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. 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 these patients compared to 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 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 that being a good 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. Wichser et al. recently reported that exhaled NO concentrations in adult asthmatics correlate with sequence variants in the neuronal NO synthase (NOS1) gene. Furthermore, the NOS1 genotypes associated with high NO concentrations were significantly more frequent in asthmatic than in control subjects. These findings supported recent evidence that the NOS1 gene is involved in the genetics of asthma. 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 process found in CF. This suggests that NO may play a different role in the pathophysiology of asthma compared to CF. However, the role of polymorphisms in NOS1 in asthma remains to be fully elucidated. The authors' 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 difference in NO 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 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 cardiopulmonary disease peripheral muscle strength correlates with maximal exercise capacity, 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 muscles. 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 should be included 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 cardiopulmonary 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 leg 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 related to a sense of tiredness or fatigue in the legs which is shortly to appear as a full paper, demonstrated in an overlapping group of patients to those we reported that those with exhaled NO concentrations $>7$ ppb after a 2 week course of oral prednisolone have persistently high NO concentrations were significantly more frequent in asthmatics than in control subjects. These findings supported recent evidence that the NOS1 gene is involved in the genetics of asthma. 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. These observations suggest that individual CF patients produce relatively high airway NO concentrations despite the absence of inducible NO, 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.
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 morbidity 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 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 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 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 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, spasitic, 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 asthma, and farming are presented.

In children whose mothers had asthma themselves much higher odds ratios 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: \( y^2 = 6.209, p = 0.013 \). 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 implications 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 this was as 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 antibiotics 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, I cannot agree with their assessment of the current evidence. The more recent review quoted 3 has been criticised on methodological grounds, and the most recent and extensive systematic review of this clinical problem published on the Cochrane database 4 refers 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 responders 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 antimicrobial regimes and different outcome measures. Several of these studies have concluded that the antibiotic regimes used did improve outcomes.

The recent inquiry into deaths from community acquired pneumonia in young adults published in this journal 5 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 need. 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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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 developed 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 parasitaemia 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. The explanation of why malaria infection in pregnancy is related to wheezing may involve mechanisms other than those related to low birth weight.

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Authors' reply While the presentation of isolated patients may relate to inadvertent "exclusion" of their inhaled medication from either published studies or 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. J KOLBE Respiratory Services, Green Lane Hospital, Green Lane West, Auckland 3, New Zealand

**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 Coughlan et al stated that we included uncontrolled trials in our analysis. This is incorrect.

We identified 12 studies—three uncontrolled, one with an untreated control, and eight controlled.3 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.4 In table 3 studies were categorised according to Sackett’s criteria.5 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.6 In addition to these eight controlled trials, Coughlan included one with an untreated control and three controlled trials published since our review.7 8 The small number of patients with GOR symptoms and its mild nature may explain the apparent lack of benefit reported by Boeree et al.8 The study by Levin et al comprised nine subjects.9 Kiljander et al reported a trend in asthma symptom improvement that may have been significant had the study been properly powered.10

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.11 Both controlled studies reported that asthma symptoms, but not pulmonary function, improved, which is consistent with our hypothesis.11 12 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.11 We would caution clinicians not to dismiss GOR as an irritant in poorly controlled asthmatics, especially those with reflux associated asthma 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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**BOOK REVIEW**

Computed Tomography and Magnetic Resonance of the Thorax. D P Naidich, R W Webb, N L Muller, (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: 020 7375 8172. Fax +44 20 7375 8246. Email: shortcourses.nhll@ic.ac.uk; www.med.ic.ac.uk/divisions/47a/mtgs.htm.