LETTERS TO THE EDITOR

Cellular mechanisms of acute lung injury: implications for future treatment in the adult respiratory distress syndrome

Although I agree that antibodies to adhesive molecules will have a role in treating the adult respiratory distress syndrome (ARDS), as neutrophil activation by C5a forms the basis of the injury I cannot understand why Drs S C Donnelly and C Haslett (April 1992;47: 260–3) fail to give credit to the overriding importance of endotoxaemia. Since there are so many mechanisms and mediators concerned in ARDS, just as there are in Gram negative bacterial shock, there has to be a common trigger—that is, usually, lipopolysaccharide (cf fig 2).

It seems that mistrust has arisen from the results of two sets of experiments conducted by Haslett *et al*, in particular the one in which a synergistic effect of a small dose of lipopolysaccharide and C5a was seen. Yet in fact endotoxin itself produces C5a. In my experiments conducted in 1970–72 it was clear that endotoxin caused acute lung injury with all the features of ARDS. The details of the mechanisms were reviewed by Brigham and Meyrick[1] in 1986.

In recent years several groups have described endotoxaemia at the onset of ARDS.[2–4] Thus I feel sure that the emphasis will switch to means of combating endotoxaemia.

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1 Brigham KL, Meyrick B. Endotoxin and lung injury. *Am Rev Respir Dis* 1986;133:913–27.
2 Parsons PE, Worthen GS, Moore EE, Tate RM, Henson PM. The association of circulating endotoxin with the development of ARDS. *Am Rev Respir Dis* 1989;140:467–72.
3 Vijaykumar E, Raziuddin S, Wardle EN. Plasma endotoxin in patients with trauma, sepsis or severe haemorrhage. *Clin Intens Care* 1991;2: 4–9.
4 Danner RL, Elin RJ, Hosseni JM, Wesley RA, Reilly JM, Parillo JE. Endotoxemia in human septic shock. *Chest* 1991;99:169–75.

AUTHORS' REPLY Dr Wardle's letter implies that the pathogenesis of ARDS was sorted out in 1970–2. Unfortunately, this is not the case. There is insufficient evidence at present to regard endotoxin as *the* central mediator of overriding importance in ARDS. Brigham's group used sheep, which are uniquely sensitive to low concentrations of endotoxin that have little effect as a single agent in other species. Although endotoxin does cause lung oedema due to endothelial damage, this model does not come close to mimicking the complex histological events of full blown ARDS. Although models such as this have proved useful for studies of endothelial injury, most workers would agree that there is, as yet, no ideal model of established ARDS.

The search for a final common mediator in ARDS, as in bronchial asthma, has so far proved disappointing. Endotoxin is undoubtedly an important mediator and, as we discussed in our article, it may exert both direct effects and important indirect effects in concert with other mediators, which themselves may assume prominence in the near future. Further, should endotoxaemia be a critical event at some stage of ARDS development, the resultant pathogenic mediator cascades may rapidly move on to stages that do not critically involve endotoxin. Thus with our present awareness of the complexity of factors concerned in the initiation of inflammatory tissue injury we cannot subscribe to a blinkered view of the *overriding* importance of endotoxin, and it would seem premature and imprudent at present to overemphasise combating endotoxaemia as a single treatment option at the expense of other options (or combinations thereof) that will soon become available.

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Treatment of relapse of small cell lung cancer in selected patients with the initial combination chemotherapy with carboplatin, etoposide, and epirubicin

I read with great interest, in the May edition of *Thorax* (1992;47:369–71), the article by Dr Ph Collard and colleagues from Belgium on the treatment of relapse of small cell lung cancer by combination chemotherapy, in particular carboplatin, etoposide, and epirubicin. The general feeling among workers in this area, particularly in the UK, has been that there is little to be gained from repeated courses of chemotherapy in small cell lung cancer, after an initial set of six to eight courses over a similar period of time.

Quality of life has always been an issue in subjecting patients to repeated courses of combination chemotherapy. For some years, however, I have been using repeated courses of combination chemotherapy in small cell lung cancer and found results similar to those in this article.

In South Lincolnshire I see on average 120 new patients a year with lung cancer, of whom 50–60% have chemotherapy. Although the numbers surviving for long periods with combination chemotherapy are small, none the less I believe that in selected patients, usually those with limited disease, repeated courses should be considered. In my experience in this group the quality of life has been good, running equally alongside the quantity.

I hope that as a result of the article by Dr Collard and others more patients with small cell carcinoma of lung will be considered for repeated courses.

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Barcelona's asthma epidemics

The article by Dr C Picado about asthma induced by soya bean dust (March 1992;47: 197–200) makes intriguing reading. Barcelona's asthma epidemics had several unusual features, which I believe suggest that attacks might be due to a novel immunological mechanism. These features include the unusually explosive onset of attacks, which were severe but short in duration; their occurrence in some with mild asthma or in smokers; the absence of a late response; and the difficulty of reproducing attacks with challenge by standard soya bean allergen.

The seeds of leguminous plants (such as soya beans) are a rich source of lectins, which may be present in order to bind species specific carbohydrates present on symbiotic nitrogen fixing microorganisms, but are also potent T cell mitogens.[1] Inhalation of another lymphocyte mitogen (lipopolysaccharide) has been suggested as the cause of bronchoconstriction, mucus secretion, fever, and fibrosis in byssinosis.[2] Different lectins have subtly different actions, but some are potent activators of interleukin-4 producing helper T cells,[3] which are abundant in the bronchial epithelium in patients with asthma.[4] Chronic inflammation of the lungs might cause local recruitment of additional T cells, explaining the apparent additive effect of cigarette smoking.

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1 Sharon N, Lis H. Lectins as cell recognition molecules. *Science* 1989;246:227–34.
2 Holt PG. Current trends in research on the etiology and pathogenesis of byssinosis. *Am J Ind Med* 1987;12:711–6.
3 Röcken M, Müller KM, Saurat J-H, Hauser C. Lectin-mediated induction of IL-4-producing CD4+ T cells. *J Immunol* 1991; 146:577–84.
4 Robinson DS, Hamid Q, Ying S, *et al*. Predominant T_H2-like bronchoalveolar T-lymphocyte population in atopic asthma. *N Engl J Med* 1992;326:298–304.

BOOK NOTICE

Clinical Tuberculosis. J Crofton, N Horne, F Miller. (Pp 210; £10·95.) London: Macmillan, 1992. ISBN 0-333-56689-0.

This book is in a class of its own. It is clear, succinct, full of information, and a pleasure to read—indeed "a useful and practical guide for the ordinary non-specialized doctor or health professional who will meet tuberculosis in the course of his work." The book begins with a general background to the worldwide problem of tuberculosis. A simple scheme of do's and dont's in tuberculosis, presented in the first few pages of the book, would alone go a long way to reduce the incidence of infectious tuberculosis. There are sections on the clinical presentations of tuberculosis, including those related to HIV infection, and the chapter on child tuberculosis is especially good. The chapter on the treatment of tuberculosis gives a welcome emphasis on accurate diagnosis, supervised treatment, management of defaulters, and ensuring that the complete course of chemotherapy is taken, preferably in the context of a national tuberculosis programme. The inclusion of 12 month regimens of treatment, which are no longer recommended, is probably unnecessary. Two features of the book are particularly helpful: bold print emphasises the key points very effectively and the case reports provide excellent and informative illustrations. The advice on the treatment of tuberculosis where there is coincident HIV infection differs from guidelines proposed by the British Thoracic Society (*BMJ* 1992;304:1231). Who would benefit from reading this book? Paediatricians and general physicians, as well as specialists in respiratory medicine, would have their awareness of tuberculosis increased. Medical students should read this book and take copies with them on their electives as helpful gifts to their hosts. The clarity of the book makes it of particular value for those in countries where tuberculosis is common and where English is not their first language. The book cannot be too widely read if we are to eradicate this curable but still widespread disease.—GB