

PostScript

LETTERS TO THE EDITOR

BMD and airways disease

The papers recently published in *Thorax* by Tattersfield *et al*¹ and Walsh *et al*² offer important information about the possible adverse effects of corticosteroids on bone mineral density (BMD). Tattersfield and her colleagues reported no change in BMD with inhaled corticosteroids for mild asthma, while Walsh *et al* found a dose related increase in the incidence of fractures in those taking oral corticosteroids. We would like to report our study of BMD in patients with airways disease, which reinforces these findings and highlights men as being particularly at risk.

We prospectively studied 100 consecutive outpatients (44 men) with steroid responsive airways disease. The formulation and cumulative dose of corticosteroid was recorded in each individual, together with all prescribed prophylaxis for osteoporosis. Bone mineral density was measured in the non-dominant forearm. We found no relationship between inhaled corticosteroid dose and BMD. Mean BMD was significantly reduced in those on oral as opposed to inhaled steroids. In men the mean Z scores for those on inhaled and oral corticosteroids were 0.1 and -0.6, respectively ($p=0.07$), while women had mean Z scores of 0.5 and -0.3 for inhaled and oral corticosteroids, respectively ($p=0.016$). Our patient numbers were insufficient to confirm a dose response. The surprising result was that men were more likely to meet the WHO criteria for osteoporosis than women (25% v 12.5%). This result is explained at least in part by the use of prophylaxis which was prescribed to 21 women but to only two men. Of those on regular oral steroids, only 5.5% of men received prophylaxis compared with 62.5% of women. Similar results have been reported in other chronic diseases, with a greater reduction in BMD being reported in men with cystic fibrosis.³

Unfortunately it appears to have been assumed that men are protected from osteoporosis by virtue of their gender. When chronic disease is treated with oral corticosteroids, both men and women are equally at risk of osteoporosis and all should be considered for prophylaxis.

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- 1 Tattersfield AE, Town GI, Johnell O, *et al*. Bone mineral density in subjects with mild asthma randomised to treatment with inhaled corticosteroids or non-corticosteroid treatment for two years. *Thorax* 2001;56:272-8.
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- 3 Conway SP, Morton AM, Oldroyd B, *et al*. Osteoporosis and osteopenia in adults and adolescents in cystic fibrosis: prevalence and associated factors. *Thorax* 2000;55:798-804.

AHR in asthma

Peat *et al*¹ have contributed a helpful review to the debate on techniques for measuring

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asthma in population studies. However, they have endorsed airway hyperresponsiveness (AHR) while neatly sidestepping the issue of what test they are discussing. Inhaled provocation tests used in epidemiological work have included histamine, methacholine, hypertonic saline, cold air, and adenosine. Exercise provocation tests have also been used. Peat *et al* have previously shown that exercise and histamine challenges may define different groups of children,² and we have shown that longer term repeatability of a free running exercise provocation test is poor within a childhood population.³ In adults quite considerable within subject variability in PD_{50} to methacholine has been observed during a 1 year period,⁴ and a childhood population study found that methacholine PD_{50} varied by >4 doubling doses within the course of a year in 33% of the subjects.⁵

We would suggest that more care should be taken to define the precise measure of AHR used before comments can be made about its sensitivity and specificity in an epidemiological survey. The medium term temporal variation in AHR seen by a number of researchers is another measure which may make it difficult to make useful comparisons between populations.

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- 2 Haby M, Anderson S, Peat J, *et al*. An exercise challenge protocol for epidemiological studies of asthma in children: comparison with histamine challenge. *Eur Respir J* 1994;7:43-9.
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Authors' reply

Primhak and Powell make the valid point that the presence of airway hyperresponsiveness (AHR) is not an absolute attribute. Abnormal AHR represents one end of a continuum of responsiveness. Furthermore, the distribution of that continuum varies according to the nature of the direct or indirect stimulus that is applied.

In our studies, referred to in the review, we have defined abnormal airway responsiveness as a decline of more than 20% in forced expiratory volume in 1 second (FEV₁) after inhalation of a cumulative dose of histamine of $\leq 3.9 \mu\text{mol}$. Using this criterion, the presence of AHR is a useful marker of airway abnormality consistent with asthma in epidemiological studies¹ and is also predictive of the subsequent course of the disease.² We acknowledge that other criteria for the presence of AHR have not been evaluated as extensively in epidemiological studies. However, there is evidence that at least some indirect agonists, such as non-isotonic aerosols and exercise, also have a high level of specificity but only moderate sensitivity as markers of asthma symptoms.^{3,4}

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One fibre or many: what causes mesothelioma?

In a recent case (00/TLQ/1284) in the Queen's Bench Division of the High Court in England, a widow sued on behalf of her husband who had died at the age of 60 of mesothelioma. Unusually for such cases, Mr Justice Curtis found for the defendants, and the grounds for his judgement were sufficiently curious to be of general interest and worthy of debate.

It was not disputed that the deceased had been exposed to substantial quantities of asbestos during two periods of employment, nor that there had been a breach of statutory duty by his employers at that time. The judgement was based, however, on the expert and agreed opinion of "two most highly qualified medical men". In their joint report and oral evidence, the judge believed these doctors to have stated that mesothelioma is the consequence of malignant transformation in a single cell, the result of a hit by either one or several fibres. This led the judge to reason that, although a fibre or fibres inhaled during one

or other period of employment may well have led to the fatal cellular transformation, it was not possible to say which, and he was therefore unable to find either responsible.

In coming to his judgement, Mr Justice Curtis made a distinction between causation and risk factors. In his words "the only relevance of the number of fibres is in connection with the risk of contracting the disease". He was thus dissuaded from being influenced by any evidence that might have shown a relationship between risk of mesothelioma and dose of asbestos, although there is much such evidence from studies both of human lungs and of animals.

I have heard the view expressed before that one fibre causes mesothelioma. It depends what you mean by "cause". It is in one sense obvious nonsense. We all have millions of asbestos fibres in our lungs and the likelihood of us developing mesothelioma depends on how many millions. This means that the disease is dose related. The problem in this case arose from confusing the disease mesothelioma with transformation in a cell, which may be a factor in the development of the disease. Take the case of the butterfly flapping its wings in the Amazon rain forest. It may be possible for an ingenious QC to prove that the hurricane that hit the coast of west Africa was caused by that insect's action, but the other side would surely point to other risk factors that, taken with the action of the butterfly, contributed significantly to the disaster.

Is it really possible to say that the only and necessary cause of mesothelioma is transformation in a cell? Are we sure that the *milieu* in which that cell lives and divides is not influential? Are we sure that inflammation in the tissue involved is not an important precondition for the development of the disease? Are we sure that the action of asbestos on other cells does not interfere with the natural defences that would otherwise eliminate the transformed cell? Are we sure that genetic factors and viruses do not also determine whether the transformation occurs or succeeds in overcoming the body's defences? Or looked at another way, experimentally, how many rats would have to be used to produce one mesothelioma after injection of one fibre into the peritoneum? Of course, no one has ever shown that one fibre causes mesothelioma. All that has been conjectured is that the malignant cells that form part of the tumour may be the genetic offspring of one transformed cell.

The judge appears in this case to have been persuaded to accept a naïve view of causation—that disease has one ultimate cause. Most who have studied the causation of disease would argue that the likelihood of disease occurring in any individual is influenced by multiple factors, the outcome of inherited and acquired susceptibility and environmental precipitants. In the case of mesothelioma, a very heavily asbestos exposed individual may have a one in 10 lifetime risk of the disease. Most of us, with very small incidental exposures, have about a one in 1 million annual risk. The risk varies with the length and intensity of exposure, as assessed by the individual's occupational history. We know from animal studies that asbestos fibres do indeed cause mesothelioma, so this evidence of a dose related association strongly suggests that factors other than transformation of one cell are also, and critically, responsible for the disease. Among these is likely to be inflammation in the pleura initiated by the presence of many fibres. Such inflammation may not only result in malignant transformation of many cells, but may also inhibit the

natural mechanisms whereby such cells are eliminated. If this is true, and it is certainly more plausible than the one fibre theory, then mesothelioma is caused by the access of large numbers of fibres to the mesothelial tissue. Since it is a dose related disease, it may be argued that all exposures to asbestos before a critical time would be expected to have contributed to the causation of the disease. Thus, attribution of blame should be on the basis of relative intensity and duration of exposure in different trades.

The moral of this story is that lawyers are clever people and part of their business is the meaning of words. The word "cause" is one that requires a bit of thought. My *Shorier Oxford Dictionary* devotes a column to it.

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Mesothelioma

We write as the three medical witnesses who provided evidence (all in writing, two orally) to the Court in the case referred to by Professor Seaton. Essentially we agree with his analysis. The medical evidence presented to the Court made it clear that the risk of mesothelioma increases in relation to the dose of asbestos and that it is not possible to identify the particular fibre or fibres involved in the genesis of a particular mesothelioma. From an epidemiological standpoint it is therefore appropriate to regard all sources of significant exposure as having contributed to causation of the disease, in the same way that all cigarettes smoked would be considered to have contributed to causation of a lung cancer.

Mr Justice Curtis, however, accepted the invitation of Leading Counsel for one of the defendants to adopt a strictly mechanistic approach to causation. He decided that, because the claimant could not show whether the fibre or fibres actually involved in the genesis of the tumour were derived from either or both of two sources of exposure, causation could not be established against either of two defendants.

More recently, a different view has been taken in a similar case by Mr Justice Mitting (Queen's Bench Division C20010111). He considered that there was "no substantial difference between saying that what the defendant did materially increased the risk of injury to the claimant and saying that what the defendant did made a material contribution to his injury". It would be "wholly artificial to require a claimant to prove which fibre or fibres, inhaled in whose employment in precisely what circumstances, caused or set off or contributed to the process by which one or more mesothelial cells become malignant". He concluded that breach of duty on the part of both defendants caused the mesothelioma.

Both cases are soon to be considered by the Court of Appeal and the outcome will determine whether the many mesothelioma victims who happen to have derived their asbestos exposure from more than one source are to be left without redress.

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Statement on malignant mesothelioma in the UK

We would like to provide the following additional material to Appendix 3 "Sources of information and help available for patients and carers" which appeared on pages 263-4 of the BTS statement on malignant mesothelioma in the UK published recently in *Thorax*.

The following Asbestos Support Groups are the major practical sources of information in the UK for people with asbestos related diseases. Most provide a drop in and telephone service, giving confidential free advice and support to patients and families. They also have particular expertise in the field of industrial injury benefits and government and civil compensation claims. Although most of the groups are in the north of England, telephone queries from any part of Great Britain are acceptable to them.

Manchester (tel: 0161 953 4037)

Sheffield (tel: 0114 282 3212 or 01709 513 587)

Liverpool (tel: 0151 236 1895)

Bradford (tel: 01274 393 949)

West Yorks (tel: 0113 243 9979)

Cheshire (tel: 01928 576641)

Nottingham (tel: 0115 927 5108)

In Scotland:

Clydeside Action on Asbestos (tel: 0141 552 8852)

Clydebank Asbestos Group (tel: 0141 951 1008)

Other important sources of help and information are:

The Macmillan Mesothelioma Information Line (tel: 0113 206 6466; email: mavisro@ulth.northy.nhs.uk) and the Occupational and Environmental Diseases Association (OEDA), both of which were mentioned in the original statement.

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Asymptomatic pulmonary involvement in RA

Dawson *et al*¹ found HRCT evidence of fibrosing alveolitis (FA) in 19% of 150 outpatients with rheumatoid arthritis (RA). The presence of FA did not relate to previously described predisposing factors such as male sex, nodular and/or extra-articular disease, disease duration and severity. Moreover, the authors did not find any relation with respiratory symptoms such as dyspnoea or cough, chest radiographic appearance of FA, or restrictive pattern at pulmonary function tests. The only features significantly associated with FA on the HRCT scan were the presence of bibasal crackles and the reduction in carbon monoxide transfer factor (Tlco). These findings are more difficult to explain, especially considering that FA was defined as an HRCT pattern