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LETTERS TO THE EDITOR

β_2 adrenoceptor polymorphisms

We read with interest the editorial by Dr Hall (April 1996;51:351–3) concerning polymorphisms in the β adrenergic receptor and asthma; however, we wish to take issue with one of his statements. He states that if the β adrenergic receptor polymorphisms are important in defining the phenotype of asthma, then it should be possible to establish linkage between markers located on chromosome 5q at the β adrenergic receptor and asthma. While this is strictly true, one could easily mistake this statement to mean that, if linkage was not established, the identified polymorphisms were not important in asthma. In particular, if these polymorphisms modify the severity of asthma but are not critical to the assignment of the asthma phenotype, then the two may not be linked even though the polymorphisms could be of major importance in asthma. Although subtle, we think this is an important distinction which needs to be clarified to avoid misunderstanding in the future.

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AUTHORS' REPLY I thank Dr Drazen and colleagues for their interest in my editorial on polymorphisms in the β_2 adrenoceptor and asthma. They raise the important point that, whilst a genetic abnormality may not contribute to the development of the asthma phenotype per se, it could still be important if it is disease modifying. As discussed in the editorial, there is good evidence that β_2 adrenoceptor polymorphisms may contribute to determining disease severity but far less evidence that the polymorphisms are risk factors for developing asthma. We have recently completed a family study in which we were unable to demonstrate an increased risk of asthma in individuals with either the Gly 16 or the Gln 27 β_2 adrenoceptor polymorphisms,[1] indicating that these polymorphisms may well be disease modifying rather than disease causing. An additional point worth bearing in mind is that in many studies asthma is considered as an all or none phenomenon rather than as a quantitative trait. Linkage and/or association studies which do not examine asthma as a quantitative trait may hence miss disease modifying genes.

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1 Dewar J, Wheatley A, Wilkinson J, Thomas N, Lawrence S, Morton N, *et al.* Association of the Gln-Glu 27 β_2 adrenoceptor polymorphism with total IgE in families with asthma. *Am Rev Respir Crit Care Med* 1996;153:A413.

Actinomycotic intracavitary lung colonisation

We read with interest the report by Hseih *et al* (February 1996;51:221–2) of a 40 year old diabetic man with pulmonary actinomycotic intracavitary colonisation with an air meniscus. They mention that fungal infections were identified in all of our four reported cases.[1] In reality the main microbiological finding in our cases consisted exclusively of actinomycotic colonisation; coexistence of fungal infection was not observed.

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1 Severo LC, Kaemmerer A, Camargo JJ, Porto NS. Actinomycotic intracavitary lung colonization. *Mycopathologia* 1989;108:1–4.

Occupational asthma

We read with interest the contribution by Meredith and Nordman on measures of frequency of occupational asthma from four countries (April 1996;51:435–40) and are grateful to the authors for quoting the medicolegal statistics we collected in Quebec.

A physician based project (PROPULSE) was conducted between October 1992 and September 1993 in Quebec and a paper is being submitted for publication. The most frequently reported diagnosis was asthma (287 cases, 63%), and all asbestos related diseases grouped together (asbestosis, mesothelioma, benign pleural diseases, lung and bronchial cancer) represented 16% of all cases. According to these data, the estimated rate of occupational asthma was calculated as 84 per million; a more conservative estimate using cases reported as highly likely gives only 36 per million. We agree with Meredith and Nordman that, as for other countries, compensation data in Quebec are underestimated because self employed persons are not included and some workers may choose not to make claims. Indeed, a crude comparison of data from our physician based system with Workers' Compensation Board data in Quebec has shown twice as many cases of asthma, even when only cases judged as highly likely were considered. However, this finding is attenuated by the results of a second study conducted on a sample of cases with occupational asthma (manuscript in preparation) in which the medical files of 120 cases reported by three chest physicians working in a specialised tertiary care clinic were reviewed to identify cases confirmed as having occupational asthma following investigation by objective means (specific inhalation challenges with or without monitoring of peak expiratory flow); 42% of highly likely or suspected cases at the initial reporting were confirmed by objective testing.

In Quebec, therefore, the physician based system might suffer from the underestimation of occupational asthma because not all suspected cases are reported, as observed with SWORD in the UK, but this effect may be counterbalanced by overestimation due to lack of confirmation in the early reporting process. The reason is that exposure to possible occupational "sensitisers" occurs frequently among asthmatic subjects in a working population, leading to overestimation of the diagnosis when based on a questionnaire. This rationale would not apply to asbestosis or silicosis because the conjunction of having evidence of lung fibrosis on a chest radiograph and being exposed to asbestos or silica dust is a rarer occurrence in a working population.

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Hepatotoxicity of antituberculosis drugs

Severe hepatotoxic reactions to antituberculosis drugs are fortunately uncommon but have led to a number of fatalities.[1,2] Such cases usually arise from inadequate clinical monitoring and failure to modify or to discontinue the treatment when clinical or biochemical abnormalities have appeared. The editorial on this topic by Ormerod and colleagues of the Joint Tuberculosis Committee of the British Thoracic Society (February 1996;51:111–3) is therefore welcome though we have reservations on certain of its conclusions.

We agree that all patients should have pretreatment measurements of liver function but strongly disagree with the proposition that, in the absence of pretreatment liver disease or liver function test abnormality, the tests need only be repeated if jaundice, other symptoms, or unexplained deterioration have occurred. Our experience is that such symptoms develop late in acute hepatic necrosis and are often associated with established liver failure.

Severe hepatotoxic reactions can certainly occur in the complete absence of preceding liver disease. Supervising physicians should, furthermore, be aware of a potential toxic hazard from concomitant medication with enzyme inducing properties such as phenytoin and possibly hormone therapy. We agree with Thompson *et al*[3] that liver function tests should continue throughout the course of treatment.

The authors of the editorial consider the difficult choice between continuing treatment in the face of liver function abnormality and of withdrawing treatment with the risk of an inadequate drug regimen leading to the emergence of resistant strains. They suggest that chemotherapy be withdrawn when liver enzyme activities reach five times the upper limit of normal; while admitting that there are no firm data, we feel that this is unduly lenient and propose that a level of three times this value should be taken as a warning and that isoniazid at least should be withdrawn at that stage.

We also have reservations about the proposals for the re-introduction of isoniazid, rifampicin, and pyrazinamide. The authors recommend restarting each drug at an interval of "2–3 days if no reaction occurs" after reaching the final dosage of the preceding

drug. We consider that this leaves insufficient time for reliable identification of the offending drug or drugs. We agree that the drugs should probably be re-introduced in this order.

A further difficult problem is the re-introduction of chemotherapy after an episode of acute liver failure. Certainly it is our policy, as discussed by Mitchell *et al*,[1] to change to drugs with no history of hepatotoxicity in patients fortunate enough to have survived this complication.

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1 Mitchell I, Wendon J, Fitt S, Williams R. Antituberculous drugs and liver failure. *Lancet* 1995;**345**:555–6.
2 Moulding TS, Redeker AG, Kanel GC. Twenty isoniazid-associated deaths in one state. *Am Rev Respir Dis* 1989;**140**:700–5.
3 Thompson NP, Caplin ME, Hamilton MI, *et al*. Anti-tuberculous medication and the liver: dangers and recommendations in management. *Eur Respir J* 1995;**8**:1384–8.

AUTHORS' REPLY The editorial set out recommendations on the management of hepatic reactions after due consideration of both the risks of tuberculosis itself and the risk from the drug treatment. There have been 45 deaths from liver reactions to currently recommended first-line antituberculosis drugs since 1963, with isoniazid implicated in a maximum of 25 of these. Over the same period of time there have been 272 000 notified cases of tuberculosis (all forms), with pulmonary disease – which makes up the majority of cases – carrying an overall mortality of some 5%. The most recently published annual infectious disease statistics show 418 deaths from tuberculosis in 1994,[1] and the level of tuberculosis deaths has been at that level for the last five years, and substantially higher in the earlier part of the period 1963–94. The risk of dying from tuberculosis is therefore clearly at least 200 times higher than that of a fatal hepatic reaction from the treatment, and inadequate treatment must intuitively raise the mortality of the disease still further.

We would agree that cases of hepatotoxic reactions may arise from inadequate clinical monitoring and particularly from failure to modify or to discontinue treatment when clinical and biochemical abnormalities have appeared. This makes it even more important that all cases of tuberculosis are under the care of physicians trained in its management, and with recommended dosages and durations of drugs.[2] In the paper by Mitchell *et al* from the King's unit referred to by Devlin and colleagues no dosages, drug durations, or patient weights were given, so it was not shown that correct management led to the problems reported.

Devlin *et al* accept that their recommendations that chemotherapy be withdrawn if liver transaminase activity reaches three times normal is not based on firm data. The suggestion that isoniazid at least should be withdrawn at this level does not seem logical. A large, mainly prospective, study of reactions to antituberculosis treatment showed that the incidence of hepatotoxic reactions was lowest to isoniazid at 0.3%, being appreciably higher to pyrazinamide (1.25%) and rifampicin (1.4%).[3]

The essential difference between Devlin *et al* and our editorial is the "balance point" between the risks of treatment and the risks of the underlying disease. To have a level of transaminases of three times normal for modification of treatment may well be unduly harsh. Some patients with such pretreatment levels of transaminases as a result of extensive or disseminated tuberculosis who already face a significant mortality would be denied the most effective antituberculosis drugs, thus increasing further their mortality from the disease. The emergence of multiple drug resistant tuberculosis, which is often due to inadequate treatment and compliance monitoring, is a further reason why standard chemotherapy should not be altered without strong justification.

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1 Office for National Statistics. *Communicable Disease Statistics 1994 England and Wales.* Series MB2, No 21. London: HMSO, 1996.
2 Subcommittee of the Joint Tuberculosis Committee of the British Thoracic Society. Chemotherapy and management of tuberculosis in the United Kingdom: recommendations of the Joint Tuberculosis Committee of the British Thoracic Society. *Thorax* 1990;**45**:403–8.
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Pneumomediastinum following Politzer's manoeuvre

The report by Dr Torres-Melero and co-authors of a case of pneumomediastinum following the use of a high speed air turbine drill during a dental extraction (March 1996; **51**:339–40) contains some interesting points about iatrogenic pneumomediastinum.

A 35 year old man was recently admitted as an emergency to our department with acute severe neck and retrosternal pain, dyspnoea, vomiting, and agitation. These symptoms suddenly appeared during Politzer's manoeuvre carried out for the treatment of acoustic problems. Clinical examination showed subcutaneous emphysema in the neck and anterior chest wall with swelling around the eyes and over the cheeks. The patient had no pre-existing lung disease. Blood pressure and pulse, laboratory tests, electrocardiography and arterial blood gas tensions were normal. Chest radiography showed pneumomediastinum, bilateral apical pneumothorax, and subcutaneous emphysema. A large quantity of air was noted in the gastrointestinal tract on the abdominal radiograph. A computed tomographic scan confirmed the presence of air in the soft tissues of the neck, extending through the mediastinum to the diaphragm, with detachment of the mediastinal pleura and the apical parietal pleura bilaterally. The lungs were not collapsed. An oesophageal contrast study was performed to exclude any lesions in the digestive tract; no abnormalities were noted. Fibreoptic endoscopy found no lesions in the mucosa of the rhinopharynx. The patient was treated conservatively and his clinical condition improved within 48 hours; he was discharged well six days after admission. A follow up chest radiograph 15 days after discharge showed almost complete disappearance of the air collection.

Our case has to be considered as another cause of iatrogenic pneumomediastinum and should be added to the others previously described.[1-3]

The Politzer's manoeuvre is a method of restoring the patency of the tubes in middle ear diseases. The aim of the technique is to balance the atmospheric pressure and the pressure inside the eustachian tube by insufflating air through the rhinopharynx with a closed epiglottis. Air can be insufflated manually with a pearpush or mechanically with a conveniently balanced compressor (usually no more than 2000 millibar). Although the exact mechanism of entry of air was not found in our patient, it is likely that malfunction of the machine (or an inappropriate use of the equipment) allowed the output of air at high pressure which diffused down the fascial planes to the mediastinum and to the soft tissues of the neck through a small laceration of the rhinopharyngeal mucosa. This suspicion was confirmed by the massive quantity of air in the digestive tract and in the anterior extrapleural space.

Pneumomediastinum must be considered as a rare complication of the use of a jet of compressed air from different medical instruments.

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1 Naughton M, Irving L, McKenzie A. Pneumomediastinum after transbronchial biopsy. *Thorax* 1991;**46**:606–7.
2 Lee HC, Dewan N, Crosby L. Subcutaneous emphysema, pneumomediastinum and potentially life-threatening tension pneumothorax. *Chest* 1992;**101**:1265–7.
3 Kern C, Tassonyi E. Pneumomediastinum due to the use of a jet of compressed air. *Can J Anaesth* 1989;**36**:78–80.

BOOK REVIEWS

Pulmonary Circulation – A Handbook for Clinicians. A J Peacock. (Pp 508; £95.00). London: Chapman & Hall, 1996. 0 412 56870 5.

This volume of over 500 pages pulls together many different strands of the anatomy, physiology, and therapeutics of the pulmonary circulation and its disorders. It is particularly strong in the evaluation of the pulmonary circulation in special environments and includes chapters by Jack Reeves on high altitude and high altitude pulmonary