LETTERS TO THE EDITOR

Different subgroups of difficult asthma in children

Payne and co-workers describe the identification of different subgroups of paediatric asthma based on airway nitric oxide (NO) concentrations. A group of asthmatic subjects who remained symptomatic after 2 weeks of treatment with oral prednisolone included both patients who continued to have raised NO concentrations and patients with normal NO concentrations before and after prednisolone.[1] Since airway NO concentrations are believed to reflect airway inflammation in asthma, the authors conclude that their findings: " . . .suggest a different basis for symptoms between the two subgroups, with inflammation playing a less important role in those patients with normal NO levels".

The current understanding of increased exhaled NO concentrations in asthma is based on the assumption that constitutive NO synthase (NOS) derived NO is of minor relevance and that increased exhaled NO levels reflect NO formation from activated inducible NOS (NOS2). This may, however, not be the case. We offer an alternative explanation for the interesting findings of the authors—namely, rather than being a direct reflection of airway inflammation, in at least a subgroup of patients differences in NO concentrations may result from variations in the genetic predisposition for NO synthesis. Wechsler *et al*[2] recently reported that exhaled NO concentrations in adult asthmatics correlate with sequence variants in the neuronal NO synthase (NOS1) gene. Furthermore, they found that NOS1 genotypes associated with high NO concentrations were significantly more frequent in asthmatic than in control subjects.[2] These findings supported recent evidence that the NOS1 gene is involved in the genetics of asthma.[3 4]

A relation between NOS1 gene variants and airway NO concentrations also exists in cystic fibrosis (CF). In contrast to asthma, mean exhaled NO concentrations in patients with CF are significantly lower than in healthy individuals, despite the inflammatory nature of the disease. This reduction of NO is caused by different mechanisms including a lack of NOS2 expression in the CF airway epithelial cells. NO is not therefore considered to be a suitable marker of airway inflammation in CF. Interestingly, however, the same alleles in NOS1 that are related to increased NO concentrations in asthmatic subjects are also associated with higher NO concentrations in CF.[5] These observations suggest that individual CF patients produce relatively high airway NO concentrations despite the absence of inducible NOS, most probably related to naturally occurring variants in the NOS1 gene. The same mechanism could explain, why individual patients with asthma have persistently high NO concentrations during treatment with steroids. Their increased airway NO levels may reflect genetically determined high constitutive NO formation and not inflammation induced NO formation.

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AUTHORS' REPLY We thank Drs Grasemann and Ratjen for their interest in our paper[1] and for drawing attention to an explanation for our findings which we had not considered in the discussion. As stated in the accompanying editorial,[2] there is a need for studies correlating airway histology and exhaled nitric oxide (NO) measurements. Data that we have published in abstract form,[3] which is shortly to appear as a full paper,[4] demonstrated in an overlapping group of patients to those we reported that those with exhaled NO concentrations of >7 ppb after a 2 week course of oral prednisolone have persistent eosinophilic airway inflammation, whereas those still symptomatic but with exhaled NO concentrations <7 ppb do not. Thus, our original conclusions are, we believe, correct, and our reported exhaled NO measurements do reflect at least two subgroups of difficult asthma—namely, an inflammatory and a non-inflammatory phenotype—rather than merely the differing genetic ability of patients to increase exhaled NO concentrations. Nonetheless, the role of polymorphisms in nitric oxide synthase genes is an important question about which more information is needed.

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Shuttle walking test

Booth and Adams' report on the use of the shuttle walking test (SWT) in breathless patients with advanced cancer[1] addresses the important role of assessing exercise limitation in disease. Although they were primarily investigating breathlessness, it was surprising that only one of the 32 patients (completing at least one SWT) complained of leg pain at the end of the test. In patients with cardiorespiratory disease peripheral muscle strength correlates with maximal exercise capacity,[2] and in one large series up to one third of patients referred for exercise testing because of breathlessness stopped because of discomfort in the exercising muscle.[3] Given that peripheral muscle deconditioning would be an expected finding in patients with advanced cancer and breathlessness, a greater proportion than that reported would be expected to stop because of subjective muscle fatigue. Often patients stop exercising because of subjective leg fatigue and breathlessness but they may not volunteer this information unless specifically asked.

Their data support the use of the SWT for assessing exercise capacity in this patient group, but it is important to realise that not all breathless patients stop exercising because of breathlessness. Assessment of peripheral muscle symptoms during exercise is simple to perform and should be included in standard tests of exercise capacity.

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AUTHORS' REPLY We completely agree with Drs Doffman and Hawkins that the comprehensive studies of Hamilton *et al* clearly demonstrate that perceived leg discomfort is an important factor limiting exercise in patients with cardiorespiratory disease. Furthermore, we would guess that, had we asked our volunteers with cancer to rate their leg discomfort, we would have found a similar outcome for the reasons that Doffman and Hawkins give. However, we did not do this because we were not convinced that our subjects could reliably scale two exercise related sensations independently within a single test. We cannot therefore quantify the extent to which leg discomfort was a factor in determining exercise tolerance in this group. We tried to ensure that all subjects included in the analysis were limited at least in part by their breathlessness. In patients with advanced cancer it is this symptom, and not leg fatigue, which causes intense distress and towards which more effective therapeutic strategies need to be developed. In this respect, the shuttle walk test would seem to be a reliable objective means of assessing the function impact of this symptom.

Doffman and Hawkins have incorrectly equated our one report of leg pain as the only instance where leg discomfort was reported in this study. This patient experienced overt pain secondary to a musculoskeletal problem and this was the reason for stopping. The leg discomfort reported by Hamilton *et al* relates to a sense of tiredness or fatigue in the legs

which is a common exercise related phenomenon. Therapeutic strategies aimed at improving peripheral muscle function may well impact favourably on perceived breathlessness as well as on leg fatigue. Further investigation of the interaction between these perceptions are warranted in cancer and other conditions where exertional breathlessness is a primary morbid symptom. The shuttle walk test would seem to be a useful tool in studies of this nature.

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Sodium cromoglycate in asthma

Recent discussion about the place of sodium cromoglycate in the management of childhood asthma[1 2] has not mentioned problems of device maintenance for users of this medication. Since the introduction of chlorofluorocarbon (CFC) free sodium cromoglycate delivered by metered dose inhalers (MDIs) in Australia, there has been a change in the manufacturer's instructions about care of the plastic MDI holder. This change in instructions has been triggered by significant problems with blockage of the device nozzle.

The new instructions for CFC free sodium cromoglycate inhalers (Aventis Pharma) recommend that the plastic holder should be washed every night. The protocol includes running hot water through the plastic holder for 1 minute, then a further 1 minute in the opposite direction, tapping the holder to remove water droplets, and allowing it to dry overnight before re-use.

These daily requirements place a considerable burden on patients or their carers. When prescribing medications for the treatment of asthma, physicians must take into account both the efficacy of each medication and the ability and willingness of the patient or carer adequately to maintain the delivery device.

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Asthma and breast feeding

Wright *et al*[1] found an increased risk for asthma and wheeze in breastfed children whose mothers had asthma themselves. Data on 9644 children aged 5–6 years from the Bavarian farmers' study[2] allowed us to test whether this somewhat unexpected finding is reproducible in a different setting.

Lifetime prevalence of doctor diagnosed asthma (physicians' diagnosis of "asthma" at least once or asthmatic, spastic, or obstructive bronchitis more than once) and symptoms of asthma (wheeze ever, ISAAC core questions) were the main outcome measures of our investigation. Odds ratios for multivariate logistic regression with adjustment for the number of older siblings, parental education, family history of atopic disease other than maternal asthma, and farming are presented.

In children whose mothers had asthma themselves much higher odds ratios for the impact of breast feeding on the risk for doctors' diagnosed asthma were found than in children without maternal asthma (adjusted odds ratio (aOR) 2.37 (95% CI 1.29 to 4.33) *v* 1.11 (95% CI 0.86 to 1.44); test for homogeneity of odds ratios: χ^2=6.209, p=0.013). As in the study by Wright *et al*, a similar but not significant effect was observed regarding wheezing (aOR for children with maternal asthma 1.32 (95% CI 0.86 to 2.01) *v* 1.03 (95% CI 0.91 to 1.17) in children whose mothers did not have asthma). In children of mothers with hay fever or eczema, breast feeding was not related to childhood asthma.

Our data confirm an increased and specific risk for doctor diagnosed asthma related to breast feeding in children whose mothers had asthma themselves, emphasising the need for further research on the causes of this association.

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Acute lower respiratory tract illness

The observational data presented by Macfarlane *et al* on the aetiology of acute lower respiratory tract illness in the community[1] confirm that the often stated assertion that these illnesses are usually caused by viral infection is incorrect. The high prevalence of bacteriological and atypical pathogens and, in particular, the high prevalence of *Chlamydia pneumoniae* in these patients is of interest and points to the need for further studies to clarify the clinical significance of these isolates. The lack of correlation between indirect evidence of infection (radiographic and CRP levels), GP assessment of the need for antibiotics, and pathogen isolation is also of great interest and has important messages for those working in the community.

The conclusions from this study do, however, need to be treated with some caution. The authors state that outcomes were similar whether or not antibiotics were used but, as this was a non-randomised observational study, we cannot say that the groups of patients who were and were not given antibiotics were comparable. The experienced GP researchers in this study may well have had particular reasons for giving or withholding antibiotics, and the significance of similar reconsultation rates in these groups is open to interpretation.

In the accompanying editorial[2] the authors state that systematic reviews of randomised controlled trials of antibiotic prescription for acute bronchitis do not support antibiotic treatment, and evidence based educational initiatives aimed at GPs are advocated as one of the strategies to alter clinical behaviour. Having recently reviewed the literature on this important clinical topic myself,[3] I cannot agree with their assessment of the current evidence. The more recent review quoted[4] has been criticised on methodological grounds, and the most recent and extensive systematic review of this clinical problem published on the Cochrane database[5] (not referred to by Macfarlane *et al*) comes to very different conclusions, commenting that "the review confirmed the impression of clinicians that antibiotics have some beneficial effects in acute bronchitis". The benefits are probably small and confined to certain patient subgroups, but the quantification of benefit and the definition of the characteristics of responder groups need further delineation. The world literature currently consists of eight small randomised controlled trials of variable quality, some 20 years old, that use different antibiotic regimes and different outcome measures. Several of these studies have concluded that the antibiotic regimes used did improve outcomes.

The recent enquiry into deaths from community acquired pneumonia in young adults published in this journal[6] revealed that the primary care management of these patients at the severe end of lower respiratory tract infection was deficient in many cases—three quarters of patients had seen their GP for the illness without a correct diagnosis and few had received antibiotics from the GP. Many areas of uncertainty remain in this field and, while observational studies such as that by Macfarlane *et al* help to bring some clarity into this confused area of daily clinical practice, well designed randomised controlled trials are still needed to produce the evidence based guidance that GPs require. The current evidence is inadequate to meet the challenge identified by Macfarlane *et al*—that of identifying the cohort of patients who will benefit from antibiotics.

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TB at the end of the 20th century

I enjoyed the paper by Rose *et al* reviewing tuberculosis at the end of the century,[1] but there was one curious piece of data which the authors did not address in the discussion—namely, that the rates in the Bangladeshi population which used to be exactly the same as in the Pakistani population are now only one third of the level. Does this indicate that Bangladeshi subjects have not been immigrating to the UK over recent years at the same rate as Pakistani subjects, or could it be that it reflects a genuine rate of reduction in tuberculosis in Bangladesh?

It is interesting that Bangladesh is one of the few countries which has received good reports from the WHO as to the effectiveness of their DOTS campaign.

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AUTHORS' REPLY We thank Dr Davies for his letter and are impressed by his attention to detail. As he correctly pointed out, rates of tuberculosis in Pakistani and Bangladeshi patients in England and Wales appear to have diverged since 1988, when both were less than 120 per 100 000 (115 and 104 per 100 000, respectively).[1] Comparison of rates in these groups for 1988, 1993, and 1998 with WHO reported rates of tuberculosis in Pakistan and Bangladesh,[2] however, reveals that Bangladeshi patients in the UK had rates of tuberculosis closely approximating those reported from Bangladesh (57 *v* 58 per 100 000, respectively) for 1998. In contrast, patients of Pakistani origin in the UK appear to have had rates more than twice those reported from Pakistan (143 *v* 61 per 100 000) in 1998.[1 2]

Dr Davies suggests that the lower rates of tuberculosis in patients of Bangladeshi origin in this country may be the result of a reduction in rates of tuberculosis in Bangladesh. WHO data, however, indicate that the rate of tuberculosis in Bangladesh has increased between 1988 and 1998.[2]

We believe that caution needs to be exercised when comparing crude rates of tuberculosis (and trends in those rates) in England and Wales for patients born abroad with rates in their countries of origin. Not only will the age and sex structures vary between these groups, but the proportion of the population that has recently emigrated will change over time. Rates of tuberculosis among recent immigrants have been observed to be especially high in England and Wales.[1]

These factors, together with an appreciation of the confidence intervals around any of the rate estimates for the subgroups in question, may account for the apparently large changes seen. The reassuring statistic is, however, that for the Indian subcontinent (India, Pakistan and Bangladesh) population in England and Wales as a whole, the overall rate of tuberculosis, even when standardised for age, place of birth and year of entry, has continued to decline.[1]

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Prenatal risk factors of wheezing at the age of four years in Tanzania

The report by Sunyer *et al*[1] of an association between malaria parasites in umbilical cord blood and wheezing at 4 years of age is of considerable interest. Their interpretation of these findings is related to an association with unspecified intrauterine events. A further explanation is that babies with cord parasitaemia were more likely to be born preterm. The importance of preterm delivery in predisposing to recurrent cough and wheeze in children (5–11 years) living in a non-malarious area has been reported, and premature babies of asthmatic mothers were found to be at very high risk of childhood symptoms.[2] Redd *et al* have also observed, in a large cohort study from Malawi, that malaria cord parasitaemia was significantly associated with preterm delivery (odds ratio (OR) 2.51, 95% confidence interval 1.45 to 4.18), intrauterine growth retardation (OR 2.49, 95% CI 1.47 to 4.06), and maternal HIV infection (OR 2.87, 95% CI 1.74 to 4.60).[3] These factors may confound the association of cord parasitaemia with wheezing reported by Sunyer *et al*. Malaria during pregnancy is well described as a major cause of prematurity and growth retardation in babies born in malarious areas,[4] and it would be helpful to know the birth status (preterm, low birth weight, or growth retarded) of the children from the Tanzanian study. In view of the high attributable risk of malaria related low birth weight in developing countries, it will be important to ascertain its possible influence on the risk of asthma during childhood.

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AUTHORS' REPLY We thank Professor Brabin and Dr Rizwan for the suggestion of potential confounding by preterm delivery in the association between prenatal malaria and childhood wheezing. We had the opportunity to analyse the role of low birth weight, an objective surrogate measure of preterm delivery, and found that 15% of the 523 newborn infants weighed less than 2500 g. Maternal malaria was related to low birth weight (26% of women with parasitaemia gave birth to babies weighing <2500 g compared with 12% of women without parasitaemia, odds ratio 2.47, 95% CI 1.62 to 3.77). However, low birth weight was not related to wheezing at 4 years of age (15% and 14% of newborn infants with low and normal birth weight, respectively, developed wheezing, p=0.9). The association between parasites in cord blood and wheezing at 4 years of age was not confounded by birth weight (either as a continuous or a dichotomous variable), nor was birth weight or gestational age associated with asthma in five consecutive birth cohorts of Finnish adolescent twins.[1] The explanation of why malaria infection during pregnancy is related to wheezing may involve mechanisms other than those related to low birth weight.

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Severe life threatening asthma

With regard to the comments by Kolbe *et al*[1] concerning life threatening exacerbations in asthmatic patients, we would like to make the suggestion that a major cause is failure to check that drug delivery still contains active drug.[2 3] The use of lactose, although unpleasant to take, is a good indicator of the presence of an active drug, better than the alternative of a visual indicator. The recent admission of a 13 year old boy with a severe asthmatic attack to our intensive care unit demonstrated this fact. He had been using a fully expired budesonide Turbuhaler for 2 weeks prior to his admission. In view of this problem, it may be prudent to add lactose rather than a visual indicator system to inhalers.

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AUTHORS' REPLY While the presentation of isolated patients may relate to inadvertent "exhaustion" of their inhaled medications, neither published studies nor clinical experience would indicate that this is a "major cause" of life threatening exacerbations of asthma. Nevertheless, instructions to patients as to how to determine whether they have

remaining medication should be an integral component of asthma medication. As indicated by the case described by Sekerel and Sackesen, this may be more of an issue with certain delivery devices.

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Gastro-oesophageal reflux and asthma

We would like to comment on the paper by Coughlan *et al* on the relationship between medical treatment for reflux oesophagitis and asthma control.[1] Gastro-oesophageal reflux (GOR) can cause dyspnoea in non-asthmatic patients with normal pulmonary function and bronchial reactivity that improves with antireflux therapy.[2 3] Coughlan *et al* state that we included uncontrolled trials in our analysis.[1] This is incorrect.

We identified 12 studies—three uncontrolled, one with an untreated control, and eight controlled.[4] We felt, however, that these studies were not amenable to meta-analysis since outcomes varied, different classes and doses of antireflux medications were used, treatment periods ranged from 1 week to 6 months, different diagnostic criteria for GOR and asthma were used, asthma severity differed, and studies were done in different populations. We excluded the open studies and the paper with the untreated control group.[5] In table 3 studies were categorised according to Sackett's criteria.[6] In the abstract, materials and methods, figure legends, results, and discussion we clearly stated that the results of the controlled trials were analysed and presented.[4] In addition to these eight controlled trials, Coughlan included one with an untreated control and three controlled trials published since our review.[5 7–9] The small number of patients with GOR symptoms and its mild nature may explain the apparent lack of benefit reported by Boeree *et al*.[7] The study by Levin *et al* only included nine subjects.[8] Kiljander *et al* reported a trend in asthma symptom improvement that may have been significant had the study been properly powered.[9]

The effects of antireflux surgery on asthma have also been reported. Most studies were uncontrolled, did not document GOR or asthma objectively, and did not measure objective outcomes.[10] Both controlled studies reported that asthma symptoms, but not pulmonary function, improved, which is consistent with our hypothesis.[11–13] An improvement in asthma symptoms was the most consistent change in both the medical and surgical antireflux therapy trials and may be an important clue to the nature of the relationship between GOR and asthma.[4 10] We would caution clinicians not to dismiss GOR as an irritant in poorly controlled asthmatics, especially those with reflux associated respiratory symptoms. We agree with Coughlan that further properly controlled and powered studies are required to assess the effects of antireflux therapy on asthmatics with GOR.

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AUTHOR'S REPLY We thank Drs Field and Sutherland for their comments on our systematic review. We are essentially in agreement that the current literature does not support a strong clinical recommendation for treating gastro-oesophageal reflux (GOR) in patients with asthma. We are also in agreement about the need for further research to clarify this potentially important trigger factor for people with asthma. As Dr Field points out, it is not only important to have adequately powered randomised trials to investigate the effects of treatment of GOR on asthma, it is also important to conduct primary research to understand the nature of respiratory symptoms which develop following GOR. This latter point is emphasised by the study showing symptom changes but not necessarily changes in lung function measures when reflux occurs in asthma.

Dr Field also comments on the process of the two reviews. A key difference is the systematic nature of our review. It is now well established that Cochrane systematic reviews are of a higher quality and are likely to be less biased than non-systematic reviews, particularly in the field of asthma.[1] We performed a Cochrane systematic review and updated it for publication in *Thorax*.

In conclusion, we agree with Dr Field about the potential importance of reflux in asthma, and also agree that clinical recommendations for treatment cannot be based on high level evidence at this stage until further research is done.

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1 Jadad AR, Moher M, Browman GP, *et al*. Systematic reviews and meta-analyses on treatment of asthma: critical evaluation. *BMJ* 2000;**320**:537–40.

BOOK REVIEW

Computed Tomography and Magnetic Resonance of the Thorax. D P Naidich, R W Webb, N L Muller, *et al*. (Pp 784; $155.00). USA: Lippincott Williams & Wilkins, 1999. 0 7817 1660 8

This is a superb book. Anybody, like this reviewer, who has ever looked at a CT scan and felt confused or uncertain as to what the appearances show will find this book enlightening. As in previous editions (under the title of *Computer Tomography of the Thorax*), the authors explain the methods of scanning, the anatomy of the thorax, and then take the reader through a series of chapters organised around the structures contained in the thorax rather than a traditional respiratory medicine breakdown based on disease categories. In all respects the text has been significantly extended and improved on its previous editions, but the inclusion of magnetic resonance scans is a major development in this new edition. However, the major strength of the text is that its clinical orientation makes it superbly accessible to all with an interest in the diagnosis and interpretation of scans of the chest. This is a comprehensive, definitive, informative, and ultimately highly accessible overview of a complex subject and is strongly recommended.—JB

NOTICE

Basic and Clinical Allergy 2002

"Basic and Clinical Allergy 2002" will be held at the National Heart & Lung Institute, Faculty of Medicine, Imperial College, London on 18–22 March 2002. Main topics include: Basic cellular mechanisms and their application in allergic disease; Allergic rhinitis; Indoor allergens; Allergen specific immunotherapy and T cell tolerance; Asthma (aetiology and pathogenesis); Treatment of asthma. CPD/CME approval pending (2001 course maximum 23.5 credits). Further details from the Short Courses Office, Education Centre, Faculty of Medicine, Imperial College, National Heart & Lung Institute, Dovehouse Street, London SW3 6LY, UK. Telephone +44 20 7351 8172. Fax +44 20 7351 8246. Email: shortcourses.nhli@ic.ac.uk; www.med.ic.ac.uk/divisions/47a/mtgs.htm.