

# Correspondence

## Is current treatment increasing asthma morbidity and mortality?

SIR,—Though it is not universally agreed that morbidity and mortality due to asthma have increased,<sup>1</sup> there has certainly been no perceptible reduction in either, and it seems probable that deaths would have risen in the absence of wide publicity about the dangers of asthma and the implementation of a policy to promote self admission by patients.

As Dr EA Mitchell (February 1989;44:81-4) points out, it is a paradox that morbidity and mortality have not declined during a period in which knowledge of the pathogenesis of asthma has greatly improved, many new and supposedly improved drugs for treating it have been introduced, and their sales have risen substantially. This paradox cannot be explained by errors in management, as these must have occurred at least as frequently before any of the modern forms of treatment were introduced.

Though it would appear that some, as yet unidentified, environmental factor has brought about a change in the nature of asthma, so that it now occurs in a severe form more frequently than in the past, the proposition that contemporary treatment might have contributed to morbidity and mortality has until now received less consideration than it merits.

Dr Mitchell refers to the finding of a rebound increase in bronchial reactivity to histamine or methacholine in patients who have ceased taking beta agonists,<sup>2</sup> and he suggests that this might have enhanced susceptibility to provocative stimuli and led to an increased number of patients with severe asthma. This hypothesis rests on the assumption that not only is there a close correlation in individual patients between severity of asthma and degree of reactivity but even a small increase of the latter, if applied to the whole population of asthmatic individuals, leads to a large increase in the proportion of those with severe disease.

In a recent study, in which responsiveness to methacholine (PD<sub>20</sub>) was estimated fortnightly in 20 patients for 12 months, no clear relation was discernible between changes in bronchial reactivity and the severity of asthma, as judged by symptoms and twice daily measurements of peak expiratory flow.<sup>3</sup> Moreover, it would seem probable that the reason why beta agonists are often ineffective in severe asthma, which Dr Mitchell suggests might be due to a rebound increase in reactivity, is their limited ability to relieve mucosal oedema and exudation.

Incrimination of isoprenaline as a major cause of deaths in the 1960s was followed by the introduction of selective beta<sub>2</sub> agonists but also led to the virtual abandonment of the "pan-adrenoceptor" agonists which, in the form of adrenaline and ephedrine, had previously been the mainstay of treatment of both acute and persistent asthma. By virtue of their ability to stimulate alpha in addition to beta receptors, it is possible that these drugs may be superior to selective beta<sub>2</sub> agonists in relieving mucosal oedema and preventing its development. Though highly speculative, this hypothesis is supported by the observation that airflow obstruction that has resisted

repeated inhalations of isoprenaline or selective beta<sub>2</sub> agonists can be partially reversed by adrenaline (my unpublished data), and it would also be consistent with the failure of circulating endogenous adrenaline to rise in acute severe asthma.<sup>4</sup>

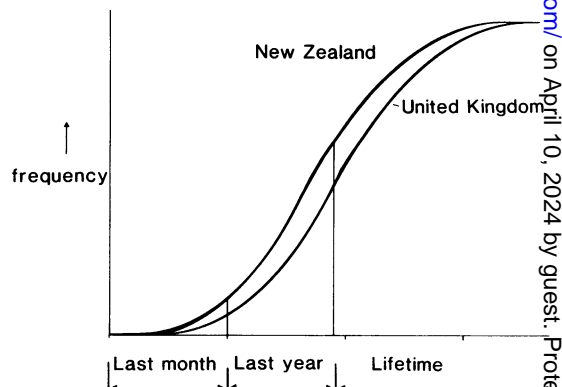
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- 1 Anderson RH. Is the prevalence of asthma changing? *Arch Dis Childhood* 1989;64:172-5.
- 2 Vathenen AS, Knox AJ, Higgins BG, Britton JR, Tattersfield AE. Rebound increase in bronchial responsiveness after treatment with inhaled terbutaline. *Lancet* 1988;i:554-8.
- 3 Josephs LK, Gregg I, Mullee MA, Holgate ST. Non specific bronchial reactivity and its relationship to the clinical expression of asthma: a longitudinal study. *Am Rev Respir Dis* (in press).
- 4 Ind PW, Causon RC, Brown MJ, Barnes PJ. Circulating catecholamines in acute asthma. *Br Med J* 1985;290:267-9.

## AUTHOR'S REPLY

It is pleasing to see that this editorial has stimulated discussion on the uncomfortable proposition that current treatment might be increasing asthma morbidity and mortality, and I would agree with Dr Gregg that this warrants more consideration than it has received in the past.

The unpublished study of just 20 patients cited by Dr Gregg, which showed no relation between changes in bronchial hyperresponsiveness and the severity of asthma, as judged by symptoms and peak expiratory flow rates, is of interest, but not surprising, in view of the wide range of asthma severity seen for any level of hyperresponsiveness. The study does not, however, invalidate the hypothesis put forward. The hypothesis rests on two assumptions. Firstly, the small deterioration in bronchial hyperresponsiveness produced by beta agonists<sup>1</sup> when applied to the whole population of asthmatics results in an increase in the severity of asthma. Secondly, this deterioration in hyperresponsive-



Prevalence of wheeze in New Zealand and the United Kingdom.

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ness, again when applied to the whole population of asthmatic individuals, leads to a disproportionate increase in the proportion of those with severe disease. The probable validity of the second assumption can be illustrated (figure) by comparing childhood asthma prevalence in England and New Zealand (EA Mitchell, HR Anderson, unpublished study). The lifetime prevalence of wheeze in Auckland, New Zealand, is 18.5% higher than in South West Thames, England (25.6% v 21.6%), the prevalence of wheeze in the last 12 months 32.1% higher (14.8% v 11.2%), and the prevalence of wheeze in the last month 87.5% higher (7.7% v 4.1%). Thus there is a difference in the distribution of asthma severity between the two countries. Could this be produced by New Zealand's higher asthma drug consumption<sup>2</sup> and the promotion of maintenance beta agonists?

Dr Gregg speculates that "pan-adrenoceptor" agonists may be superior to selective beta<sub>2</sub> agonists in relieving and preventing mucosal oedema. These drugs were effective when used intermittently for acute severe asthma. The hypothesis, however, relates to long term regular use. The recent report suggesting that fenoterol, a less selective beta<sub>2</sub> agonist, might increase the risk of death in patients with asthma<sup>3</sup> indicates the need for caution before returning to even less selective adrenoceptor agonists.

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- 1 Vathenen AS, Knox AJ, Higgins BG, Britton JR, Tattersfield AE. Rebound increase in bronchial responsiveness after treatment with inhaled terbutaline. *Lancet* 1988;i:554-8.
- 2 Keating G, Mitchell EA, Jackson R, Beaglehole R, Rea H. Trends in sales of drugs for asthma in New Zealand, Australia and the United Kingdom, 1975-81. *Br Med J* 1984;289:348-51.
- 3 Crane J, Flatt A, Jackson R, *et al*. Prescribed fenoterol and death from asthma in New Zealand, 1981-3: case-control study. *Lancet* 1989;i:917-22.

## Book notices

**Directions for New Anti-asthma Drugs.** S R O'Donnell, C G A Persson. (Pp 325; \$58.) Basel: Birkhauser, 1988. ISBN 3-7643-1957-7.

This book presents the proceedings of a workshop held in 1987 in Australia as a satellite meeting of the Xth International Congress of Pharmacology and attended by pharmacologists mainly engaged in asthma research. It covers recent advances in our understanding of the mechanisms underlying asthma, with particular emphasis on possible new classes of antiasthma drugs and on improvements of established ones. The first chapter underlines the necessity to control airway inflammation as a basis for antiasthma treatment. In the section on "symptomatic" treatment, beta adrenergic drugs, calcium ion blockers, potassium channel activators, and inhibitors of arachidonic acid metabolites are reviewed. Xanthines, anticholinergics, antagonists of platelet activating factor, glucocorticoids, and drugs interfering with microvascular leakage are discussed under the "non-symptomatic-prophylactic" heading. The remaining chapters

include synopses on routes of administration and on future directions for the twenty first century. Although the classification of these agents into "symptomatic" and "non-symptomatic" categories seems to me to be quite arbitrary (for example, antiallergic and cholinergic drugs are dealt with in the same chapter in the "non-symptomatic/prophylactic" section), this book gives an overall state of the art account of these established or potential antiasthma drugs. Most chapters provide an overview, but some authors present only detailed data of specific experiments. Many potential drugs have not yet reached the stage of clinical testing but a succinct account of the effects of these drugs on *in vitro* systems or in animals is given. The chapter on antiasthma glucocorticoids is an excellent review of their possible mode or modes of action. This book provides a fresh impetus to newer pharmacological approaches to asthma and should be of interest to both pharmacologists and clinicians interested in the treatment of a condition which is increasing in prevalence and severity.—FC

**Bronchopulmonary Dysplasia.** T A Merritt, W H Northway Jr, B R Boynton. (Pp 452; £45.) Oxford: Blackwell, 1988. ISBN 0-86542-047-5.

One of the most striking changes in neonatal intensive care over the last 20 years has been the recognition and proliferation of bronchopulmonary dysplasia. This condition, which carries a mortality rate of up to 20%, has emerged as techniques for keeping ever more immature babies alive have become more successful. There remains considerable dispute on the aetiology, management, and long term outcome of this condition. This book provides a very useful, up to date, and comprehensive review of the subject. The book is introduced by a historical overview of neonatal respiratory support. The second section covers the pathogenesis and pathophysiology, including tracheal cytology, the role of barotrauma, and defects of the antioxidant and antiprotease systems. The third part, which will be of most use to clinicians, considers clinical manifestations and critically reviews the various treatments that are currently in use. The remainder of the book examines possible new approaches to treatment and prevention and reviews the various studies in the long term outcome. The authors have recruited 32 contributors. I enjoyed reading all the sections, though there was some overlap, particularly in the sections on pathogenesis. It is also not obvious why the editors have included two sections on lung function abnormalities in bronchopulmonary dysplasia. This is a book that all those concerned with intensive neonatal care, or with a specialist interest in respiratory problems in early childhood, will find of great value and I would certainly hope that this would be seen as a high priority book in hospital and university libraries. I am very pleased that as a result of reviewing this book I have my own copy.—ADM

**Thymic Tumors.** R Sarrazin, C Vrousos, F Vincent. (Pp 172; £76.90.) Basel: Karger, 1989. ISBN 3-8055-4800-1.

This book contains a comprehensive series of monographs resulting from presentations made at the 7th Grenoble