

Clinical effects of nedocromil sodium on challenges invoking neuronal mechanisms and on virally induced symptoms

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Although sensory nerve activity may be important to the human airway in numerous possible ways, the relevance of "neurogenic inflammation" to the onset and development of asthma is unknown. However, several of the symptoms of asthma (bronchoconstriction, cough, and dyspnea) have a neuronal component that can be modeled in the laboratory by various stimuli that are thought to invoke sensory nerve activation. Nedocromil sodium is highly effective against bronchoconstriction induced by bradykinin, the tachykinins substance P and neurokinin A, and sulfur dioxide and metabisulfite. The results for induced cough in healthy subjects are equivocal, although the drug is effective on spontaneously occurring cough in patients with asthma. Nedocromil sodium had a modest but significant effect on symptoms associated with episodes of viral infection. (J Allergy Clin Immunol 1996;98:S135-42.)

Key words: Bronchoconstriction, cough, nedocromil sodium, neuronal stimuli, viral-induced symptoms

Neurogenic mechanisms involving the release of neuropeptides from sensory nerves of the airways may contribute to asthmatic inflammation in several ways.^{1,2} The characteristic shedding of the airway epithelium in asthma results in exposure of sensory nerve endings and stimulation by a variety of environmental factors such as chemicals, cold, and fog. The nerve endings may be further sensitized by mediators such as prostaglandins and cytokines that originate from inflammatory cells.³ The sensitized nerve endings can then be activated by bradykinin, an inflammatory peptide.⁴ Once activated, these sensory nerves release neuropeptides (substance P and neurokinin A) and calcitonin gene-related peptide that can cause many of the pathologic features of asthma such as bronchoconstriction, vasodilatation, plasma exudation, and mucus secretion. The effects of tachykinins may be exaggerated by loss of epithelial cells because these are the major source of the tachykinin degrading enzyme, neutral endopeptidase.

Whether neurogenic inflammation is important

in asthma is uncertain.⁵ However, neuronal mechanisms underlie some of the symptoms in asthma, such as cough and dyspnea, as well as bronchoconstriction in response to certain stimuli that invoke neuronal mechanisms. These symptoms may be modeled in the clinical pharmacology laboratory in the form of challenge tests, for example, bronchoconstriction induced by bradykinin, tachykinins (substance P and neurokinin A), or sulfur dioxide and nebulized metabisulfate. Inhibition of sensory nerve activity by a drug should be reflected in protection against these stimuli. Similarly, a protective effect on induced cough (e.g., by capsaicin, citric acid, or fog) can be measured in the laboratory.

Viral infections are a very important cause of asthma attacks in children and adults. It has been estimated that up to 60% of asthma attacks in childhood are triggered by viral infections.^{6,7} One reason why viral infections have such a marked effect in asthma may be that the virus inactivates epithelial neutral endopeptidase, leading to amplified tachykinin activity.²

BRADYKININ

Dixon and Barnes⁸ studied the effect of nedocromil sodium, 4 mg, compared with cromolyn sodium, 10 mg, and placebo in patients with mild asthma. They concluded that both active drugs gave significant protection against bradyki-

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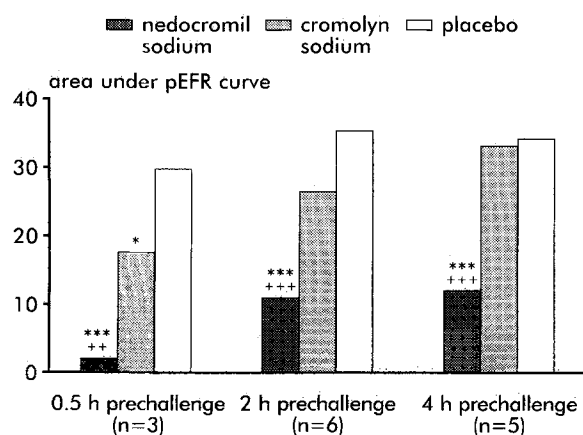


FIG. 1. Comparison of the effect of nedocromil sodium, cromolyn sodium, and placebo on partial expiratory flow rate (pEFR) after challenge with sulfur dioxide. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ vs placebo; ++ $p < 0.01$; +++ $p < 0.001$ vs cromolyn sodium. (From Altounyan RE, Cole M, Lee TB. Inhibition of sulphur dioxide-induced bronchoconstriction by nedocromil sodium and sodium cromoglycate in nonasthmatic, atopic subjects. *Eur J Respir Dis* 1986;69(suppl 147):274-6.)

nin-induced bronchoconstriction when compared with placebo, with no significant differences between the active drugs. All subjects reported cough with bradykinin inhalation and this was reduced, again in all subjects, after nedocromil sodium pretreatment. Bradykinin-induced dyspnea was also reduced.

TACHYKININS (SUBSTANCE P AND NEUROKININ A)

The bronchoconstrictor effects of the tachykinins are thought to involve cholinergic nerves and/or mast cells and a direct action on airway smooth muscle.⁹ Crimi et al.¹⁰ showed that PD₂₀ after substance P inhalation was significantly greater when the patients were pretreated with nedocromil sodium, 4 mg, compared with placebo. Two placebo-controlled studies, both in patients with asthma, demonstrated a significant protection from neurokinin A-induced bronchoconstriction by nedocromil sodium metered dose inhaler, in a dose of 4 mg.^{11, 12}

SULFUR DIOXIDE (AND SODIUM METABISULFITE)

Dixon et al.¹³ showed a significant attenuation of the maximum bronchoconstrictor response to inhalation of sulfur dioxide with a 4 mg dose but not with a 2 mg dose of nedocromil sodium; both the 2 and 4 mg doses significantly reduced the duration of bronchoconstriction. Both doses of nedocromil

sodium also reduced the sulfur dioxide-induced dyspnea. Altounyan et al.,¹⁴ in a study in atopic nonasthmatic subjects, showed that nedocromil sodium, 4 mg, was significantly superior to cromolyn sodium, 10 mg, in terms of both efficacy and duration of action (see Fig. 1). Bigby and Boushey¹⁵ examined the dose-response effect of nedocromil sodium, 2, 4, and 8 mg, in a group of patients with mild asthma. All three doses afforded significant protection, and although there was a tendency for the effect to increase with increasing dose, they did not differ significantly from each other.¹⁵

Nedocromil sodium, 8 mg, was significantly better than placebo or cromolyn sodium, 4 mg, in protecting from nebulized sodium metabisulfite-induced bronchoconstriction; it blocked the response in 15 of 20 subjects and reduced it in two, whereas cromolyn sodium blocked the response in three of 20 subjects.¹⁶ In a second study,¹⁷ nedocromil sodium, 4 mg, was significantly more effective than cromolyn sodium, 10 mg. Nedocromil sodium also reduced the cough associated with higher concentrations of metabisulfite.

PROVOKED COUGH

In healthy subjects, nedocromil sodium was tested for preventing cough provoked by several triggers. The results have been equivocal:

1. Capsaicin. Collectively, four studies have investigated the efficacy of nedocromil sodium in preventing capsaicin-induced cough. Two studies demonstrated protective effects of the drug; one study¹⁸ used the 8 mg dose, whereas the dose was unspecified in the other study.¹⁹ The two studies that reported no protective effects of nedocromil sodium used a 4 mg dose.^{20, 21}
2. Citric acid. In two separate studies, doses of 4 mg or 8 mg failed to prevent citric acid-induced cough in healthy subjects.^{19, 22}
3. Fog. When patients were given fog challenges, nedocromil sodium significantly prevented cough.^{19, 23}

Thus the effect of nedocromil sodium on provoked cough in healthy subjects is still somewhat uncertain. A final conclusion is even more difficult to make because of the fact that almost all relevant studies were published only as abstracts.^{18-20, 22, 23}

Some evidence suggests that the cough reflex is sensitized, or upregulated, in situations of chronic inflammation, such as asthma.^{24, 25} It would therefore be more logical to test the effects of a drug against an upregulated reflex. In one study, the effects of nedocromil sodium (16 mg/day for 7

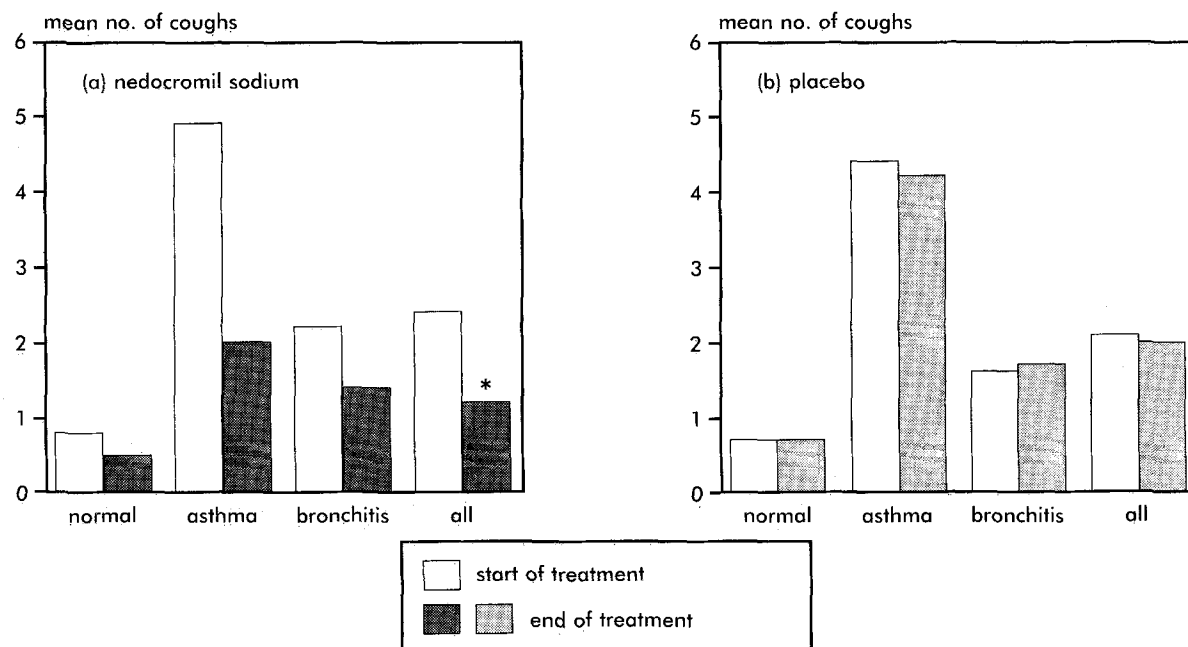


FIG. 2. Effect of nedocromil sodium, 4 mg four times daily for 7 days, on citric acid-induced cough in 27 subjects (10 volunteers, 7 patients with asthma, and 10 patients with bronchitis) in a double-blind, placebo-controlled crossover study. All of the patients with asthma were taking inhaled bronchodilators, and five were taking inhaled steroids. * $p < 0.05$ vs placebo. (Data from Rees PJ, Barros MJ. Nedocromil sodium and citric acid induced cough in normal subjects and in asthmatic and bronchitic patients. *Thorax* 1991;46:761P.)

days) and placebo against citric acid-induced cough were compared in healthy subjects and in patients with chronic bronchitis and chronic asthma. With only a small number of patients in each subgroup, a statistically significant reduction in cough was observed only in all patients combined, but it is interesting to note that, first, the patients with asthma were more responsive to citric acid than patients with bronchitis or healthy subjects, and, second, nedocromil sodium appeared to have the greatest effect in the patients with asthma, blunting the upregulated response rather than abolishing what is an important defensive mechanism (Fig. 2).²⁶

SPONTANEOUS COUGH IN PATIENTS WITH ASTHMA

The best overview of the effect of nedocromil sodium on cough in clinical trials was done in a meta-analysis by Edwards and Stevens.²⁷ These authors reviewed both published and unpublished controlled studies that involved a total of 4723 patients. The authors concluded that nedocromil sodium, administered at a frequency of either twice (8 mg) or four times (16 mg) daily, had a significant effect in reducing cough (Fig. 3) when:

1. Added to baseline treatment consisting of bronchodilators alone
2. Added to baseline treatment consisting of bronchodilators alone; oral bronchodilators were partially or completely withdrawn during the treatment period
3. Added to inhaled corticosteroid therapy that was reduced (but not withdrawn) before the baseline period (tested only for doses of 16 mg/day)

Interestingly, in patients whose asthma was not adequately controlled with inhaled corticosteroids, nedocromil sodium did not show a significant reduction in cough when added to the patients' treatment regimen. Nedocromil sodium also did not show a significant reduction in cough in the patients whose asthma was adequately controlled with inhaled corticosteroid therapy that was withdrawn during the baseline period.

Collectively these studies demonstrate that in challenge tests nedocromil sodium exerts protective effects against cough induced by fog and, possibly, capsaicin. Citric acid-induced cough was reduced after 7 days' treatment. In clinical trial results, several individual studies^{28, 29} confirm the

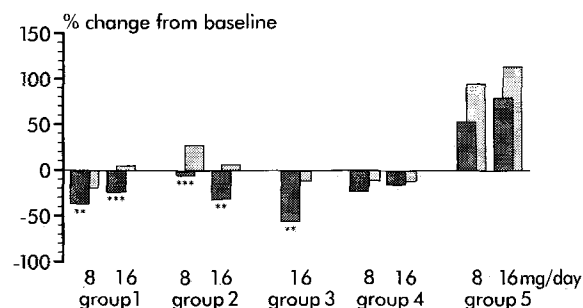


FIG. 3. Effect of nedocromil sodium on cough: results from meta-analysis of controlled studies. The effects on cough were significantly in favor of nedocromil sodium in groups 1, 2, and 3 and in all groups combined ($p < 0.001$) but not in groups 4 and 5. The groups are as follows: Group 1: Nedocromil sodium added to bronchodilators. Group 2: The same as in group 1, but oral bronchodilators were reduced or withdrawn. Group 3: Nedocromil sodium substituted for part of inhaled corticosteroid dose, reduced prior to baseline. Group 4: Nedocromil sodium added to inhaled corticosteroids in patients not well controlled on inhaled corticosteroids. Group 5: Nedocromil sodium added to inhaled corticosteroids, which was then withdrawn. (Data from Edwards AM, Stevens MT. The clinical efficacy of inhaled nedocromil sodium (Tilade) in the treatment of asthma. *Eur Respir J* 1993;6:35-41.)

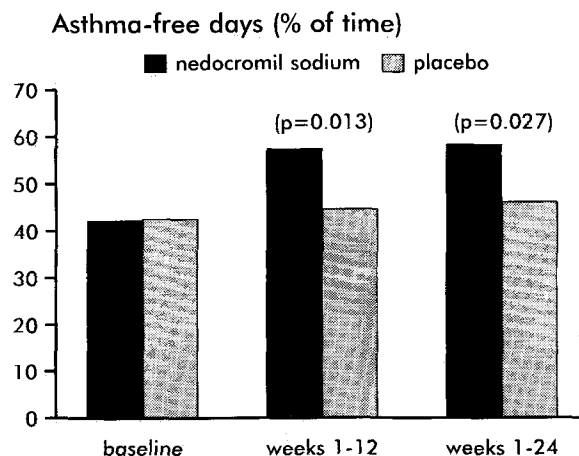


FIG. 4. Percentage of asthma-free days during baseline, for the first 3 months, and for the entire 6 months. (From König P, Eigen H, Ellis MH, et al. The effect of nedocromil sodium on childhood asthma during the viral season. *Am J Respir Crit Care Med* 1995;152:1879-86.)

conclusions (stated previously) reached by Edwards and Stevens.²⁷ Thus nedocromil sodium has a convincing effect on cough in asthma under most circumstances. Although the antiinflammatory properties of nedocromil sodium have been characterized in detail throughout the literature, the specific mechanism identifying how the drug actu-

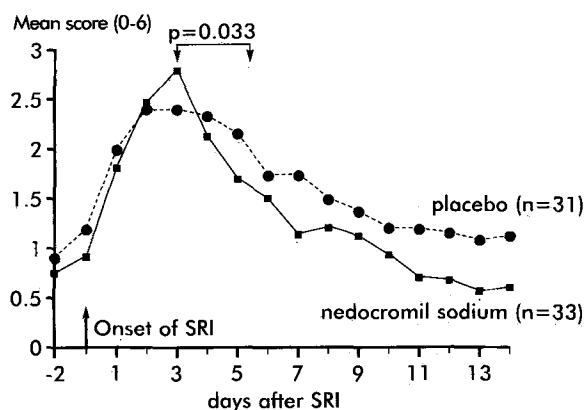


FIG. 5. Asthma summary score before, during, and after the first respiratory infection. (From König P, Eigen H, Ellis MH, et al. The effect of nedocromil sodium on childhood asthma during the viral season. *Am J Respir Crit Care Med* 1995;152:1879-86.)

ally regulates cough in patients with asthma is only now being investigated.

VIRAL-INDUCED ASTHMA

Children have between two and eight episodes of viral upper respiratory infections per year, most of which occur during the peak viral season (September through March in the United States). Therefore, the effect of a drug on viral-induced asthma can be studied by either investigating all or part of the viral season or just by looking at symptoms during a confirmed viral infection. We have recently done a study in which both of these approaches were used.

Nebulized nedocromil sodium (10 mg three times daily) was given for 6 months during the viral season to 93 children aged 6 to 12 years with mild to moderate asthma in a multicenter, double-blind, placebo-controlled, parallel-design study.³⁰ Most of the viral infections occurred in the first few months, and it was during these months that most of the significant differences in favor of nedocromil sodium were found. Thus nedocromil sodium was found to be significantly better than placebo on asthma summary score (weeks 1 to 4 and 1 to 12), daytime asthma (weeks 1 to 4 and 1 to 12), cough (weeks 1 to 4), asthma-free days (weeks 1 to 12 and 1 to 24), and morning peak expiratory flow (weeks 9 to 12; see Fig. 4).

At the onset of viral respiratory infections, asthma symptoms increased dramatically and were correlated to the severity of the viral infection. The peak of the asthma symptoms after the viral infection was not prevented by nedocromil sodium. However, the resolution of symptoms was faster.

The difference reached statistical significance in favor of nedocromil sodium between days 2 to 4 after onset of the viral infection for summary symptom score (see Fig. 5) and also for nocturnal asthma. For daytime asthma and cough, the results approached significance ($p = 0.079$ and 0.084 , respectively). Bronchial hyperreactivity at the time of the viral infection, measured as PD₂₀ methacholine, also showed an almost significant difference ($p = 0.053$) in favor of nedocromil sodium.

The early viral-induced asthma symptoms are probably the result of the shedding of viral-infected epithelial cells, which is apparently not protected by nedocromil sodium. Consequently an inflammatory response occurs, and this may be where nedocromil sodium exerts its antiinflammatory effects, thus speeding up the recovery process.

Wood et al.³¹ performed a study for 3 months during the viral season in younger children (2 to 4 years of age) who were more likely to have more viral infections per year. They found statistically significant differences in favor of nedocromil sodium for symptom-free days, daytime asthma, daytime cough, and summary symptom score.

These two studies support a modest but significant effect on asthma symptoms induced by viral respiratory infections.

Viral infections are very potent triggers of asthma, and trials of other drugs have not been very successful. Continuous treatment with cromolyn sodium was ineffective in preventing viral-induced attacks (although symptom resolution was not specifically analyzed)³² and inhaled corticosteroids given in large doses at the onset of viral infection achieved a significant effect on only a few of the criteria followed.³³

In conclusion, nedocromil sodium has a protective effect against direct-acting stimuli such as bradykinin and neuropeptides (substance P and neurokinin A), as well as against indirect triggers such as sulfur dioxide and sodium metabisulfite. Its effect on provoked cough in healthy subjects is less clear and may be limited to certain triggers such as fog, whereas the effect on spontaneous cough in patients with asthma is well documented. On viral-induced asthma symptoms, nedocromil sodium has a modest but statistically significant protective effect.

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DISCUSSION

P. J. Barnes. Do you have information about dose-response studies and duration of protection? These are important issues that are often overlooked. One of the problems with chromones is their short duration of action, so that the very impressive effects in challenge studies do not always translate into clinical practice, where it is necessary to prevent symptoms over a long period.

E. R. Bleecker. In our laboratory we looked at 2, 4, and 8 mg of nedocromil sodium against allergen challenge. There appeared to be a dose-response up to 4 mg, and then it evened off. There are about 30 papers in the literature on this that generally confirm our own findings. Pelikan's work, which shows that when nedocromil sodium was given 45 minutes before the anticipated delayed response it blocked the delayed response, gives

us some information about duration of effect. We also did an exercise study and saw no effect at 4 hours after administration.

P. König. Roger Altounyan's study showed that at 4 hours nedocromil sodium was still effective in protecting against the effects of sulphur dioxide. All the studies I quoted were with the 4 mg doses used in clinical practice.

L. T. Rodwell. We have not investigated the duration of action of nedocromil sodium against the salt water aerosol challenge in patients with asthma. However, for exercise challenge, cromolyn sodium provides about a 2-hour protection. With both hyperventilation and exercise challenges there is an increased clearance of the drug from the airways. When we investigated the protective effect of inhaled furosemide against hyperventilation challenge we saw quite a big diuretic effect that was less when investigating furosemide against hypertonic saline solution challenge.

R. J. Davies. What did Gene Bleecker mean by antiinflammatory? Can you classify a drug as antiinflammatory just on the basis of clinical data, or should you look at bronchial biopsy specimens?

E. R. Bleecker. I was being deliberately controversial, but there are three possible approaches. One is to look at clinical trial data, and when drugs that are not intrinsic bronchodilators change airflow obstruction over time, you have to try to explain how that is happening. It may be happening through mechanisms that are not directly related to airway smooth muscle. The next, indirect, approach is to look at the spectrum of challenge results. Allergen exposure is one the major environmental causes of asthma, and if allergic inflammation really does reflect some of the underlying processes then this would make the allergen model more relevant. Yet we all have problems with its relevance to clinical asthma. The third approach is to look at all the cellular elements and mediators in bronchoalveolar fluid and the morphology of bronchial biopsies, but even these do not give us all the information we need to answer a very complex question.

R. Beasley. To put it another way to Robert Davies, were you surprised that your biopsy data were not more convincing in view of the very dramatic effect on the late allergen response?

R. J. Davies. Yes; that is why I asked the question.

S. T. Holgate. We are getting to the core of the problem now, and it relates to the relevance of allergen in the chronicity of asthma. My view is that it plays a relatively minor role. That is not to say that on top of a basal level of inflammation there are not superimposed viruses, allergens, and other things that can change the state of asthma over time, but the driving force that is pushing the chronicity over years is probably not allergen. The disease process is triggered, probably in childhood or early adulthood, by exposure to allergen, just as occupational asthma is with isocyanate. But then there is a phase of continued disease in the absence of allergen exposure, just as can occur when you take somebody out

of the occupational environment. The only way you can explain that is that the tissue itself, the constitutive cells, have taken over the responsibility of supporting the inflammation, just as happens in glomerular nephritis or in rheumatoid arthritis.

J. P. Seale. When we talk among ourselves we all have our own idea of what is meant by the term "antiinflammatory," but I think we should move away from this imprecise term and describe exactly what phenomenon we are studying and how a drug alters it. When we talk to others we need to use simple terms like "preventers" and "relievers" to categorize drugs. The term "antiinflammatory" sits in a middle zone that is halfway between the language we use for the patients and the language we use to talk among ourselves; it really does not mean very much to us at all.

S. T. Holgate. Leanne Rodwell showed evidence that hypertonic stimuli in patients with asthma mediate a constrictor response that she thinks is largely, or partly, mast cell dependent. When we were discussing mechanisms of all the different drugs, epithelial cells were included in the equation. How are those two cellular elements talking to each other in terms of evoking a particular constrictor response?

L. T. Rodwell. It is highly likely that mast cells are involved in the airway response to hypertonic saline solution challenge in patients with asthma. Antihistamines taken before challenge inhibit the airway response, suggesting the involvement of histamine and implicating the mast cell. The epithelial cell may act like an osmometer, regulating the amount of water in the airway lumen. When the airways become hyperosmolar, water may move outward from the epithelial cell and from the submucosa in an attempt to reduce the osmolarity. When the osmolarity of the submucosa increases, this could trigger the osmotic release of histamine from mast cells. Nedocromil sodium and cromolyn sodium may block volume regulation of the epithelial cells and stop the movement of water from the submucosa. This would protect the submucosa from an increase in osmolarity and prevent mast cells from releasing histamine.

E. W. F. W. Alton. Do you think the effect is just a consequence of altered access to the cells in the submucosa? As you alter cell volume and, thus, intercellular spaces, then antigen and viral infection and so on might find it easier to get through to the submucosal surface.

S. T. Holgate. That is a nice hypothesis.

R. Beasley. Can you tell us the clinical relevance of the hypertonic challenge?

L. T. Rodwell. Gibson, who is doing work in Australia, has shown a correlation between mast cell numbers and PD₂₀ to hypertonic saline solution. We may therefore be able to use this challenge as an easy way of investigating airway hyperresponsiveness and inflammation in asthma. For example, if a doctor wants a patient with asthma to begin taking inhaled corticosteroids, then a hypertonic saline solution challenge could be performed before the start of treatment and again perhaps 2

months later to see if the response has been inhibited or even blocked. If the response has not been blocked, it suggests the presence of inflammatory cells, which suggests the need for additional medication that could include nedocromil sodium or cromolyn sodium. The hypertonic saline solution challenge is technically easy to perform, it is cheap, and it is useful in a laboratory setting to investigate the effectiveness of asthma drugs because a dose-response curve can be plotted.

P. J. Barnes. Steve Holgate showed that with steroids, mast cells disappear completely, and yet Leanne Rodwell is saying that she is still seeing a response.

S. T. Holgate. The mast cells reduced with steroids but did not disappear; the eosinophils disappeared completely.

L. A. Laitinen. In our work with budesonide we found that mast cells reduced by about half from the initial values, and eosinophils decreased to zero in all but one patient.

P. J. Barnes. That must be very important in the context of our discussions, because if there is residual mast cell activity that cannot be controlled by steroids, this may be inhibited by nedocromil sodium. This suggests that a combination of inhaled steroids and nedocromil sodium might be the best treatment, although my concern is still the short duration of effect of nedocromil sodium. Roger Altounyan showed that verapamil increased the duration of action of cromolyn sodium, and perhaps we should be looking at whether steroids alter their duration of action too.

S. E. Wenzel. Hypertonic saline solution has been used to induce sputum, and I wonder if you have noticed whether nedocromil sodium had any effect on the amount of mucus produced in your patients.

L. T. Rodwell. No, we have not looked at this, so I cannot comment.

P. König. Coming back to Peter Barnes' comment just now, I remember a study by Lundgren, who showed that about 10 years of treatment with inhaled corticosteroids reduced the biopsy to almost normal appearance, and yet those patients still had bronchial hyperreactivity and symptoms. So there is more to it than inflammatory changes.

S. T. Holgate. Peter Barnes and our own group, among others, have all shown that inhaled steroids can reduce adenosine monophosphate (AMP) responsiveness, for example, quite dramatically, while there is only a minor effect on methacholine responsiveness. I wonder whether we have the right marker with methacholine responsiveness; it has so many components that it is a black box.

R. Beasley. What is the clinical relevance of the differences observed between methacholine and adenosine?

S. T. Holgate. Simon Godfrey published a study in *Thorax* last month comparing AMP challenge with exercise and histamine challenge, in which AMP scored very highly as a diagnostic test for asthma. It looked as if exercise and AMP were giving the same sort of information, which was very interesting. We have just completed a study in children treated with beclomethasone dipropionate, 400 µg/day. The readout was meant to be

improvement in virus-induced episodes, but instead of that we found that BDP prevented the children growing by 1.6 cm. What is interesting is that the clinical improvement in the baseline symptoms, not the acute episodes of virus-induced asthma, correlated extremely closely to a reduction in AMP responsiveness but failed to correlate with methacholine responsiveness. AMP could be a better challenge that reflects the disease activity because, like hypertonic saline solution, it is closer to the inflammation end of the pathway, whereas methacholine and histamine are too far down the stream.

L. T. Rodwell. With indirect challenges, endogenous mediators are released, and the airways of the patient being tested have to be sensitive to these mediators. It is these endogenous mediators that cause the airways to narrow. This is where hypertonic saline solution has

an advantage over histamine and methacholine—it causes the release of these endogenous mediators to which the patient is sensitive. To follow on from Peter Barnes' comment on duration of action of nedocromil sodium and cromolyn sodium, patients who have asthma induced by, say, exercise, are very grateful to have their asthma blocked by an acute dosing of a drug.

P. J. Barnes. That leads to an important question, which is how we should recommend that nedocromil sodium be used. It is typically given as a chronic fixed dosage, but it might be better to give it as needed. It could be taken before challenge or even during a challenge because it works acutely and it is completely different from a steroid. I suspect that we are not getting the maximal potential from the drug, because it is highly effective in short-term challenge studies.