

## 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