LETTERS TO THE EDITOR

Atopy phenotype

In the short paper by Li and Hopkin¹ which appeared in the July issue of *Thorax* the genotyping data were taken from a paper by Shirakawa *et al.*² which reported two coding variants (Leu 181 and Leu 183) in the FcεRI-β gene in randomly ascertained and family based UK samples. The original paper reported associations between the presence of the Leu 181 variant and raised total serum IgE levels and positive skin prick tests to grass pollen in the random sample and an association between Leu 181 and atopy in the family sample. Li and Hopkin now add associations between Leu 181 and raised IgE levels and positive skin prick tests to grass pollen in the family sample.

The original study reported the Leu 181 polymorphism at a frequency of 15% in the randomly ascertained sample and in 17% of the families studied.² However, since the Leu 181 and 183 variants were first identified in 1994, these polymorphisms have been studied by several independent groups and now appear to be very rare.³ No sequence variants were identified with the original ARMS assay described by Shirakawa *et al.*² in two Japanese samples^{4,5} and in one Italian population.⁶ An improved version of the ARMS assay identified variants in the FcεRI-β gene in about 5% of individuals in an Australian population⁷ but these variants were exclusively Leu 181/Leu 183 double substitutions and, using the same revised assay (with a positive control), no variants could be identified in a second Australian sample.⁸

Both ARMS assays were problematic and lacked reproducibility and, despite publications affirming the clinical significance of these variants, no simple reliable assay for their detection has yet been established. To overcome the problems associated with the ARMS assay several groups have investigated the frequency of the Leu 181/Leu 183 variants by direct cycle sequencing. In our laboratory we have tested 300 individuals drawn from an asthma enriched sample (n=120) and from a randomly ascertained sample (n=180); the wild type sequence was observed in every case. Similarly, using a variety of sequencing methodologies, no substitutions were identified in 120 subjects from 40 nuclear families with at least one atopic subject,⁹ 65 UK asthmatic subjects,¹⁰ 80 Dutch asthmatic subjects and 46 controls,¹¹ and 58 Australian individuals with bronchial hyperresponsiveness and/or atopy.¹² It would therefore appear that, in most populations, these variants are extremely rare and can have little clinical relevance. Given the strong evidence against Leu 181, the crucial issue of the validity of these variants and the controversy over their identification was not adequately addressed in the paper.

In addition, while the subunits that comprise the high affinity IgE receptor are good candidate genes for asthma and atopy, and while it is reasonable to postulate that mutations within the subunits could alter receptor

function, there are no functional data to suggest that Leu 181 lies in "a critical region within the β subunit for efficient and intact FcεRI display". On the contrary, introduction of these variants by site-directed mutagenesis could demonstrate no effect on IgE binding for the Leu 181/Leu 183 substitutions. An additional coding variant has now been identified in the β subunit gene (E237G).¹³ This uncommon variant has been identified in several populations and may be associated with asthma and atopy, but again any biological or functional consequences of E237G will have to be demonstrated.

Therefore, it would be wrong for the readership of *Thorax* to be given the impression that these variants are found ubiquitously in different populations and that they are potentially important in modulating the function of the intact tetrameric FcεRI receptor complex. At the recent American Thoracic Society meeting in San Francisco part of the symposium on the Human Genetics of Asthma was devoted to a discussion of the problems of assaying for the Leu 181 variants, with several negative reports, although no clear explanation for the discordant results could be derived.

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AUTHOR'S REPLY It is good to see the Holgate/Morton axis shift from a state of frank denial to begrudging interest over the link between chromosome 11 and the genetics of atopy and asthma. This isn't an easy field, not least because of the undoubted genetic heterogeneity, and its investigation has not been helped by an atmosphere of carping criticism and frank enmity at times.

For the record, our short paper did point to the difficulties surrounding the Leu 181 variant; other more easily detected variants of FcεRI-β also associate with atopy. We shall see in due course whether FcεRI-β is the atopy locus on chromosome 11, but my guess is that the crucial functional studies will need to be more searching than those hitherto conducted.

Any members of the Southampton group interested in constructive dialogue are welcome to visit my laboratory in Oxford. This is to repeat an invitation previously made in private, but I thought I should repeat it in public for the benefit of your readers.

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Lung volume reduction surgery

The recent editorial by the self-styled "Lung Volume Reduction Surgery Trial Project Team" raises some important issues.¹ It does not, however, present a balanced debate of the arguments and is somewhat economical with the truth. The authors plead for funding for a multicentre trial but do not disclose the details of their protocol. It is important to consider their proposals both in the light of the medical infrastructure of the UK and the ethics surrounding this particular proposed randomised controlled trial.

Superficially, it appears difficult to argue against a randomised controlled trial in this area. However, more careful consideration uncovers factors which now make such a trial impossible. Rehabilitation for COPD has been widely practised in Europe and North America but has not, until recently, been available in the UK. Even today it is not available routinely in many centres including those that propose to take part in the trial. At the same time, the worldwide experience of lung volume reduction surgery is growing rapidly and there have already been some randomised controlled trials comparing the details of the procedure.² Observational studies have also confirmed that, in highly selected patients, lung volume reduction surgery is capable of improving airway function where no other medical or rehabilitative process can do so.³ If we accept that, in some patients, lung volume reduction surgery can improve FEV₁, then the aim of future trials should surely be to identify which patients would benefit and what surgical techniques are necessary. This work has already been conducted in Europe. Since in the UK there is little experience of the practice of either lung volume reduction surgery or rehabilitation, it would be necessary to acquire these skills before a randomised controlled trial will produce any meaningful results. It is not appropriate to learn the techniques of surgery or rehabilitation during the conduct of a clinical trial.

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Our main concern, however, about the proposed trial is the ethics of randomisation. Lung volume reduction surgery and rehabilitation are not strictly comparable. Pulmonary rehabilitation is universally applicable to all forms of lung disease and can improve disability and reduce handicap. It does not have any impact on impairment (FEV₁). By contrast, lung volume reduction surgery has been demonstrated to improve FEV₁. The indications are that this benefit is retained for at least three years.⁴ Patients who are so desperately affected by breathlessness that they are willing to undergo surgery with informed consent are unlikely to subsequently accept randomisation to a no surgery group. In fact, the control group may well be prejudiced by the negative effect of declining surgery to those who are psychologically adjusted to the expectation. In the NIH trial in the United States it is possible that patients randomised to rehabilitation alone may withdraw and seek surgery outside the trial since private insurers have not blocked reimbursement.

We believe that the opportunity to conduct a conventional, randomised, controlled trial of rehabilitation versus lung volume reduction surgery in emphysema has passed. The UK is already so far behind Europe and North America in the provision of both lung volume reduction surgery and pulmonary rehabilitation that the results of such a trial are unlikely to be generalisable. The funding of the proposed trial would therefore be a waste of valuable research funds. Of course the UK can contribute to studying the effects of lung volume reduction surgery but this should be done after the technical expertise has been acquired and is generally available. Furthermore, future trials – if they ever hope to be successful in recruitment – will need to compare different surgical techniques or offer delayed surgery to control groups to assess the cost implications. The selection criteria for lung volume reduction surgery are already becoming established and therefore a straight trial of surgery versus rehabilitation is well past its “sell by date”. We, as UK clinicians, have an obligation to act in the best interests of our patients. We must accept that we have been overtaken by international experience and not arrogantly dismiss the published results but use the heuristically acquired knowledge to shape our future scientific investigation.

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- 1 Lomas DA, Caine N, Wells FC. Health technology assessment: time for a randomised controlled trial of the role of lung volume reduction surgery in the treatment of emphysema. *Thorax* 1997;52:755–6.

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AUTHORS' REPLY We are grateful to Dr Morgan and colleagues for their interest in our call for a UK trial to assess lung volume reduction surgery¹ but are disappointed that they are apologists for a therapy based on anecdotal reports and small, often uncontrolled, clinical trials. Indeed the “randomised controlled trial” they cite in support of their argument² studied 20 patients after three months of follow up and was neither randomised nor controlled! Our call for a multicentre randomised controlled trial is not as arrogant as they imply and supports the view held by the American Thoracic Society,³ an NHLBI workshop,⁴ the Medicare funding agency, a number of editorials in other journals, and many health care purchasing authorities in the UK. That said, we do share some of their reservations about the proposed US trial as many of the control group are likely to use their health insurance to seek surgery in non-participating centres.⁵ It is for this reason that we believe the UK is an ideal place in which to assess this new technology and feel that a clinical trial would be a small price to pay compared with the widespread adoption of an unproven, expensive operation with a potentially high mortality.

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- 1 Lomas DA, Caine N, Wells FC. Health technology assessment: time for a randomised controlled trial of lung volume reduction surgery in the treatment of emphysema. *Thorax* 1997; 52:755–6.
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BOOK REVIEW

Progress in Respiratory Research. Volume 28: The Tobacco Epidemic. Bolliger CT, Fagerström KO. (Pp 266; £141.00). Switzerland: Karger, 1997. ISBN 3 8055 6531 3

This is an interesting book. After three chapters on the history, economics and prevalence of tobacco use and two on health effects, the remaining two thirds of the book's 15 chapters all relate to aspects of smoking behaviour, psychology, cessation, and prevention. These succeed in providing a comprehensive, informative, provocative, and absorbing review which, by virtue of having been published within eight months of commissioning, are also extremely topical. This is the main strength of the book which, with the chapter on prevalence of smoking around the world which also provides an excellent summary of recent data, is a credit to its authors and editors. The two chapters on health effects are thin, but this is perhaps not a major weakness since this information is readily available elsewhere. The only disappointment for me lay in the chapter on the economics of tobacco use. Comprising 52 pages (20% of the entire book) it was a thorough review of the tobacco industry in the USA, with topical references to the “global settlement” of legal claims progressing there, and was well written and interesting. My disappointment arises from the fact that the authors or editors seem either to have missed, ignored, or otherwise omitted to recognise the fact that the tobacco epidemic to which the title of this book refers is actually taking place in that part of the world that lies beyond the horizon of United States territory. If the next edition can succeed in recognising and addressing this, it will be impressive indeed. – JB

NOTICE

International Conference on Paediatric Asthma

An International Conference on Paediatric Asthma will be held at the Maastricht Exhibition and Congress Centre, The Netherlands on 3 and 4 March 1998. For a copy of the provisional programme please write to the Conference Secretariat, Castle House Conferences, 3 Linden Close, Eridge Road, Tunbridge Wells, Kent TN4 8HH, UK. Telephone: +44 (0)1892 539606. Fax: +41 (0)1892 517773/517005. Information can also be accessed on the following web site address: <http://www.castlehouse.co.uk>.