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Correspondence

Absence of refractoriness in asthmatic subjects after exercise with warm, humid inspirate

SIR,—That Dr AG Hahn and his colleagues demonstrated, as implied in the title of their article (June 1985;**40**:418–21), absence of refractoriness to exercise induced asthma after exercise with warm humid inspirate I would not dispute. Indeed, they did it most beautifully. In their other experiment, however, they did not demonstrate refractoriness in cold, dry air.

They justified the conclusion of no refractoriness by the difference in response in percentage terms from two different baselines. This difference has no meaning in absolute terms, as the position of the second baseline is quite arbitrary. If one refers to the true baseline, FEV_1 at complete relaxation, one can see that there is an additional response to the second exercise test, though less than to the original one. This only represents refractoriness if an increased stimulus produces the same response—that is, if the relationship between the stimulus and its ultimate effect is linear throughout. If the four points in figure 2, where the two tests are shown in sequence, were regarded as a continuous plot, then they might well fit on the same exponential curve.

As the study is attempting to look at bronchoconstriction, the results should be thought of in terms of effect of contraction of bronchial musculature. This influences FEV_1 through reduction in the radius of the bronchial lumen. Although the relationship is not simple, as we are not dealing with a long, uniform pipe, the fourth power of the radius is important in determining the relationship between the two. The force of bronchial muscle contraction required to reduce bronchial lumen is related inversely to the fourth power of the radius, which itself is related to flow directly. In other words, there is an exponential relationship between bronchial muscle contraction and its effect on FEV_1, particularly in the middle part of the curve. This is probably modified close to the two reference points (complete relaxation and maximal contraction). At the beginning of contraction "taking up of slack" would reduce the initial effect. At the end physical limitations of deformation, intrinsically in bronchial muscle, and extrinsically in constriction of the bronchial wall, would further diminish the effect of contraction as the limit is reached. The results presented in figure 2 are perfectly compatible with continued stimulation of bronchial muscle contraction in this model.

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*** This letter was sent to the authors, and Dr Nogrady replies below.

SIR,–In essence we are forced to agree with a lot of the suggestions and comments of Dr Connolly. He points out one of the fundamental problems of all forms of asthma research—namely, that of varying baselines. It makes study of any bronchoconstrictor or bronchodilator effect difficult, especially when such studies require repeated exposures over a short period of time.

We too have been struck by the similarity of the FEV_1/time curves, during both the initial and the subsequent challenges. If one ignores the differing baselines, absolute volumes of FEV_1 are similar for initial and for subsequent "refractory" challenges.

This puts the whole idea of refractoriness in dispute. However, clinical observation reveals that refractoriness is a true phenomenon. Subjects do experience a considerable diminution of exercise induced asthma during a second challenge. This could be explained in two ways. The traditional explanation would be that the body perceives limitation of air flow as a change rather than as an absolute value. The alternative hypothesis, one to which we are increasingly drawn, is that the sensation of refractoriness occurs during rather than after exercise and relates to the amount of bronchodilatation seen within the second exercise period. As subjects start from a lower baseline they have substantially greater bronchodilatation during the exercise periods. Many subjects have volunteered that the second exercise "gives them relief" from the initial exercise induced attack regardless of the fact that the FEV_1 might fall to the same levels after the second challenge.

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Pulmonary veno-occlusive disease after chemotherapy

SIR,—We read with interest the report by Drs BA Knight and AG Rose (Nov 1985;**40**:874–5) describing a patient with pulmonary veno-occlusive disease (PVOD) after cytotoxic chemotherapy for cervical carcinoma. They refer to our reported case of PVOD in association with Hodgkin's disease[1] and they suggest that the association of PVOD was with the chemotherapy given. This cannot be the explanation since in our patient the symptoms and clinical features of PVOD preceded the administration of cytotoxic chemotherapy by several weeks, as indicated in our report.

The reported pathological changes in cases of lung disease associated with cytotoxic agents do not suggest predominant disease of the pulmonary veins as in PVOD, and we suggest that venous disease in this condition may be a secondary effect. Furthermore, lung damage by cytotoxic agents may, in some circumstances, be reversible, whereas PVOD has not been reported to show appreciable reversal, either spontaneously or in response to attempted treatment.

We agree with Drs Knight and Rose that PVOD is probably not a single disease entity and that various aetiological agents may be responsible, but we do not share their view that in patients with malignant disease cytotoxic chemo-

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