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-

therapy is the responsible agent rather than the underlying disease.

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1 Capewell SJ, Wright AJ, Ellis DA. Pulmonary veno-occlusive disease in association with Hodgkin's disease. *Thorax* 1984; 39:554–5.

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

SIR,—I agree with Drs Ellis and Capewell that the likeliest sequence of events in their patient is that pulmonary veno-occlusive disease (PVOD) antedated the chemotherapy. However, their patient's pretreatment lung biopsy specimens showed no evidence of congestion, haemorrhage, lymphatic dilatation, iron deposition, or other feature suggestive of PVOD. Since the second lung biopsy, which showed both PVOD and iron deposits within thick walled alveoli, was taken after chemotherapy, the possibility that the latter may have played a part in the pathogenesis of the venous changes would at least appear to have warranted discussion in their paper. It is unfortunate that no necropsy was performed in their case.

Until further cases similar to theirs are published, a fortuitous association between PVOD and malignancy cannot be excluded. Their belief that PVOD in patients who received alkylating agents for malignancy is due to the malignancy rather than the treatment does not appear to be justified. Such an approach to patients with coexistent bleomycin pulmonary toxicity and PVOD requires one to ascribe the venous fibrosis to the underlying malignancy, while the parenchymal fibrosis observed in the same histological sections is attributed to bleomycin toxicity.

Regarding the reversibility of lung damage by cytotoxic agents, only the acute lesions are likely to be reversible and intimal fibrous obliterative lesions of PVOD, no matter what the cause, are likely to be equally permanent.

In order to try to resolve the unanswered question of whether PVOD in patients with malignancy is related to chemotherapy or the underlying disease, pathologists should examine stored lung sections from patients with malignant disease from the prechemotherapy era as well as postmortem material from untreated patients. If the postulate of Drs Ellis and Capewell is correct then the incidence of PVOD should be higher in such subjects than in the general population. At the present time the ratio of treated to untreated cases in the literature is four to their one case. A report of three cases of hepatic veno-occlusive disease associated with mitomycin C therapy[1] raises the possibility that different alkylating agents may affect different venous territories.

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1 Gothfried MR, Sudilovsky O. Hepatic veno-occlusive disease after high-dose mitomycin-C and autologous bone marrow transplantation therapy. *Hum Pathol* 1982;13:646–50.

Henry Hyde Salter (1827-71): a biographical sketch

SIR,—I read with interest the paper by Dr A Sakula (December 1985;40:887–8) but unfortunately there are several errors of fact, particularly about Salter's medical career, which need correcting.

It was Salter's failure to succeed Professor Robert Bentley Todd, who held the chair in physiology and morbid anatomy at King's College, that resulted in his move to Charing Cross in 1854. He was appointed lecturer in physiology and became an assistant physician in 1862. In 1866 he was appointed physician and lecturer in medicine and became a member of the board of management of the School, posts which he held until his death; and he was Dean of the School from 1867 to 1868.[1]

Naturally enough, at Charing Cross we are proud that such a distinguished clinician played such a prominent part in our school and would like the record to be corrected.

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1 Hunter W. *Historical account of Charing Cross Hospital and Medical School*. London: John Murray, 1914.

Notice

XI World Congress on Sarcoidosis

The XI World Congress on Sarcoidosis and other Granulomatous Diseases will be held in the Università Statale, Milan, Italy, from 6 to 11 September 1987 under the auspices of the International Committee on Sarcoidosis and other Granulomatous Conditions and the Comitato Italiano della Sarcoidosi. The last date for receipt of abstracts is 14 January 1987. Further details may be obtained from the Secretariat of the XI World Congress on Sarcoidosis, Congress Studio, Via Cappuccio 19, 20123 Milano, Italy.