could have resisted the fantastic enthusiasm bursting out of Jack Howell – he and his patients just flattened any doubts ... I wonder how many of your drugs sit falsely convicted by experts on their shelves, just where Intal would still have been but for the 'Jack Howell's' of this world. Gentlemen, beware of the expert, by the time he is generally recognised as such, in my experience, he should usually be referred to in the past tense" [48].

On 9th September 1967 Roger Altounyan and Jack Howell published a paper in the "Lancet" on "A Double-Blind Trial of Disodium Cromoglycate in the Treatment of Allergic Bronchial Asthma". They concluded:

"There was a significant clinical improvement in all patients ... Subsequent experience over periods of up to 26 months has confirmed the therapeutic value and safety of FPL 670 in the management of allergic bronchial asthma" [49].

Sodium cromoglycate was introduced into therapy under the name Intal® in 1968. Intal® was an abbreviation for the effect "Interfere with Allergy" [50]. In 1971 Rynacrom® nasal spray was registered, it was first available in Britain, Australia and South Africa. Then followed Opticrom® eye drops and in 1977 Nalcrom® capsules were brought on to the market to treat food allergies.



A DOUBLE-BLIND TRIAL OF DISODIUM CROMOGLYCATE IN THE TREATMENT OF ALLERGIC BRONCHIAL ASTHMA

J. B. L. HOWELL
M.B., Ph.D. Lond., F.R.C.P.

R. E. C. ALTOUNYAN
M.B. Cantab.

Reprinted from THE LANCET, *September 9, 1967, pp. 539-542*

Fig. 2: Reprint of the Lancet publication by Howell and Altounyan (1967)

5. The search for "oral Intal®" and the introduction of nedocromil

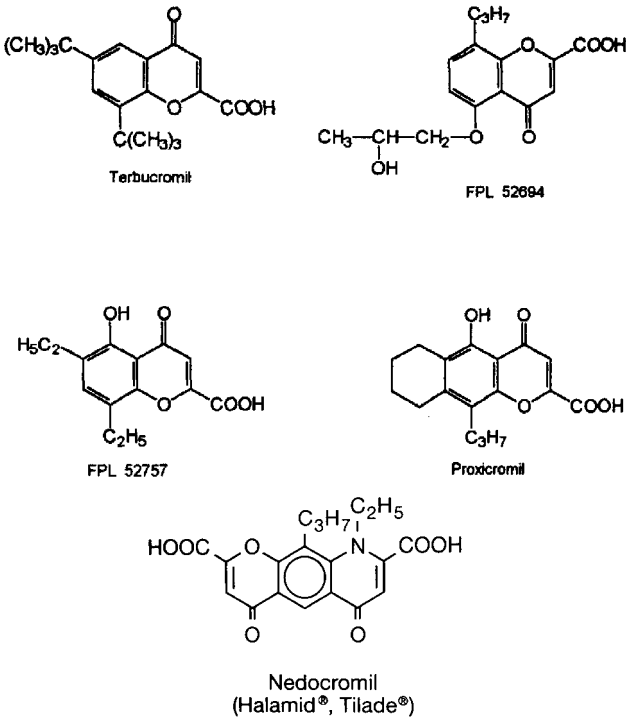
Even after the introduction of sodium cromoglycate Fisons were still intensely involved with chromones and related substances [51], such as FPL 55712, a leukotriene antagonist [52]. The aim was still to develop an anti-asthmatic preparation for oral use as before [53]. When the subject of launching Intal® successfully was readdressed [54], they selected the aforementioned BLA 8 which had been tested early on as the starting point [55].

They had particular faith in FPL 52757 [56], FPL 57787 (proxicromil) [57] and FPL 52791 (terbucromil) [58] which were not only effective in experiments but also in clinical trials. In addition, FPL 52694 also seemed notable as it blocked pentagastrin-induced gastric acid secretion and was undergoing clinical trials for the treatment of ulcers [59]. FPL 52757 was discontinued on account of potential liver toxicity [60].

"This was a major setback for the team as this compound had gone through chronic toxicological testing without any problems in 5 animal species, including 2 primate species – yet another example of the problems and potential dangers of trying to extrapolate from animals to man" [61].

Nevertheless, on 22nd May 1979 Fisons shareholders were informed at the Annual General Meeting that proxicromil had reached the stage of clinical trials and a *"successful product launch"* was likely [62]. In January 1981 Fisons had to announce that clinical trials had been abandoned due to *"unexpected findings of toxicity in long-term animal studies"* which were now statutory following changes to the pharmaceutical legal requirements [63]. The launch of proxicromil had been scheduled for September 1981.

Important attributes in favour of an oral application for chromone were greater convenience, improved compliance and greater acceptance among patients. *"Proxicromil was expected to have a considerably larger potential market than sodium cromoglycate."* The news of the discontinuation of the proxicromil development therefore led to a short-term dip in Fisons shares, but did not permanently damage the reputation of the company [64]. Fisons stressed that they still had other effective anti-asthmatic substances in the "pipeline" [65], but had to concede that these were still in the early stages of research [66]. Ultimately, nedocromil (Tilade®) which was also tested by Altounyan was launched in 1985, although this also had to be inhaled like DSCG. With this substance they hoped that it would work better than sodium cromoglycate especially on older patients and in non-allergic asthma forms [67]. Fisons urgently required an innovation to counter the glucocorticoid inhalants which were becoming increasingly popular. However, Nedocromil failed to prove to be more effective [68], Fisons managed only to produce an in-house rival with a "me too" preparation. Positioning of the two substances then proved even more difficult [69].



6. The global search for "mast cell stabilisers"

Altounyan never kept the importance of the self-testing for the sodium cromoglycate development secret in any way. In 1967 he published a brief notice on the "Inhibition of experimental asthma by a new compound – Disodium Cromoglycate" in the "Acta Allergologica". He wrote:

"Asthma was induced in an atopic subject (RECA) by the inhalation of ... antigens ... The activities of anti-allergic compounds were assessed by comparing the FEV_1 changes which occurred during control and test experiments conducted at intervals of 3-4 days. Over the past nine years a large number of compounds have been examined for anti-allergic activity by this method; of this disodium cromoglycate, Intal®, showed outstanding protective activity when inhaled before antigen challenge" [70–72].

Altounyan refrained from making any comment on the possible effect mechanism, a publication from the Fisons Research Laboratory appeared in "Nature" on this subject on 30th December 1967. On the basis of a range of tests, the conclusion was: *"Disodium cromoglycate had few general pharmacological effects, was rapidly excreted and seemed to have a low order of toxicity."* The effect mechanism was alleged to be: *"The compound appeared to inhibit specifically the anaphylactic process initiated by reaginic antibody-antigen interactions"*. This is how mast cell stabilisers came to be *"crucial to any allergic reaction"* [73]. This cell had only ever attracted interest from a pathological [74] viewpoint but not in therapeutic terms. Prior to the publication in "Nature", we could only find one single publication where "mast cell stabilisation" was even mentioned as a potential pharmacological point of application and this was in a purely hypothetical context [75].

The "Nature" publication which has been quoted thousands of times only mentioned the self-testing by Altounyan of FPL 670 in passing. Any uninitiated reader would be bound to assume that sodium cromoglycate was discovered with the experimental models specified (passive cutaneous anaphylaxis in monkeys and rats, passive inhalative anaphylaxis in claw foot monkeys, histamine and leukotriene release from human lung fragments and contraction of human bronchus fragments) [76].

On the basis of the hypothesis described in "Nature" of the "mast cell stabilising" effect of sodium cromoglycate, a global search began for similar agents, whereby the models specified and related models were employed. Even in chemical terms sodium cromoglycate was taken as the basis, then they moved on to heterocyclene containing nitrogen, modified this further and finally discovered "end products", from which it was often difficult to identify the

starting point. A typical example for this is lodoxamid (Alomide®) [77].
In 1984 the Japanese partner Fujisawa submitted a report to Fisons of numerous companies who were involved in "mast cell stabiliser" development [78]. The majority of the substances specified were mentioned in the literature evaluated by us. In addition around 60 further substances were listed. As with anti-histamines it is impossible to present comprehensive figures, over 40 health care companies were involved.
However, the large number of compounds tested, especially compared to antihistamines, bears no relation to the number of substances actually introduced. Inquiries about the "whereabouts" of the substances specified here have met with very little success.
Only the product repirinast was introduced in 1987 as oral asthma treatment (Romet®), whereby the structures of the virtually active repirinast metabolite and sodium cromoglycate are clearly related [79]. In 1991 pemirolast followed [80].
Roger Altounyan would not have been surprised by these numerous setbacks. He questioned the hypothesis of "mast cell stabilisation" in 1969 already at a Congress in Groningen in public: *"The simple unitarian theory of the drug's action has subsequently been progressively eroded by further work"* [81]. In 1980 he summarised his argument:
"I will give you five points which suggest that cromoglycate does not act only on the mast cell . . . The first piece of evidence is in exercise asthma. Many careful workers have failed to detect the release on any mediators after exercise . . . The second . . . is that if the same receptor for cromoglycate is involved in both exercise and antigen-induced bronchospasm, then pharmacologists would expect the dose-response curve of the drug to be parallel in both situations . . . It is evident that the . . . curves are . . . divergent . . . My third point is from another experimental model, the inhibition of sulphur dioxide-induced bronchospasm . . . We were unable to detect mediator release during SO_2 challenge . . . Again there is a clear divergence of the two dose-response curves and again this implies that there are two different receptors for the drug. The fifth piece of evidence derives from work in animals" [82].
One of the principle methodical problems is that there is no correlation between the individual pharmacological models, e.g. the effectiveness of a substance in passive cutaneous anaphylaxis in rats and testing human lung fragments.
Also, it was known that other asthma treatments, such as beta-sympathomimetics [83] and theophylline [84] exercised a mast cell stabilising effect, without the addition of the allergen-protective effect comparable to sodium cromoglycate.
Last but not least decisive were substances which performed far better than sodium cromoglycate in experiments and were far less effective in clinical therapy than Intal®.
In 1982 the Institute for Drug Research at the Academy of Sciences in the GDR were clearly disillusioned:
"As there are currently no better, more valid models, methods or ways available apart from those specified for identifying and developing anti-anaphylactica, they are applied and followed extensively . . ." Although this raises *"the question of whether the spectrum of methods applied currently is at all relevant for these problems"* [85].
Other experts showed a similar reaction or were even more sceptical:
"Clearly, these models are not predictive of antiasthmatic activity" [86].

7. Self test and pharmacological models – the development of sodium cromoglycate as a teaching lesson?

In 1956, the year Roger Altounyan joined Bengers Laboratories, they gave *"awards for hunches . . . A hunch, based on an observation made by a general practitioner might . . . lead to most important avenues of diagnosis or treatment"* [87]. This prize had more to do with marketing than science, although curiously enough, the intuition of the general practitioner, Altounyan coupled with determination did in fact lead to a completely new approach to treatment in asthma and allergy therapy. He deliberately chose the acute high-risk [88] route of self-testing to test the khellin derivatives because he doubted the value of models based on animal experimentation and Altounyan ultimately paid the price. The head of the Fisons Research Department commented in retrospect in 1989:
"It cannot be denied that the some 3,000 bronchial challenges that Roger Altounyan conducted on himself at Manchester must have insulted an already injured organ, and may have contributed to his death from asthma in December 1987 [89]. *It was, however, in the nature of 'the man' to sacrifice all to 'his work' and my company and medical science are the richer for it"* [90].
Roger Altounyan does not seem to have regretted his decision [91], but supported the view that medical researchers have to take certain risks anyway. In 1976 Altounyan compared the completely atypical development of sodium cromoglycate for the 1950's and 1960's with pharmacological research today and drew the following conclusions:
"New potential drugs are tested more carefully and the evidence for their safety is scrutinised for months by independent experts before even <u>one</u> molecule reaches a patient . . . I am sure you all approve of these developments in principle, but as you have heard it is not always possible to predict with confidence what will happen in man if you have conducted exhaustive tests in lower primates. We humans are a peculiar breed . . . I should therefore like to make a plea for more common sense lest we stop research altogether. In the case of DSCG we were able to reach our goal in 8 years in the '<u>bad</u> old days' – today under existing regulations we would be far from the end now in 1976 – in fact it would have taken generations of researchers another 650 years to reach DSCG . . . In research there is no <u>sure</u> route to success. Research is like going on holiday . . . In my opinion we should allow – even encourage – anyone who feels the urge to travel as they wish . . . in search of their goal or destination, and 'Good luck to them all', I say, provided of course they really PROMISE to leave no LITTER" [92].
Knowing the "true" story behind the discovery of sodium cromoglycate, it is not surprising that the global search for (oral) "mast cell stabilisers" has been more or less a total washout. The companies involved were insufficiently well informed about the genesis of sodium cromoglycate and did not have a "Roger Altounyan" who would have conducted systematic screening via self-testing.
The development of "mast cell stabilisers" ended up in a similar 'no way out situation', as did psychopharmaceuticals according to the former Research Director of the Basle-based Hoffmann-La Roche AG, Jürgen Drews, in 1986:
"Fixing understanding of illness to 'successful' therapy of the condition, has in turn defined synthesis programmes in chemical labs and tests and selection procedures in pharmacological labs in the pharmaceutical industry . . . Industrial pharmacology would do well to remain sceptical of

circular arguments concerning links between findings from animal experimentation and pathophysiological mechanisms in humans. It should rely ... less on mechanical and more on complex, but pharmacologically relevant models" [93].

The unique input of Altounyan who always remained an outsider as a general physician of Mediterranean origin among British pharmacologists and allergists, earns our respect. Millions of asthmatics and allergic people have him to thank for relieving their suffering, and often can even lead a normal life. Even after using sodium cromoglycate for decades severe side effects are minimal. Apart from a few phytopharmaca, there cannot be many preparations with such a clear-cut use/risk balance.

Roger Altounyan has been largely forgotten in Britain, in Germany he never achieved wide recognition [94]. This paper is dedicated to the memory of the life and work of this exceptional doctor and personality.

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