LETTERS TO THE EDITOR

Bone turnover and inhaled corticosteroids

We wish to take issue with several statements made by Kerstjens *et al* in their recent paper (July 1994;**49**:652–6). We believe that their conclusion that there is no clear evidence of a detrimental effect of inhaled corticosteroids on bone metabolism is unsubstantiated by the results of their study. They were able to demonstrate a significant fall in osteocalcin levels after four weeks of inhaled corticosteroid treatment, which implies a reduction in bone formation. This fall was no longer evident after two years of treatment. A less benign interpretation of these results is that reduced bone formation occurred at the start of treatment,[1] resulting in a fall in bone density. At a later stage bone metabolism may have returned to its previous equilibrium; any bone loss may not have been rectified by a later increase in bone formation. Unfortunately it is impossible to put the authors' results into a clinical context because they importantly failed to measure bone density.

A confounding factor in the interpretation of the effects of inhaled corticosteroids is the effect of courses of systemic corticosteroids. Some patients in study II of their paper must have received systemic corticosteroids yet we are given no information about this. It would be important to know whether the control and treated groups received equivalent doses of systemic corticosteroids over the 2·5 year study period.

The authors question the validity of osteocalcin measurements and suggest that measurement of serum levels of propeptide of type I collagen (PICP) may be a more valid marker of bone formation than osteocalcin (which was measured in our study). Nevertheless there is contrary evidence indicating that PICP may be a less sensitive marker of bone formation than osteocalcin.[2]

Our study on the effects of inhaled beclomethasone dipropionate on bone metabolism and density[3] is referenced by Kerstjens *et al* as one of several previous studies on the subject which were short term and uncontrolled. In fact, our study did include a well matched control group of patients with asthma who had not previously received corticosteroids. Furthermore, the median duration of treatment among the asthmatic subjects in our study who were receiving high dose inhaled corticosteroids was three years.

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1 Reid DM. Corticosteroid-induced osteoporosis. In: Smith R, ed. *Osteoporosis*. London: Royal College of Physicians of London, 1990:99–117.
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3 Packe GE, Douglas JG, McDonald AF, Robins SP, Reid DM. Bone density in asthmatic patients taking high dose inhaled beclomethasone dipropionate and intermittent systemic steroids. *Thorax* 1992;**47**:414–7.

AUTHORS' REPLY We believe there are three relevant questions at stake with respect to inhaled corticosteroids and bone turnover. (1) Do they cause fractures? (2) Do they cause excess fractures? (3) If so, how does that influence therapeutic decisions in patients with asthma?

(1) Determining the number of fractures asks for extremely long trials of 20 years or more. Proxies are therefore often employed in studies and subsequently cited. We particularly addressed the value attached to short term changes in blood parameters of bone formation. Since the human body has a remarkable capacity for correcting acute imbalances in many systems, we made the point that long term changes in bone turnover, and especially increases in fractures, should not be deduced from short term (often four weeks or less) changes in blood parameters such as osteocalcin. Additionally, we agree with Drs Packe and Douglas that measurement of bone density as a proxy of future fractures is perhaps the best – though still imperfect – parameter available at this moment. A randomised three year study is currently ongoing: in the EUROSCOP trial of inhaled corticosteroids versus regular treatment without inhaled corticosteroids (in patients with COPD) bone densitometry is followed up, at least in some centres.[1]

(2) Withholding inhaled steroids from patients with mild and moderately severe disease leads to more courses of oral steroids.[2,3] An unknown number of patients will eventually receive maintenance dosing of oral steroids; the amount can be reduced or abolished by inhaled corticosteroids.[4] Any definitive study on the effect of inhaled corticosteroids on any marker of bone turnover should therefore be prospective, randomised, and should compare patients with the same severity of disease. In our opinion the study by Dr Packe and colleagues was relatively uncontrolled; the retrospectively defined comparison group with "steroid naive" and hence very mild asthmatics does not represent a relevant control group. Their study was certainly non-randomised. Although we agree with Dr Packe that we should have mentioned the number of prednisolone courses administered in our study (36 one week courses in the 70 patients on inhaled corticosteroids and 74 courses in the 85 patients not on inhaled corticosteroids), the important point is that our study represented the clinical situation; if *by design and at random* inhaled corticosteroids are not administered, the proper comparison of effects on bone turnover can be made with the patients not having received inhaled corticosteroids.

(3) Finally, doctors and patients should be aware of adverse effects of any medication taken, but the final therapeutic decision will always have to be one of balancing the beneficial with the adverse effects, all relative to the severity of the disease. Based on clinical impressions after 22 years of use, it seems reasonable to expect at best a relatively small excess probability of fractures with inhaled corticosteroids. The largest adverse effect of inhaled corticosteroids in moderate, and certainly in severe, asthmatics might well be to withhold them.

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1 Pauwels RA, Lofdahl CG, Pride NB, Postma DS, Laitinen LA, Ohlsson SV. European Respiratory Society study on chronic obstructive pulmonary disease (EUROSCOP): hypothesis and design. *Eur Respir J* 1992;5:1254–61.
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Malignant pleural effusion

The editorial by Drs Reid and Rudd (August 1993;**48**:779–80) is a succinct up to date contribution. Many of the questions they raise about the efficacy of various sclerosing agents will require further data as they indicated. I would like to take issue primarily with their concern regarding the cost factor and possible morbidity and mortality of pleurodesis with thoracoscopic talc poudrage. They mentioned the 5% mortality and considerable morbidity in the patients studied by Ohri *et al*.[1] However, this series included terminally ill patients. As pointed out by Sahn,[2] pleurodesis is best reserved for those patients expected to live for several months. With this approach we have found the mortality after thoracoscopic talc poudrage to be zero and morbidity limited to occasional cellulitis of the chest tube site and short lived fever.[3,4]

As for cost, USP talc is sold locally for US$4.95 a pound, a life time supply for many hospitals. We sterilised enough talc for our entire region (comprising a 2·5 million catchment area) in a single sitting.[5] If we use the operating room this adds some cost, but our average four day hospital stay[3] is considerably shorter than most reports with tetracycline, and the fact that we need to do the procedure only *once* – even with low pH effusions[6] – suggests that thoracoscopic talc poudrage should cost considerably less than pleurodesis with tetracycline or bleomycin.

I expect that a serious look at thoracoscopic talc poudrage would show it to be both effective and as cost effective in the UK as it is elsewhere.

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1 Ohri SK, Oswal SK, Townsend ER, Fountain SW. Early and late outcome after diagnostic thoracoscopy and talc pleurodesis. *Ann Thorac Surg* 1992;**52**:1038–41.
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AUTHORS' REPLY We thank Professor Aelony for his information regarding thoracoscopic talc poudrage and pleurodesis in the man-

agement of malignant pleural effusion. Thoracoscopic inspection of the pleural space provides optimal conditions for effective pleurodesis by facilitating a dry pleural cavity and may be more important, with regard to success, than the choice of sclerosant. Nevertheless his experience with talc is most interesting, and we agree that further data in the form of a prospective randomised trial are required to clarify management which remains largely a matter of personal experience and reflects local expertise.

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Corynebacterium parvum for malignant pleural effusions

I have read the article by Dr AG Villanueva *et al* (January 1994;**49**:23–5) on tetracycline pleurodesis for malignant pleural effusions. Tube thoracostomy drainage before instillation of tetracycline is necessary to achieve successful pleurodesis, and the authors found that short term drainage was as effective as long term drainage. Since insertion of a drainage tube is uncomfortable, the use of a sclerosing agent which can be injected into the pleural cavity without an intercostal tube is preferable. *Corynebacterium parvum* (CBP), unlike other sclerosing agents, has this feature. In fact, in the study by Leahy *et al*[1] treatment with CBP was as effective as tetracycline injected via an intercostal tube.

I wish to report results on 28 consecutive patients treated with intrapleural CBP (Coparvax, Wellcome Foundation, London, UK) without intercostal tube drainage. Four patients were not evaluable as they died within one month. A complete response (total resolution of pleural effusion after a maximum of three injections of CBP) was seen in 22 of the remaining 24 patients. The side effects were fever (in 50% of patients) usually lasting 2–3 days, and mild or moderate chest pain (32% of patients), both of which were effectively controlled with paracetamol or non-steroidal anti-inflammatory drugs.

These data confirm that instillation of CBP without intercostal tube drainage is an effective, simple, and well tolerated method of controlling malignant pleural effusions. Our patients had a longer survival time (mean 7·7 months) than that reported by Villanueva *et al*, and three are still alive with survival times of 11·3, 9·9, and 5·1 months. Our results are also superior to those of patients treated with talc (1·9 months in patients with low pleural fluid glucose levels and low pH and 5·7 months in patients with high glucose and high pH levels),[2] and to those treated with mustine (3·9 months).[3] This fact is emphasised by other authors[3 4] and suggests that CBP may be acting, not only as a sclerosant, but also as an immunostimulant.

Unfortunately, CBP has been discontinued by the Wellcome Foundation, as has injectable tetracycline. In Italy injectable tetracycline, doxycycline, minocycline, and rolitetracycline are not available. The treatment of malignant pleural effusions therefore currently requires more expensive agents or more invasive methods.

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1 Leahy BC, Honeybourne D, Brear SG, Carrol KB, Thatcher N, Stretton TB. Treatment of malignant pleural effusions with intrapleural *Corynebacterium parvum* or tetracycline. *Eur J Respir Dis* 1985;**66**:50–4.
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BOOK NOTICE

Diseases of Occupations. 8th Edition. PAB Raffle, PH Adams, PJ Baxter, WR Lee. (Pp 804; £145.00). London: Edward Arnold, 1994. 0 340 55173 9.

Most British chest physicians also practise general medicine, and all will have passed the MRCP. At one time Hunter's *Diseases of Occupations* was essential reading for those taking the examination, not least because Donald Hunter was a notoriously idiosyncratic examiner. The original classic textbook in its later editions lost much of its value except as an historical reference, but this 8th edition has been completely rewritten, breaking at last with the original format but honouring the original purpose "to review with emphasis on its clinical aspects the problem of disease in relation to occupation". This task inevitably requires a team of contributors, and the editors have selected a strong one. They have also achieved a reasonable uniformity of style and structure which makes the book easy to read and clinically informative.

The first five chapters contain information on preventive legislation, compensation, and medical report writing that is not readily available elsewhere. The rest of the book consists of descriptions of occupational diseases as seen nowadays, properly emphasising the common problems of musculoskeletal, psychological, skin, and hearing diseases that are of interest to other specialists. The chapters on occupational lung disorders are concise, clearly written and accurate, but necessarily lack the detail to be found in more specialised textbooks. The short chapter on indoor air pollution is one that many who are confused by the various "sick building" syndromes will find particularly helpful.

This is a much better book than the 7th edition, and deserves to be in all hospital and medical school libraries. All doctors training in general medicine should read it and will find it opens their eyes to previously unappreciated causes of disease and possibilities for prevention. And with the growing interest in environmental causes of disease, who knows – it could even once again become essential reading for passing the MRCP! – AS

NOTICES

Scadding-Morriston Davies Joint Fellowship in Respiratory Medicine 1995

This fellowship is available to support visits to medical centres in the UK or abroad for the purpose of undertaking studies related to respiratory medicine. Medical graduates practising in the UK, including consultants and irrespective of the number of years in that grade, may apply. Applicants should submit a curriculum vitae together with a detailed account of the duration and nature of the work, the centres to be visited, confirming that these have agreed to provide the facilities required, and giving the sum of money needed for travel and subsistence. A sum of up to £12 000 can be awarded to the successful applicant, or the sum may be divided to support two or more applications. Applications should be sent by **31 January 1995** to Dr I A Campbell, Secretary to the Scadding-Morriston Davies Fellowship, Llandough Hospital, Penarth, South Glamorgan CF64 1XX.

Lung and Asthma Information Agency

The Lung and Asthma Information Agency aims to bring together, interpret, and disseminate information about lung disease in order to increase awareness and understanding of the burden of lung disease and of its prevention and care. It is jointly supported by the National Asthma Campaign, the British Lung Foundation, and the British Thoracic Society. Since its launch at the BTS Summer Meeting in July 1992 it has concentrated on three areas: the production of factsheets, developing a comprehensive respiratory database, and providing an information service to the sponsors. So far, it has produced factsheets on asthma mortality in the elderly, pneumonia mortality in the elderly, pleural mesothelioma, sickness absence from respiratory disease, respiratory tuberculosis, lung cancer and smoking, GP prescribing of drugs for respiratory disease, RSV in children, seasonal variations in asthma, air pollution, and asthma prevalence. From 1995 further factsheets will be distributed with *Thorax*, the first on "Trends in hospital admissions for asthma" appearing with this issue. Multiple copies of factsheets, back copies of earlier factsheets, and further information about the Agency may be obtained from: Elizabeth Limb, The Lung and Asthma Information Agency, Dept. of Public Health Sciences, St George's Hospital Medical School, Cranmer Terrace, London SW17 0RE. Tel: 0181 725 5489.