

## LETTERS TO THE EDITOR

### Alveolitis associated with sulphamethoxy-pyridazine

Dr J C Porter and others (September 1989; 44:766-7) report on a patient who developed alveolitis associated with the administration of sulphamethoxy-pyridazine for bullous linear IgA disease. The patient had previously had a reaction to dapson. The dose of sulphamethoxy-pyridazine was 250 mg thrice daily, increasing to 500 mg thrice daily, with prednisolone 15 mg daily for six months, during which time she became increasingly short of breath. Her drug induced alveolitis was reversed when the sulphonamide was stopped and the dose of prednisolone was raised to 60 mg daily.

The recommended dose of sulphamethoxy-pyridazine for a urinary tract infection is, or was, 1-2 g immediately, followed by 500 mg daily. Because of the long plasma half life of the drug there is no advantage in giving the drug more frequently than once daily—indeed, peak plasma concentrations will be lower if the dose is split. Can the authors explain why they chose to give three times the recommended dose and why they used thrice daily dosage? And this to a patient with bullous skin disease who had already shown hypersensitivity to dapson—and for six months . . .

The authors were fortunate that the daily prednisolone presumably damped down the progressive alveolitis and prevented any of the other severe reactions that might have been associated with prolonged overdosage.

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**AUTHOR'S REPLY** Dr Lenox-Smith's observations are correct concerning the use of sulphamethoxy-pyridazine in urinary tract infections, for which it is no longer licensed, but they do not apply to bullous skin diseases. For over 30 years it has been prescribed in dermatitis herpetiformis.<sup>1</sup> It is also used, on a named patient basis, in linear IgA disease, which is an intensely pruritic condition. Dose is titrated against clinical response and, in Oxford, there are 12 patients receiving doses of up to 1.5 g of this drug daily with good effect. It is commonly given when a patient is intolerant of dapson. The alternative is sulphapyridine, which causes nausea and is associated with renal failure and agranulocytosis. The main purpose of our letter and of the article by Dr C L Steinfors and others (April 1989;44:310-1) was to report the alveolitis, which is a previously undetected but serious complication of sulphamethoxy-pyridazine. As we suggested, routine three monthly spirometry and chest radiography

may be indicated in patients receiving sulphamethoxy-pyridazine.

The final point of Dr Lenox-Smith's letter, concerning dosage interval, is entirely correct. The stated regimen in our letter is inadvertently incorrect and the patient actually received a once daily dose.

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1 Jefferson J. Sulphamethoxy-pyridazine in dermatitis herpetiformis. *Br Med J* 1958;ii: 209-10.

### Significance of antibodies to cytoplasmic components of neutrophils

D J Harrison and colleagues (May 1989;44:373-7) cast further light on the usefulness of serum antibodies to neutrophil cytoplasmic antigens (ANCA) in the diagnosis of Wegener's granulomatosis and other vasculitides, by their detailed description of the various different fluorescent patterns.

Despite the seemingly high specificity of ANCA for certain diseases, their exact role is unclear. It might be a pathogenetic factor responsible for tissue injury or, alternatively, might simply be an epiphenomenon resulting from the increased leucocyte turnover, which has been shown to occur in systemic vasculitides.<sup>1</sup> To further address this issue we tested for the presence of ANCA in a group of patients who had lymphoproliferative diseases and had reduced leucocyte counts resulting from chemotherapy.

Serum samples from 18 patients, 10 male and eight female, ranging in age from 15 months to 81 years (median 39 years), were tested for presence of ANCA by indirect fluorescence as previously described.<sup>2</sup> Nine patients had leukaemia, five multiple myeloma, three lymphoma, and one polycythaemia vera. Pretreatment leucocyte counts ranged from 4.0 to 26.0 (mean 31.8)  $\times 10^9$  cells/l and post-treatment lowest counts ranged from 0.1 to 3.2 (mean 2.1)  $\times 10^9$  cells/l. Serum from all patients was negative for ANCA, in contrast to the serum from our positive control subjects.

Thus patients with significant destruction and turnover of leucocytes do not appear to produce ANCA, strengthening the theory that these antibodies may be responsible for the pathological lesions in Wegener's granulomatosis, possibly by activating neutrophils, rather than simply being a response to neutrophil destruction.

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- 1 Falk RJ, Jennette JC. Anti-neutrophil cytoplasmic autoantibodies with specificity for myeloperoxidase in patients with systemic vasculitis and idiopathic necrotizing and crescentic glomerulonephritis. *N Engl J Med* 1988;318:1651-7.
- 2 van der Woude FJ, Rasmussen N, Lobatto S, et al. Autoantibody against neutrophils and monocytes: tool for diagnosis and marker of disease activity in Wegener's granulomatosis. *Lancet* 1985;ii:425-9.

### Effect of inhaled leukotriene B<sub>4</sub> alone and in combination with prostaglandin D<sub>2</sub> on bronchial responsiveness to histamine in normal subjects

We read with interest the paper by Dr P Black *et al* (June 1989;44:491-5) and would like to support their findings with our own observations in the dog.<sup>1</sup>

We measured the change in airway responsiveness to methacholine and the cell content of bronchoalveolar lavage fluid one, three, and six hours after administration of aerosolised leukotriene (LT)B<sub>4</sub> (10  $\mu$ g) to beagle dogs. In contrast to previous reports in the dog,<sup>2</sup> we found that airway responsiveness was reduced after LTB<sub>4</sub> administration at each time point, despite a threefold increase in lavage fluid neutrophils.

These results show that the recruitment of neutrophils to the airways did not cause a concomitant increase in airway responsiveness to methacholine. The mechanism by which LTB<sub>4</sub> reduces airway responsiveness is unknown. A similar result has been reported in the guinea pig.<sup>3</sup>

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- 1 Imai T, Adachi M, Takahashi T. The effects of inhalation of leukotriene B<sub>4</sub> on airway responsiveness of dogs [in Japanese]. *Jap J Thorac Dis* 1989;27:267.
- 2 O'Byrne PH, Leikauf GD, Aizawa H, et al. Leukotriene B<sub>4</sub> induces airway hyperresponsiveness in dogs. *J Appl Physiol* 1985;59: 1941-6.
- 3 Silbaugh SA, Sengel PW, Williams GD, et al. Effects of leukotriene B<sub>4</sub> inhalation. *Am Rev Respir Dis* 1987;136:930-4.

### Pulmonary eosinophilia

In the study reported in the two articles on pulmonary eosinophilia published in November<sup>1,2</sup> 33 patients met the criteria for allergic bronchopulmonary aspergillosis and 32 were labelled as having "non-allergic bronchopulmonary aspergillosis" (the latter an unfortunate misnomer). The subsequent comparison of these two groups in respect of clinical and haematological features, response to prednisolone, and prognosis assumed a common pathological basis within each group, which neither in fact possessed. The weakness of that assumption is reflected in the negative nomenclature of the "non"-allergic bronchopulmonary aspergillosis group, and the authors themselves admit that this group "may be associated with several different syndromes whose underlying pathogeneses remain unclear."

At first sight it might seem reasonable for the authors to assume that patients who met the criteria for allergic bronchopulmonary aspergillosis, unlike those in the other group, did indeed have disease with a common pathological basis, but that too is open to question. Pathological differences within that group could have been recognised, or at least suspected, from the nature of the radiological