

## LETTERS TO THE EDITOR

### Lung donors for cystic fibrosis patients

As a centre involved in the care of patients with cystic fibrosis both before and after transplantation, we read with considerable interest the experience of Ryan and Stableforth of lung transplantation for their patients (March 1996;51:302-5). Their observation that one third of their patients die while awaiting transplantation in the UK is well made. It is predicted that transplant programmes will only provide a limited service for the expanding adult cystic fibrosis population in view of the limited number of lung donations within the UK over the next decade.<sup>1</sup>

In 1994 there were 7.1 cadaveric thoracic organ donations per million population made in the North West of England, compared with 9.8 per million for the Northern/Yorkshire region. In contrast, there were 26.4 cadaveric renal transplant donations per million population in the North West of England and 31.9 per million in the Northern/Yorkshire region.<sup>2</sup> The fact that donor rates vary suggests that local factors may result in unequal emphasis on the promotion and management of multiorgan donations in different regions of the country. A study of the factors that influence local lung donation rates is required to clarify these issues. We believe that a combined initiative from the British Thoracic Society and the cystic fibrosis community is needed to maximise donor availability in the face of the expanding need for lung transplantation.

With such a demand for organs the question remains whether colonisation with *Burkholderia cepacia* represents a contraindication to transplantation. Although the patients colonised with *B cepacia* in the Birmingham study have not done well following transplantation, we believe that there is currently insufficient evidence to preclude these patients from transplantation absolutely. The overall experience in the UK and in some North American centres is that there is not a substantial difference in survival between patients with cystic fibrosis colonised with *B cepacia* and those not colonised with the organism.<sup>3,4</sup> It is important to note that, in the series reported from Toronto,<sup>5</sup> *B cepacia* was identified for the first time after transplantation in one third of patients colonised with the organism. In this subgroup there was an 80% mortality which suggests that either there was nosocomial transmission between patients within the hospital or the referring units may have incorrectly identified the *Pseudomonas*. Incorrect characterisation may have led to an insufficiently aggressive prophylactic antibiotic regimen following surgery. Although these organisms have *in vitro* resistance, it is possible to achieve *in vivo* activity with appropriately high doses of antibiotics and this approach may influence outcome. The continuing controversy regarding *B cepacia* highlights the need for a multicentre study to define the outcome of patients following transplantation based on risk stratification for a wide range of recipient and donor factors.

The issue of palliative care is important, but bridging to transplantation via non-invasive nasal intermittent positive pressure ventilation (NIPPV) does not preclude palliative care being administered at an appropriate time. The timing and appropriateness of NIPPV and palliative care can only be effectively administered in specialist cystic fibrosis centres that have a close liaison with a transplant centre.

We welcome the analysis from the Birmingham centre and hope that it promotes awareness for an initiative to facilitate lung donations. Despite their pessimism regarding the outcome of patients colonised with *B cepacia*, we support these patients in their quest for transplantation and assess each individual on the basis that colonisation with *B cepacia* represents a relative contraindication to transplantation.

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- 1 Elborn JS, Shale DJ, Britton JR. Heart-lung transplantation in cystic fibrosis: predictions for the next decade in England and Wales. *Respir Med* 1994;88:135-8.
- 2 United Kingdom Transplant Support Services Authority. *Fourth annual report of the special health authority* 1994-5.
- 3 Egan JJ, McNeil K, Bookless B, Gould K, Corris P, Higenbottam T, *et al*. Post-transplantation survival of cystic fibrosis patients infected with *Pseudomonas cepacia*. *Lancet* 1994;334:552-3.
- 4 Flume PA, Egan TM, Paradowski LJ, Detterbeck FC, Thompson JT, Yankaskas JR. Infectious complications of lung transplantation. Impact of cystic fibrosis. *Am J Respir Crit Care Med* 1994;149:1601-7.
- 5 Snell GI, de Hoyas A, Kraiden M, Winton T, Maurer JR. *Pseudomonas cepacia* in lung transplant recipients with cystic fibrosis. *Chest* 1993;103:466-71.

### Hepatotoxicity of antituberculosis drugs

I have some concerns about the editorial by Ormerod and associates (February 1996;51:111-3) on the hepatic toxicity of antituberculosis agents. The figures they present for reported hepatic reactions, fatal and otherwise, include a large number due to rifampicin and a few due to ethambutol. Since ethambutol has not previously been recognised as hepatotoxic and rifampicin is thought to cause only mild hepatitis as part of a generalised hypersensitivity,<sup>1</sup> I would like to know on what basis reactions were attributed to these drugs.

Despite reports of fatalities and severe reactions requiring transplantation,<sup>2</sup> they continue to recommend monitoring of liver function only in the presence of symptoms. Unfortunately by this time we may be dealing with a severe and, indeed, reversible situation.<sup>2</sup>

Finally, they unaccountably advise challenging the patient with the various drugs once the reaction has subsided, and even mention desensitisation although the reactions to isoniazid and pyrazinamide are not due to hypersensitivity. Unless there are no alternatives, this recommendation would

seem unwise since rechallenge may result in a severe and possibly fatal reaction.<sup>3</sup>

The Joint Tuberculosis Committee may be interested in my approach based on many years of "hands on" experience in treating tuberculosis. In patients aged 20 years or over who are receiving potentially hepatotoxic drugs I measure serum levels of alanine transaminase (ALT) every two weeks for the first three months. If values of over 100 units are persistently obtained, or increasing values approaching 100 units, I discontinue isoniazid and also pyrazinamide if the patient is receiving it. With active disease, treatment can be safely continued with rifampicin and one of ethambutol, ciprofloxacin, or streptomycin. If a patient is being treated with prophylactic isoniazid it may be prudent simply to stop treatment. Patients with pre-existing liver disease are generally treated with alternative regimens. I have never had a fatality or a patient who required transplantation.

- 1 Sherlock S. Hepatic reactions to drugs. *Gut* 1979;20:634-8.
- 2 Mitchell I, Wendon J, Fitt S, Williams R. Anti-tuberculous therapy and acute liver failure. *Lancet* 1995;345:555-6.
- 3 Maddrey WC, Boitnott JK. Isoniazid hepatitis. *Ann Intern Med* 1973;79:1-12.

**AUTHORS' REPLY** The data presented in the table in our editorial were those supplied by the Committee on the Safety of Medicines (CSM) which have been continuously compiled since 1963. Those reactions attributed to a single drug and those due to multiple constituent products were clearly differentiated from each other. The CSM investigates these reports and satisfies itself of the likely causal agent for single agent products.

As discussed in the editorial, the report by Mitchell *et al*<sup>1</sup> of four cases of hepatotoxicity is seriously flawed; it did not include any dosages or patient weights and thus cannot even show that correct dosages for weight were given, and none of the cases seemed to have been managed according to national recommendations.<sup>2</sup> The discussion in the paper also took no account of the fact that the mortality from tuberculosis itself is many times higher than that from any possible drug toxicity and therefore made no attempt at any reasoned risk/benefit analysis.

Desensitisation was clearly listed only as a last option when the choice of alternative drugs is so limited as to leave no alternative.

Dr Kahana's approach to the management of minor abnormalities of liver function (ALT levels approximately twice normal) would seem potentially to deny many patients the benefits of the most effective bactericidal drug (isoniazid) and the drug which allows six month short courses of chemotherapy (pyrazinamide) by unnecessarily withholding or stopping them. The withdrawal of pyrazinamide means that treatment duration needs to be extended to at least nine months, and there is little evidence concerning the effective duration for a regimen of rifampicin with either ciprofloxacin or streptomycin.

All three physicians who contributed to the editorial are practising thoracic physicians in districts with a high incidence of tuberculosis

who also have many years of "hands on" experience. My unit has managed over 1500 patients since 1978 in the manner described, also without any hepatic fatality or need for transplantation.<sup>3</sup>

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- 1 Mitchell I, Wendon J, Fitt S, Williams R. Anti-tuberculous therapy and acute liver failure. *Lancet* 1995;345:555-6.
- 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.
- 3 Ormerod LP, Horsfield N. Frequency and type of reactions to antituberculosis drugs: observations in routine treatment. *Tuberc Lung Dis* 1996;77:37-42.

## BOOK REVIEWS

**The Thorax. Part A: Physiology; Part B: Applied Physiology; Part C: Disease (Lung Biology in Health and Disease Series, No 85).** 2nd edition, revised and expanded. Charis Roussos. (Pp 2880; \$495.00 sold as set only.) New York: Marcel Dekker, 1995. ISBN 0-8247-9647-0.

The second edition of *The Thorax* is mainly concerned with the respiratory muscles and certainly has the feel of a tome, containing three parts and nearly 3000 pages. There are more than 100 contributing authors from North and South America, Europe, and Australia. Most have personal, practical experience in the field of respiratory muscle physiology and are authorities on the subject.

The book aims to provide the clinical investigator with comprehensive, up to date information of physiology and pathophysiology of respiratory muscles, and the diagnosis and treatment of respiratory muscle dysfunction. It is divided into three parts. Part 1 begins with chapters on physiology of skeletal muscle followed by information on structure, function, and metabolism of the respiratory muscles. This section provides the clinician or investigator with the opportunity to understand in depth the properties of the respiratory muscles. Part 2 illustrates clearly every method for measuring respiratory muscle function and explains function in some activities such as speech, sleep, and exercise. Some chapters are very good reviews – for example, chapter 49 on respiratory muscle fatigue by Roussos himself which includes more than 200 references up to 1994 and provides state of the art information on function and fatigue of the respiratory muscles. There is also a good chapter on respiratory muscle activity during sleep which does not include the effect of sleep disordered breathing on the respiratory muscles, but covers the outcome of a combination of sleep studies and respiratory muscle studies. Part 3 deals with the diagnosis of respiratory muscle dysfunction and pathophysiology in various clinical conditions as well as treatment. Most chapters are excellent, a noteworthy one

being that by De Troyer on respiratory muscles in COPD which deals in detail with static and dynamic function and structure of the respiratory muscles in those patients. There are also good chapters on mechanical ventilation which is useful for the clinician working in the intensive care unit.

On the whole, the standard of writing, the quality of discussion, and the level of explanation of this book are of a high order. Most of the chapters include up to date references, apart from chapter 37 on rib motion in health and disease where all the references come from before 1972. There are some trivial problems – for example, some chapters cite references using consecutive numbers and some use the authors' names and year of publication. Chronic obstructive pulmonary disease is abbreviated to COPD in one place and CAO in another. There is a fair amount of overlap and repetition between reviews – for example, measurement of maximal transdiaphragmatic pressure is illustrated in chapter 38, chapter 63, and chapter 64; mechanisms of dyspnoea are repeatedly described in chapter 43, chapter 60, and chapter 61. If some repetition had been avoided the book might have been thinner! There is some contradiction between chapters – for example, breathlessness and dyspnoea are used interchangeably in chapter 60, yet in chapter 61 they are clearly meant to represent different phenomena.

Although there are small defects, this book is still a noteworthy effort. It will provide invaluable information to the respiratory physician. At a price of \$495 it will probably be destined for the library and the respiratory muscle laboratory rather than chest physicians' shelves. – YML and SGS.

**The Molecular Biology and Pathology of Elastic Tissue.** DJ Chadwick and JA Goode Road. (Pp 361; £49.94). Chichester, UK: John Wiley & Sons, 1995. 0 471 95718 6.

I took my son to the Science Museum in Boston a few years ago. I think I was more impressed than he was. In one of the exhibitions they had two pumps (each representing a heart), one extruding its liquid into a solid plastic pipe and the other into an elastic tube. In one the flow was pulsatile, in the other continuous. This was a wonderfully dramatic demonstration of the importance of elastic vessels to ensure continuous perfusion of our body tissues.

The functional importance of elastic tissue has been known for many years but its composition has been poorly understood. Interest has not been helped by observations of its apparently amorphous structure (a feature which I learned from this book is unfounded and likely an artefact of conventional microscopy techniques) and its resistance to biochemists attempting to solubilise and study it. In the last 20 years or so, largely aided by techniques of cell and molecular biology, our view of elastic tissues has altered radically.

We now realise that elastic tissues such as the lung and blood vessels are characterised by a high content of elastic fibres. These fibres consist of elastin and the so-called 'elastin-associated microfibril'. The latter contains at least seven glycoproteins including fibrillins 1 and 2 and microfibril-associated glycoprotein, MAGP. Elastin gene and protein structure is now quite well understood. The protein is encoded from a single gene on chromosome seven. The

primary transcript, tropoelastin, undergoes several post-translational modifications including hydroxylation, oxidative deamination of lysines catalysed by lysyl oxidase, and stabilisation by covalent cross link formation between modified and normal lysine residues.

Abnormal deposition of elastin occurs in several respiratory disorders, including pulmonary hypertension and pulmonary fibrosis. In contrast, a diminished amount of elastin is a feature of pulmonary emphysema. There are also some rare heritable disorders in which there are abnormal elastic fibres (e.g. Marfan's syndrome and supravalvular aortic stenosis), reduced synthesis (Cutix laxa), or overproduction (pseudoxanthoma elasticum and Buschke-Ollendorff's syndromes).

This book is timely and as up to date as it can be in a field which is moving rapidly. I often judge a book like this in two ways. Has it presented what I already knew clearly and have I learned new things? By and large it succeeds on both counts. The chapters on protein and gene structure were of interest scientifically, placing the older work in historical perspective. The chapter on elastin gene structure was informative but spoiled by very poor quality diagrams for which the hatching was often indecipherable. This fault in this chapter and others was my single greatest criticism and the publishers of a book such as this owe it to their readers to get this aspect right.

There were many good chapters but some may be of particular interest to the lung research community. The chapter on elastin synthesis was of interest partly because it emphasised how little we know of the molecules regulating elastin production. The chapter on fibrillin stressed the importance of this protein in the mechanical properties of elastic tissues as manifested by the observation that Marfan's syndrome involves a defect in the fibrillin gene. The structural role of elastin has begun to be investigated using transgenic mice into which different tropoelastin gene constructs had been inserted. Of particular interest to the respiratory world was the suggestion that animals lacking exon 33 develop a lung morphology characteristic of emphysema. The parity between this model and human emphysema was argued in the discussion which followed this paper, and there was some debate as to how closely they resembled one another and whether or not the model represented a developmental defect rather than emphysema. Although this model has some limitations, it still strikes me that it may share some common mechanisms with emphysema. The publication of discussion is the tradition of this series - this should be continued as it is a great help to readers to get a feel for the current thinking of those working in the field.

Finally, on reading this book I realised I had already heard of the meeting from which it emanated. Bob Mecham visited us in London a year or so ago and told me he was on the way to Kenya for a Ciba Elastin Meeting. I remember thinking how smart these elastin people are. The last Ciba meeting I attended, although very pleasant, took place in wintry London one mile from where I work. Presumably, the environment in Kenya was a little more enticing.

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