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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