

existence of an entire fleet of ships. For chiral molecular enantiomers, it may be advantageous to use binoculars.

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Reply

To the Editor:

To Canada:

"When you have eliminated the impossible, whatever remains, however improbable, must be the truth." Sherlock Holmes, *The Sign of Four*, ch. 6
Sir Arthur Conan Doyle (1890)

I am delighted to have the opportunity to continue a dialogue with Dr. Cockcroft and associates regarding their article.¹ I have long been an admirer of the work emanating from this laboratory and am eager to resolve any points of dissension between us.

The data in Table 2 of the study by Cockcroft et al.¹ are open to a number of forms of analysis, both technically and conceptually, and I am confused about the authors' statement as to why parametric techniques cannot be employed. They themselves used such an approach with paired *t* tests and an unspecified analysis of variance. A log transformation of the data may or may not have normalized distribution, but it had the important consequence of reducing the variance. Unfortunately, because of the numbers involved, this is not a trivial issue. Thirteen patients are listed in Table 2; 12 of them have complete methacholine data and 11 participated in all arms of the study. In the methacholine placebo phase, the arithmetic PC₂₀ of the 12 subjects rose from 2.0 to 18.0 mg/ml with the acute administration of salbutamol ($p = 0.008$ by paired *t* test). In the salbutamol phase, the baseline PC₂₀ rose 14% ($p = \text{NS}$), and the protection offered by acute administration of salbutamol decreased (2.3 to 13.5 mg/ml; $p = 0.01$). The difference in the responses seen between the placebo and the 2 weeks of β_2 -agonist administration did not quite reach statistical significance when the absolute values were analyzed ($p = 0.053$). The magnitude of the diminution in methacholine prophylaxis, however, is very small and of uncertain clinical significance (see page 645, J ALLERGY CLIN IMMUNOL 1995;95:641-51). Repeating this simple analysis in 11 patients for whom complete data sets were collected changes the results. Now, neither the absolute ($p = 0.075$) nor the percentage changes ($p = 0.06$) in methacholine prophylaxis differ significantly between the placebo and salbutamol phases. Hence, the "deleterious effects" of salbutamol on this variable can be made to come and go with the addition or removal of a single patient.

In the antigen phase of the trial, the authors did not carry one patient forward from the placebo phase to the salbutamol phase because he or she did not respond to allergen after salbutamol administration. Because the hypothesis being tested suggested that frequent β_2 -agonist use would, if anything, reduce the PC₂₀ to antigen, there does not seem to be any compelling scientific reason to have taken this action. Carrying the patient throughout the analysis, assuming either no change in PC₂₀ antigen or even a 20% reduction after 14 days of salbutamol treatment, does not support the

authors' contentions that the β_2 -agonist worsens airway responses. In fact, because of the variance of the data, the opposite happens. Even if the issue with this one patient is ignored and only the 11 subjects with complete data are included in the analysis, one is left with the disconcerting observation that in the placebo phase, salbutamol did not significantly shift the antigen dose-response curve (allergen PC_{20} ; no treatment = 947; after salbutamol administration = 1609; $p = 0.10$), whereas in the salbutamol phase it did (716 vs 3132; $p = 0.002$). Consequently, one could conclude from this trial that 2 weeks of salbutamol treatment proved quite beneficial to patients, for it allowed them to develop protection from antigen that they did not have previously.

My arguments are not specious, but derive from a need to understand the significance of your observations. It matters little to me as to who is right or wrong in an absolute sense in this instance, for time and further experience will sort that out. We can analyze data any way that we wish to justify conclusions, but if one or another statistical technique makes an event come or go, it is the technique and not necessarily the observations that drive the results. How robust are such data and how secure can we then be of the overall importance of such deductions? Should not the rock of certitude on which we build our patients' trust be made of sterner stuff?

I, of course, cannot comment on the subsequent studies that the authors quote as confirming their observations, for I have not had the privilege of reviewing them. I eagerly look forward to their publication so that all of my doubts can be dispelled. I do, however, reserve the right to follow the dictates of Rene Descartes:

"The first precept was never to accept a thing as true until I knew it such without a single doubt."

Le Discourse de la Methode (1637)

To England:

"There is nothing more difficult to take in hand, more perilous to conduct, or more uncertain in its success than to take the lead in the introduction in the new order of things."

The Prince, Chapter 6

Niccolo Macchiavello (1532)

To the above, one might also add the discomforts of attempting to restrain people from blandly accepting theorems that contain discordant observations without first placing them into the context of what is known so that a proper perspective can be developed. I appreciate that this fragmented approach is frequently forced on us by the nature of our experiments, but it rarely works well, particularly when rushed; and in matters as important as the treatment of asthma, prudence demands that we take extra care in our deliberations. In my view, this extra care has not been taken, and our patients may be ill served as a result.

England calls my request that judgments about the concerns with β_2 -agonists be based on verifiable, solid,

objective evidence to be disingenuous, and alleges that such an approach precludes consideration of theoretic deficiencies that are not necessarily manifested as increased morbidity or mortality. If these theoretic differences have no impact on such major components of the β_2 -agonist controversy, how important can they be clinically? Are they in the nature of improving efficacy or safety?

Drs. Costello, Crowther, Page, and Morley move from asthmatic patients to animals to diastereoisomeric enantiomers in their arguments but do not provide a critical examination of the strengths of the links between them. Unfortunately, many of these links are tenuous at best, or perhaps even nonexistent. For example, we have repeatedly been disappointed in attempts to translate animal data to human asthma. Why are the studies quoted any better? They do not deal with the disease in question. This type of reasoning is precisely the phenomenon that the "voice" in my article was crying out against. We can erect hypotheses to be tested, but they must be identified as such. Syllogistic reasoning without verification of the integrity of interrelationships between the major and minor premises of our data and the integrity of the conclusions drawn from them is not a valid deductive process; rather, it is a form of medical Pointillism that does not lead to light—only heat. We must still fulfill Koch's postulates before cause and effect can be established. Far too often, we fail to do so, and that failure dooms us to a constant cycle of navigating through the stormy crests and troughs of fashion. As one of your former First Lords of the Admiralty wrote:

"I pass with relief from the tossing sea of Cause and Theory to the firm ground of Result and Fact."

Sir Winston Churchill

Intrigued by the clever seagoing metaphor begun by England, I cannot pass the opportunity to smile at the lack of precision with which their national naval history is quoted. In the battle of Copenhagen, Vice Admiral Lord Nelson put his glass to his blind eye, not to dispute the existence of an entire fleet of ships as alleged, but rather to avoid seeing the signal to retire hoisted by the squadron commander, Admiral Parker.² Parker, held from the battle by unfavorable winds, deduced from the sounds he heard and the smoke he saw that the English cause was lost. Nelson's direct disobedience of this order turned what would have been a rout into a great victory that removed the threat of the Russian, Danish, and Swedish governments making common cause with the French. Then, as now, a view based on verifiable fact and tempered by perspective provided a better outcome than an unsubstantiated concern over potential dangers.

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Cromolyn metered dose inhaler

To the Editor:

Hendeles et al. have described a well-controlled challenge study to compare the protection afforded by individualized doses of theophylline and a cromolyn metered dose inhaler (MDI) during allergen provocation (*J ALLERGY CLIN IMMUNOL* 1995;95:505-14). The dose of controlled-release theophylline tablets was slowly titrated, as tolerated, over a 9-day period with a final mean serum theophylline level of 16.2 $\mu\text{g/ml}$ just before allergen challenge. Both drugs afforded comparable protection (about 50%) in attenuating airway responses to inhaled antigen. Moreover, the authors imply that the 1 mg/puff cromolyn MDI (2 mg dose) may be subtherapeutic in some patients.

Clearly, any dose of almost any drug may be subtherapeutic in some patients. I do not believe that this study permits any such speculation regarding the cromolyn sodium MDI.

First, it is well recognized that acute challenge studies, with allergen or exercise, are not good predictors of long-term clinical benefit of asthma drugs.

Second, at least one well-controlled multicenter clinical study has taken patients with asthma that was well controlled with cromolyn (20 mg four times daily) delivered through a turbo-inhaler and switched them to the MDI (2 mg four times daily) formulation or to placebo.^{1,2} There was no indication of marked clinical deterioration during the MDI phase versus the baseline (turbo-inhaler) phase.

Third, Fisons Pharmaceuticals has informed me that Intal Aerosol (MDI) formulation required a full New Drug Application for Food and Drug Administration (FDA) approval. It is reasonable to presume that the product was judged to be both safe and *effective* for its approved indication, namely, asthma of mild to moderate severity.

Finally, the authors emphasize the lower plasma levels obtained in pharmacokinetic studies with the cromolyn MDI compared with the 20 mg capsule (turbo-inhaler) and nebulizer solution (20 mg) formulations. This is superficial reasoning: it does not take into account particle size and distribution of drug within the lungs. Anderson et al.³ found cromolyn sodium delivered through an MDI to be superior to the powder (capsule) formulation in blocking exercise-induced asthma.

The authors describe theophylline as a drug that has both bronchodilator and antiinflammatory properties. Before the early 1980s, all of our patients were receiving

sustained-release theophylline preparations as first-line therapy for pediatric asthma, with careful monitoring of blood levels.

However, since altering our maintenance treatment strategy for pediatric asthma over the past 13 years from controlled-release theophylline to cromolyn or an inhaled corticosteroid (depending on severity), we have seen a remarkable reduction in emergency department visits and hospitalizations. This experience calls into question the clinical relevance of any role for theophylline as an important antiinflammatory agent.

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Reply

To the Editor:

Dr. Selcow disagrees with our conclusion that cromolyn delivers less drug to the lungs from the MDI than from either the older Spincap formulation or nebulizer solution.

First, he claims that allergen challenge studies are not good predictors of long-term clinical benefit, but there are no data to support or refute his claim.

Dr. Selcow cites two studies in which patients were switched from cromolyn Spincaps to MDI and claims that there was no marked clinical deterioration during the MDI phase. However, it is noteworthy that several clinical end points were not significantly different from placebo in those studies. In the study by Selcow et al.,¹ peak expiratory flow rate, FEV₁, β -agonist use, and physician assessment were not significantly different. In the study by Blumenthal et al.,² wheeze and nocturnal symptoms were not significantly different between cromolyn MDI and placebo.

Dr. Selcow points out that in order to get a new drug application approved by the FDA, the sponsor had to prove that the drug was safe and effective. Although this