metered dose inhalers[1] and tachycardia and prolonged Q-T interval have been reported principally with nebulised or oral β agonists.[2] The advised total daily dose of oral bambuterol (20 mg) is 200 times that of inhaled salmeterol (100 μg).[3]

Secondly, Dr Lindmark reiterates our point that the results must be interpreted with caution because the study was observational, and more definitive evidence would come from a prospective randomised trial. Nevertheless, hypotheses about drug safety concerns are often generated from observational studies.[4] Such studies drive further research because they provide an "a priori" hypothesis and allow the formulation of a clinically relevant end point. Until results from prospective trials become available, observational research using cohort or case-control techniques remains an important source of evidence about the safety of drugs.

Thirdly, he states that a review by Astra Draco has found no evidence from pre-marketing or post-marketing studies of an association between bambuterol and cardiac failure. In general, pre-marketing studies have their own limitations,[5] as evidenced by the recent withdrawal on safety grounds of two newly launched drugs.[6] Similarly, different types of post-marketing surveillance studies, including PEM, have different advantages and disadvantages and, in general, one system cannot be relied upon to provide all the evidence needed.[7] This point also applies in response to the fourth comment. In particular, it should be noted that there is gross under-reporting of suspected adverse drug reactions to the Committee on Safety of Medicines[8] and other regulatory authorities, and there are many difficulties associated with interpreting data from spontaneous reporting schemes.[7]

Finally, as is stated clearly in our paper, it is possible that the association may be explained by factors such as confounding by concomitant disease and disease severity. Interestingly, the rate of cardiac failure associated with bambuterol in the first month of treatment was higher than for 11 cardiovascular drugs previously studied by PEM (table 1). Only two cardiac drugs, including the inotropic sympathomimetic xamoterol (licensed for use in mild heart failure) had higher rates of cardiac failure. Since it is highly unlikely that the rate of cardiovascular disease in the bambuterol cohort was higher than in cohorts of patients taking cardiac drugs, and the bambuterol cohort was the youngest, these data provide further evidence that an association cannot be discounted. Our findings require confirmation, but we remain concerned about the size and biological plausibility of the association.

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1 Nelson HS. β-adrenergic bronchodilators. *N Engl J Med* 1995;**333**:499–506.
2 Suissa S, Hemmelgarn B, Blais L, *et al.* Bronchodilators and acute cardiac death. *Am J Respir Crit Care Med* 1996;**154**:1598–602.
3 Joint Formulary Committee. *British National Formulary Number 33*. London: British Medical Association and Royal Pharmaceutical Society of Great Britain, 1997:125–6.
4 Olsen JH. Interpretation in drug epidemiology. *Lancet* 1998;**352**:162–3.
5 Waller PC, Coulson RA, Wood SM. Regulatory pharmacovigilance in the United Kingdom: current principles and practice. *Pharmacoepidemiol Drug Safety* 1996;**5**:363–75.
6 Li Wan Po A, Zhang WY. What lessons can be learnt from withdrawal of mibefradil from the market? *Lancet* 1998;**351**:1829–30.
7 Lawson DH. Pharmacovigilance in the 1990s. *Br J Clin Pharmacol* 1997;**44**:109–10.
8 Martin RM, Kapoor KV, *et al.* Underreporting of adverse drug reactions to newly marketed, black triangle drugs in general practice in England: observational study. *BMJ* 1998;**317**:119–20.

Genetics and tuberculosis

Dr Richard Bellamy alludes to the important fact, frequently ignored by immunologists, geneticists and epidemiologists, that tuberculosis has several different clinical forms.[1] Physicians have emphasised the difference between primary tuberculosis, which is comparable to Lurie's susceptible rabbits with disseminated disease, and post primary tuberculosis, best characterised by smear positive pulmonary tuberculosis and Lurie's "resistant" rabbits. HLA associations with tuberculosis have indeed been inconsistent when all forms of tuberculosis are included. However, the HLA association with DR2, and particularly with its subtype DR15 in linkage disequilibrium with DQ5, was found only in patients with smear positive pulmonary tuberculosis.[2,3] These observations have been refined using DNA based HLA typing and have confirmed a link with the genes *DRB1*1501* and *DQB1*0502*.[4] Antibody levels to epitopes of the 38kDa antigen of *Mycobacterium tuberculosis* restricted antigens were higher, suggesting an enhanced immune responsiveness in those with HLA-DR15.[3] The relative importance of the genes involved in susceptibility can be assessed by the gene frequency, but also by the attributable risk—that is, how much of the disease can be attributed to the presence or absence of a particular gene (34% with 95% confidence intervals of 16 to 43% were suggested for DR15 in one population[3]).

The Lurie experiment suggests that a comparison between patients with different forms of tuberculosis, matched by ethnic origin, may be valuable in identifying candidate genes for susceptibility to tuberculosis. Since smear positive pulmonary tuberculosis is responsible for transmission of the disease, an understanding of its pathogenesis will be especially important in finding new ways to control tuberculosis.

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1 Bellamy R. Genetic susceptibility to tuberculosis in human populations. *Thorax* 1998;**53**:588–93.
2 Brahmajothi V, Pitchappan RM, Kakkanaiah VN, *et al.* Association of pulmonary tuberculosis and HLA in South India. *Tubercle* 1991;**72**:123–32.
3 Bothamley GH, Schreuder GMT. Human leukocyte antigen, tuberculosis and *Mycobacterium tuberculosis*-specific antibody. *J Infect Dis* 1992;**165**:598.
4 Meyer CG, May J, Stark K. Human leukocyte antigens in tuberculosis and leprosy. *Trends Microbiol* 1998;**6**:148–54.

Chlamydia pneumoniae and asthma

The paper by Cook *et al*[1] examines the possible association between *Chlamydia pneumoniae* infection and asthma. The authors conclude that their data do not support this association. However, we feel that the serological tests performed give important information on the prevalence of infection, but are not sufficiently complete to make definitive conclusions on the incidence of acute *C pneumoniae* infection in the populations under study. The major pitfall in the study, as pointed out by the authors, is the small proportion of patients from whom a convalescent serum sample was drawn. Moreover, the arbitrary exclusion of IgM positive patients for the diagnosis of acute *C pneumoniae* infection may have been misleading since the possibility of cross reactivity with rheumatoid factor could have been effectively ruled out by using IgG absorption prior to IgM microimmunofluorescence determination.[2] Notwithstanding these facts, the authors conclude that the study does not support "an association between *C pneumoniae* antibody titres and the incidence of acute asthma attacks".

Analysis of table 1 indicates that the acute asthma and control populations appear to be significantly different in terms of age and sex distribution, the control population being significantly older and showing a male predominance. Both these factors are associated with increased *C pneumoniae* incidence and prevalence. The authors report using a logistic regression modelling method in which the age value is implemented as "± 10 years", which is roughly equivalent to the difference in mean age between the acute asthma and control populations.

This study is certainly noteworthy in that it underlines an association between *C pneumoniae* infection and severe chronic asthma, particularly "brittle" asthma, which will require further investigation in the future.

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1 Cook PJ, Davies P, Tunnicliffe W, *et al. Chlamydia pneumoniae* and asthma. *Thorax* 1998;**53**:254–9.
2 Verkooyen RP, Hazemberg MA, Van Haaren GH, *et al.* Age-related interference with *Chlamydia pneumoniae* microimmunofluorescence serology due to circulating rheumatoid factor. *J Clin Microbiol* 1992;**30**:1287–90.

I read with interest the recent report by Cook *et al*[1] in which they report that, compared with hospital controls, outpatients with chronic severe asthma had significantly more *C pneumoniae* antibody titres (IgG 64–256 and/or IgA ≥8) indicating previous infection, whereas unselected patients admitted to hospital for acute asthma attacks had titres similar to controls. They also found that serological evidence of acute (re)infection (presence of IgM, a fourfold change in titre, and/or IgG titre ≥1:512) was equal among groups.

These data are in accord with previous evidence suggesting an important role for chronic *C pneumoniae* infection as a promoter

of asthma symptoms but a lesser role for acute infection as a cause for asthma exacerbations.[2] An additional recent report of positive therapeutic responses to antibiotics in severe steroid dependent asthmatic patients (aged 13–65) further supports the possibility that antibody titres indicative of "previous infection" may also indicate persistent chronic infection.[3]

Acute primary (presence of IgM) or secondary (fourfold change in titre without IgM) *C pneumoniae* infection has been reported to initiate asthma in previously non-asthmatic individuals.[4] Since the incidence of asthma in adults is very small (around one per 1000 per year) it is likely that most of the acute exacerbations occurred in patients who had had previous wheezing episodes. It would be interesting to know whether Cook *et al* can retrospectively identify any patients who had their very first wheezing episode; this might be easier in general practice than in a hospital based study.

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2 Hahn DL. Intracellular pathogens and their role in asthma: *Chlamydia pneumoniae* in adult patients. *Eur Respir Rev* 1996;**6**:224–30.
3 Hahn D, Bukstein D, Luskin A, *et al.* Evidence for *Chlamydia pneumoniae* infection in steroid-dependent asthma. *Ann Allergy Asthma Immunol* 1998;**80**:45–9.
4 Hahn D. Incident wheezing and prevalent asthma have different serologic patterns of "acute" *Chlamydia pneumoniae* antibodies in adults. *Proceedings of the Third Meeting of the European Society for Chlamydia Research, Vienna, Austria.* Bologna: Società Editrice Esculapio, 1996: 226.

Non-Hodgkin's lymphoma with CFA

We read with interest the case report by Orchard *et al* on non-Hodgkin's lymphoma arising in cryptogenic fibrosing alveolitis (CFA).[1] Although the authors state that this has not been described previously, we recently reported six cases of pulmonary B cell non-Hodgkin's lymphomas arising in patients with autoimmune disorders, three of whom had CFA.[2] As in the case described by Orchard *et al*, prognosis in these three patients was much poorer than that in the patients with high grade pulmonary non-Hodgkin's lymphomas unassociated with CFA, presumably due to the combined effects of the two diseases.

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1 Orchard TR, Eraut CD, Davison AG. Non-Hodgkin's lymphoma arising in cryptogenic fibrosing alveolitis. *Thorax* 1998;**53**:228–9.
2 Nicholson AG, Wotherspoon AC, Jones AL, *et al.* Pulmonary B-cell non-Hodgkin's lymphoma associated with autoimmune disorders: a clinicopathological review of six cases. *Eur Respir J* 1996;**9**:2022–5.

AUTHOR'S REPLY We are grateful to Dr Nicholson and Professor Corrin for pointing out their very interesting report, which was published after the original writing of our case report.

In the patient we reported the association was with cryptogenic fibrosing alveolitis (CFA) alone whereas, interestingly, the three patients they report had CFA associated with other systemic autoimmune disorders. The fact that CFA alone may be associated with B cell lymphomas, and the poorer prognosis seen by Nicholson and Corrin in their patients, as well as ours, supports the hypothesis that chronic local stimulation of the lymphoid system may play an important part in the aetiology and prognosis of these tumours.

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BOOK REVIEWS

Asthma: Basic Mechanisms and Clinical Management. 3rd Edition. Barnes PJ, Rodger IW, Thomson NC, eds. (Pp 942; hardback; $150.00). London: Academic Press, 1998. 0 12 079027 0.

This is the third edition of an established book. Aiming to bring together all the recent information on basic mechanisms of asthma and also cover clinical aspects and therapy in depth, this is achieved successfully. The scope of the book provides accessible reviews of all facets of asthma, from epidemiology and physiology to allergen avoidance, including recent developments in these fields. Modifications to the popular second edition include separate chapters on mediator antagonists and immunomodulators with consideration of the potential therapeutic benefits of intervening in the complex inflammatory and pharmacological pathways systematically covered in previous chapters. A new chapter on the pharmacoeconomics of asthma treatments provides a pertinent reminder that, after the wonders of basic science and the development of beneficial interventions, a wider perspective is required to successfully deliver benefits to those who require them. The addition of colour plates provides a welcome change to the previous black and white prints of the old edition which look a little drab in retrospect.

Well written by authorities in their fields and uniformly edited with an attractive presentation, this is an excellent book which succeeds in linking the rapidly developing body of knowledge on asthma with current treatment, while keeping the future constantly in mind.—AF

Respiratory Measurement. Göran Hedenstierna. (Pp 184, paperback; £19.95 (UK), £22.00 (overseas)). London: BMJ Books, 1998. ISBN 0 7279 1207 0.

A large amount of information has been packed into the 184 pages of this new guidebook in the Principles and Practice Series. This is a comprehensive review of the principles of ventilation and gas exchange with special emphasis on the application of pulmonary function measurement during anaesthesia. The book details physiological principles and gives practical measurement guidance, with common sources of error, in the normal circumstances and during anaesthesia. The content is concise, the style direct and occasionally hard going. The text is clear and the diagrams are worth a special mention for their clarity and simplicity. This is not a textbook for beginners and requires a moderate familiarity with the principles of respiratory physiology, and the rules which govern respiratory mechanics and gas measurement. This guide represents excellent value for money and would be equally at home in the pulmonary function laboratory as well as the anaesthetics department. —SR

CORRECTION

Clinical features of non-smokers with α_1-antitrypsin deficiency

The authors of the paper entitled "Clinical features and prognosis of life time non-smokers with severe α_1-antitrypsin deficiency" by N Seersholm and A Kok-Jensen, which appeared on pages 265–8 of the April issue of *Thorax*, regret that some errors occurred in the text and in table 3. On page 267 the first line of column 1 should have read: ". . . 50 years at entry was **56%** compared with **50%** for the subjects over 50 years . . .". Table 3 is reproduced here with the corrections shown in bold italics.

Table 3 Mean (SD) FEV_1 % predicted and FEV_1/FVC of index and non-index cases stratified by age at entry

	Index cases	*Non-index cases*	*p value (t test)*
All age groups	n = 27	n = 40	
FEV_1 (% predicted)	54 (25)	100 (21)	<0.001
FEV_1/FVC	0.57 (0.18)	0.79 (0.13)	<0.001
N (%) with FEV_1 % pred ≤70%	20 (74%)	3 (8%)	<0.001
Age at entry <50 years	n = 8	n = 26	
FEV_1 (% predicted)	***56 (37)***	***100 (19)***	<0.001
FEV_1/FVC	***0.53 (0.20)***	0.80 (0.12)	<0.001
N (%) with FEV_1 % pred ≤70%	4 (50%)	2 (8%)	<0.001
Age at entry ≥50 years	n = 19	n = 14	
FEV_1 (% predicted)	***50 (20)***	***101 (24)***	<0.001
FEV_1/FVC	0.58 ***(0.17)***	0.78 (0.14)	<0.001
N (%) with FEV_1 % pred ≤70%	16 (84%)	1 (7%)	<0.001