Thorax

Editorials

Leukotriene receptor antagonists: useful in acute asthma?

L M Kuitert, N C Barnes

The leukotriene receptor antagonists (LTRAs) constitute the first completely new class of drugs for use in asthma for 25 years. Their development was based on the recognition that cysteinyl leukotrienes exhibit biological activities that mimic some of the clinical features of asthma and are detectable in increased amounts in asthmatic patients, particularly during exacerbations of asthma. Potent and specific LTRAs have been developed and marketed for use in the treatment of asthma in the UK. Their use by clinicians in the UK is usually as "add-on" therapy in chronic asthma at steps 3, 4, or 5 of the BTS asthma guidelines.

In this issue of *Thorax* Dockhorn *et al* compare the effect of intravenous and oral administration of the LTRA montelukast on airway function.[1] Their results confirm those of previous studies that have shown improved pulmonary function after administration of an LTRA in asthmatic patients, and they also found that intravenous montelukast had a rapid onset of action and a duration of action of about 24 hours in 51 patients with mild to moderate asthma.

Early studies with the LTRAs showed that administration of a single dose (orally or intravenously) was predictably associated with an improvement in lung function.[2 3] This suggested that, in patients with asthma, leukotrienes were contributing to the increase in airway smooth muscle tone. This is in contrast to that of normal subjects in whom the LTRAs do not lead to any alteration in lung function. In the study by Hui *et al* the improvement in forced expiratory volume in one second (FEV_1) was apparent even in those patients treated with inhaled corticosteroids.[2] Studies of corticosteroid inhibition of stimulated leucocytes in vitro have shown variable effects on leukotriene production.[4–6] In vivo, however, steroid treatment of asthmatics suggests that corticosteroids, both oral and inhaled, have little effect on the basal and stimulated generation of leukotrienes.[7 8] Pretreatment of asthmatic patients with inhaled fluticasone was also unable to inhibit generation of leukotrienes in response to allergen challenge. This suggests that antagonism of the effects of the leukotrienes might provide additional benefit by suppressing that part of the asthmatic response not sensitive to inhaled and/or oral corticosteroids.

While treatment with inhaled and oral corticosteroids results in improvement in lung function, studies with montelukast and zafirlukast have shown that, even in the presence of moderate and high dose inhaled steroids, further improvements in lung function are possible.[9 10] In one study with zafirlukast 80 mg twice daily, patients already on high dose inhaled steroids continued to show an improvement in lung function for more than six weeks.[9] This gradual improvement may be secondary to an anti-inflammatory activity additional to that of inhaled steroids since the LTRAs also reduce peripheral blood, sputum, and airway eosinophilia.[11 12] In a four way comparison between placebo, montelukast alone, 400 μg beclomethasone alone, or montelukast plus beclomethasone, the greatest improvement was seen with combination treatment.[10] A steroid tapering study has also shown that it is possible to maintain asthma control while reducing inhaled steroids by adding montelukast to the treatment regimen.[13]

An unexpected finding of some of the early studies of the LTRAs was the additive improvement in lung function seen with the β_2 agonists and the LTRAs. The study by Hui *et al* showed that, while ICI 204,219 (zafirlukast) caused bronchodilatation, the addition of inhaled salbutamol caused a further improvement in lung function.[2] Gaddy *et al* reported similar findings with MK-571 given intravenously.[3] Again there was bronchodilatation with a further improvement with inhaled salbutamol and then nebulised salbutamol. While both β_2 agonists and LTRAs improve lung function, they appear to do it by separate yet complementary mechanisms; however, the exact mechanism is not yet clear. It is possible that β_2 agonists and the LTRAs act at anatomically distinct sites, with some of the actions of the LTRAs being due to their effects on airway oedema. Clinical studies suggest that the two treatments are complementary and therefore can be used together to improve function.

Increased levels of leukotrienes are detectable in peripheral blood, bronchoalveolar lavage (BAL) fluid, sputum, and urine of patients with asthma, even when stable.[14–16] In BAL fluid and urine there is, however, a considerable overlap between asthmatic patients and normal subjects. Leukotriene levels rise further following allergen challenge, and following aspirin challenge in aspirin sensitive asthmatic subjects.[17 18] Several studies in adults and children have reported increased levels of leukotrienes in acute asthma that fall as the attack resolves.[16] While existing studies have focused on the use of the LTRAs in chronic asthma, the findings in the paper by Dockhorn *et al* raise the possibility that leukotriene inhibition may also be beneficial in acute asthma. Dockhorn *et al* demonstrated a rapid onset of bronchodilatation, particularly with the intravenous formulation, but even the oral formulation achieved a peak effect within two hours. With these results it is tempting to speculate, as the authors do, that montelukast should be considered for the treatment of acute asthma. It is worth noting that the patients studied by Dockhorn and colleagues had mild to moderate asthma, in whom conventional treatment usually works. It may be that in these patients treatment with an additional drug will not provide a significant benefit over and above the usual treatment, but in those with more severe asthma, where aerosolised drug distribution to the airways in the presence of severe airways obstruction may be poor, the availability of an intravenous (or oral) drug with significant bronchodilator effect would be advantageous. It would be interest-

ing to see if these results are also applicable to acutely unwell severe asthmatic subjects. There are anecdotal reports of the use of LTRAs in patients who are ventilated with acute severe asthma.

Finally, the effect of montelukast on airway function relates to the dosages used. The authors used 7 mg intravenously, based on previous pharmacokinetic and pharmacodynamic data which suggested that the maximum benefit obtained was with 10 mg orally. Preliminary dose response studies with montelukast showed that there was little further bronchodilation above 10 mg daily, even when doses as high as 50 mg were used.[19] The results of Dockhorn and colleagues show, however, that superior bronchodilatation is achieved with intravenous montelukast in a dose of 7 mg compared with an oral dose of 10 mg which suggests that the oral dose of 10 mg may not, in fact, be the dose associated with a maximal clinical response. At present it is only licensed for use in the UK as a 10 mg tablet in adults and a 5 mg chewable tablet in children over the age of six years.

It is hoped that the study by Dockhorn and colleagues will pave the way for more studies of the use of the LTRAs in the treatment of acute asthma and, in particular, to examine whether they prevent hospital admissions, reduce the length of hospital stay, and prevent intubation and ventilation for acute severe asthma. Any such studies should evaluate doses of 10 mg and higher.

L M KUITERT
N C BARNES

Department of Respiratory Medicine,
London Chest Hospital,
London E2 9JX,
UK
email:lkuitert@aol.com

1 Dockhorn RJ, Baumgartner RA, Leff JA, *et al*. Comparison of the effects of intravenous and oral montelukast on airway function: a double blind, placebo controlled, three period, crossover study in asthmatic patients. *Thorax* 2000;**55**:260–5.
2 Hui KP, Barnes NC. Lung function improvement in asthma with a cysteinyl-leukotriene receptor antagonist. *Lancet* 1991;**337**:1062–3.
3 Gaddy JN, Margolskee D, Bush RK, *et al*. Bronchodilatation with a potent and selective leukotriene D_4 (LTD_4) receptor antagonist (MK-571) in patients with asthma. *Am Rev Respir Dis* 1992;**146**:358–63.
4 Balter MS, Eschenbacher WL, Peters-Golden M. Arachidonic acid metabolism in cultured alveolar macrophages from normal, atopic, and asthmatics subjects. *Am Rev Respir Dis* 1988;**138**:1134–42.
5 Sebaldt RJ, Sheller JR, Oates JA, *et al*. Inhibition of eicosanoid biosynthesis by glucocorticoids in humans. *Proc Natl Acad Sci USA* 1990;**87**:6974–8.
6 Crocker IC, Zhou CY, Bewtra AK, *et al*. Glucocorticosteroids inhibit leukotriene production. *Ann Allergy Asthma Immunol* 1997;**78**:497–505.
7 Dworski R, Fitzgerald GA, Oates JA, *et al*. Effects of oral prednisone on airway inflammatory mediators in atopic asthma. *Am J Respir Crit Care Med* 1994;**149**:953–9.
8 O'Shaunessey KM, Wellings R, Gillies B, *et al*. Differential effects of fluticasone propionate on allergen-evoked bronchoconstriction and increased urinary leukotriene E_4 excretion. *Am Rev Respir Dis* 1993;**147**:1472–6.
9 Virchow JC, Hassall SM, Summerton L, *et al*. Improved asthma control over 6 weeks with Accolate (zafirlukast) in patients on high dose inhaled corticosteroids. *J Invest Med* 1997;**45**:286A.
10 Malmstrom K, Herbert J, LaForce C, *et al*. Montelukast (MK 0476), a leukotriene receptor antagonist, provides additional clinical benefit to chronic asthma patients using inhaled beclomethasone. *Eur Respir J* 1998;**12**(29 Suppl):19S.
11 Hodges MK, Weller PF, Gerard NP, *et al*. Heterogeneity of leukotriene C_4 production by eosinophils from asthmatic and from normal subjects. *Am Rev Respir Dis* 1988;**138**:799–804.
12 Leff JA, Pizzichini E, Efthimidiadis A, *et al*. Effect of montelukast (MK-0476) on airway eosinophilic inflammation in mildly uncontrolled asthma: a randomised placebo-controlled trial. *Am J Respir Crit Care Med* 1997;**155**:A977.
13 Löfdahl C-G, Reiss TF, Leff JA, *et al*. Randomised, placebo controlled trial of effect of a leukotriene receptor antagonist, montelukast, on tapering inhaled corticosteroids in asthmatic patients. *BMJ* 1999;**319**:87–90.
14 Lee TH, Crea AEG, Gant V, *et al*. Identification of lipoxin A_4 and its relationship to the sufidopeptide leukotrienes C_4, D_4, and E_4 in the bronchoalveolar lavage fluids obtained from patients with selected pulmonary diseases. *Am Rev Respir Dis* 1990;**141**:1453–8.
15 Westcott JY, Bratton DL, Krawiec ME, *et al*. Urinary leukotriene E_4 (LTE_4) levels in children. *Am J Respir Crit Care Med* 1999;**159**:A96.
16 Sampson AP, Green CP, Spencer DG, *et al*. Leukotrienes in the blood and urine of children with acute asthma. *Ann NY Acad Sci* 1991;**629**:437–9.
17 Christie PE, Tagari P, Ford-Hutchinson AW, *et al*. Urinary leukotriene E_4 concentrations after aspirin challenge in aspirin-sensitive asthmatic subjects. *Am Rev Respir Dis* 1991;**143**:1025–59.
18 Taylor GW, Taylor IK, Black PN, *et al*. Urinary leukotriene E_4 after allergen challenge and in acute asthma and allergic rhinitis. *Lancet* 1989;i:584–8.
19 Noonan MJ, Chervinsky P, Brandon M, *et al*. Montelukast, a potent leukotriene receptor antagonist, causes dose-related improvements in chronic asthma. *Eur Respir J* 1998;**11**:1232–9.

Thorax 2000;**55**:256–257

Stopping smoking: the importance of nicotine addiction

Angela Hilton

The Royal College of Physicians has produced several reports on the adverse effects of smoking on health in the past 40 years.[1–5] Its latest report entitled "Nicotine Addiction in Britain" emphasises the importance and role of nicotine addiction as a major factor in making many smokers unable to stop.[6] Recognition of the addictive nature of nicotine has important implications for the way that nicotine products should be regulated in society, and one important conclusion of the report is that tobacco based nicotine products should be subject to the same regulatory control as any other drug delivery device. However, the report also argues that nicotine addiction should become recognised and accepted as a medical problem, much as any other manifestation of drug addiction, and this argument has special relevance to respiratory physicians.

Most people who attempt to stop smoking relapse within a very short time and, in the USA, less than 10% of smokers who stop for one day remain non-smokers at 12 months.[7] Nicotine replacement therapy has been shown to improve cessation rates in many controlled randomised studies, but these success rates apply mainly to smokers recruited from the general population and general practice.[8] However, smokers are a heterogeneous population and those with established smoking related diseases often have even greater difficulty in quitting smoking. Furthermore, amongst patients admitted to hospital, the relative effectiveness of nicotine replacement therapy and of counselling and psychological support may be different, since three multicentre studies of smoking cessation in hospital inpatients and outpatients carried out in the 1980s by the British Thoracic Society showed that simple advice from chest physicians with follow up letters of support and encouragement improved quit rates at one year, and that in this context nicotine replacement therapy did not improve the success rate.[9–11] The importance of psychological support and counselling in achieving a quit rate of over 20% at one year, with or without nicotine replacement treatment, has been confirmed by a recent study from Cardiff in hospital patients.[12]

Patients with smoking related diseases present to a wide range of hospital specialities. However, respiratory physicians in particular see large numbers of patients with lung cancer and chronic obstructive pulmonary disease (COPD), diseases where smoking is the major aetiological

factor, and most of the deaths caused by smoking are in fact due to respiratory diseases.[6] Smoking cessation in patients with COPD reduces the accelerated rate of decline of forced expiratory volume in one second (FEV_1) and is one of only two interventions which improve the long term prognosis, the other being long term oxygen therapy.[13 14] Active support and treatment of nicotine addiction in these patients should therefore be considered to be an essential component for medical management of this disease.

If nicotine addiction is accepted to be a fundamental issue in preventing smokers from successfully stopping smoking, it is clear that simple advice alone is not always adequate to address the problem. Active help and support such as psychological counselling and pharmacological treatments need to be made available to increase the chances of success. Other addictions such as those to heroin and alcohol are already treated and funded by the NHS, and although funding is now being made available to establish smoking cessation services in selected areas of Britain, it is time to make the treatment of nicotine addiction available and affordable for all smokers through the NHS. Smoking cessation interventions give good value for money and the cost implications of providing smoking cessation services in the UK are well established.[15] The report by the Royal College of Physicians adds further urgency to the need for the implementation of smoking cessation services.

It is also important for all health professionals to take an active role in advising and helping smokers to stop.[16] For this to be achieved, there must be better education and training for health professionals in both the knowledge of the adverse effects of active and passive smoking and in smoking cessation methods. Unfortunately, marked deficiencies in knowledge of tobacco control and prevention have been shown amongst medical students from all over the world.[17] Few medical schools include education on tobacco issues in their undergraduate curriculum and the prevalence of smoking amongst medical students increased during their medical school careers. Even for specialist registrars training in respiratory medicine, the current curriculum does not include a recommendation for training in smoking cessation as an essential part of the syllabus.[18]

What messages can respiratory physicians take from the latest Royal College of Physicians report? Many of our patients need help and support to stop smoking and, because so many of our patients have smoking related diseases, it would be appropriate for respiratory specialists to take ownership of the problem and become lead physicians for tobacco control within their NHS trusts or districts. This would involve a more active role in the education and training of medical students, junior doctors, general practitioners, and other health care professionals in smoking issues especially, and for respiratory physicians to become expert in smoking cessation interventions. Respiratory physicians should actively campaign for and request the appointment of smoking cessation counsellors in all NHS hospitals to provide advice and psychological support for patients and staff. They could work closely with such individuals who could have their base within respiratory medicine departments. The pharmacological aspects of smoking cessation could also become part of the expertise of the respiratory specialist.

ANGELA HILTON

Consultant Respiratory Physician
& Chairman of the BTS Tobacco Committee,
North West Lung Centre,
Wythenshawe Hospital,
Manchester M23 9LT,
UK

1 Royal College of Physicians. *Smoking and health. A report on smoking in relation to lung cancer and other diseases*. London: Pitman Medical, 1962.
2 Royal College of Physicians. *Smoking and health now. A new report on smoking and its effects on health*. London: Pitman Medical, 1971.
3 Royal College of Physicians. *Smoking or health*. London: Pitman Medical, 1977.
4 Royal College of Physicians. *Health or smoking. A follow-up report*. London: Pitman Medical, 1983.
5 Royal College of Physicians. *Smoking and the young*. London: Pitman Medical, 1992.
6 Royal College of Physicians. *Nicotine addiction in Britain*. London: Pitman Medical, 2000.
7 Fiore MC. Trends in cigarette smoking in the United States: the epidemiology of tobacco use. *Med Clin North Am* 1992; **76**: 289–303.
8 Silagy C, Mant D, Fowler G, *et al.* The effect of nicotine replacement therapy on smoking cessation. Cochrane Library (Issue 1), 1997.
9 British Thoracic Society. Comparison of four methods of smoking withdrawal in patients with smoking related diseases. *BMJ* 1983; **286**: 595–7.
10 British Thoracic Society. Smoking withdrawal in hospital patients: factors associated with outcome. *Thorax* 1984; **39**: 651–6.
11 British Thoracic Society. Smoking cessation in patients: two further studies. *Thorax* 1990; **45**: 835–40.
12 Prathiba BV, Tjeder S, Phillips C, *et al*. A smoking cessation counsellor: should every hospital have one? *J R Soc Health* 1998; **118**: 356–9.
13 Fletcher CM, Peto R. The natural history of chronic airflow obstruction. *BMJ* 1977; 1: 1645–8.
14 US Department of Health and Human Services. *The health benefits of smoking cessation. A report of the Surgeon General*. Washington: US Government Printing Office, 1989.
15 Parrot S, Godfrey G, Raw M, *et al.* Guidance for commissioners on the cost effectiveness of smoking cessation interventions. *Thorax* 1998;**53**(Suppl 5, Part 2):S1–38.
16 Raw M, McNeill A, West R. Smoking cessation guidelines for health professionals. *Thorax* 1998;**53** (Suppl 5, Part 1):S1–19.
17 Richmond R. Teaching medical students about tobacco. *Thorax* 1999;**54**: 70–8.
18 Joint Committee for Higher Medical Training (JCHMT). *Curriculum for higher specialist training in respiratory medicine*. Royal College of Physicians, July 1998.

Thorax 2000;**55**:257–259

Orthostatic increase of respiratory gas exchange in hyperventilation syndrome

William Gardner

The paper by Malmberg *et al* in the current issue of *Thorax*[1] deals with the difficult subject of the hyperventilation syndrome and finds that these patients have a disproportionately high ventilatory response to change of body position from supine to standing. The authors suggest that this can be used as a diagnostic criterion for hyperventilation syndrome. Hyperventilation is a confused and poorly documented subject and the publication of this paper provides an opportunity to review some of the particularly controversial aspects of this subject.

The first issue concerns the basis for the labelling of these patients as "hyperventilation syndrome". Some of the controversies about the use of this term have recently been reviewed by Folgering[2] and by Gardner.[3] The physiological definition of hyperventilation is alveolar ventilation that is inappropriately high for the metabolic production of carbon dioxide, leading to reduction of arterial P_{CO_2} (Pa_{CO_2}) below the normal range (hypocapnia) and respiratory alkalosis. The combination can lead both to vasoconstriction in selected vascular beds and to neuronal

hyperexcitability producing symptoms involving most systems of the body. Many psychosomatic syndromes have been described in the past in which hyperventilation has a variable and uncertain role but the term "hyperventilation syndrome" was first used in 1938 to describe patients with the somatic symptoms of both hypocapnia and anxiety.[4] This theme was extended by subsequent authors[5–7] and the definition arrived at by Lewis and Howell in 1986 on the basis of a questionnaire of delegates at a psychophysiology meeting[8] was "a syndrome induced by physiologically inappropriate hyperventilation and usually reproduced in whole or in part by voluntary hyperventilation". However, the term "hyperventilation syndrome" is now used in so many different contexts that it could be argued that it has ceased to have any universal meaning. Some physicians diagnose it in the presence of the somatic symptoms of hypocapnia either at rest or induced by voluntary overbreathing without assumptions about aetiology,[9] or regard it primarily as an abnormality of respiratory control[10] or as a variant of disproportionate breathlessness.[11 12] Folgering accepts that anxiety may be absent and has recently suggested a new definition as "a dysregulation of ventilation causing hypocapnia in the absence of organic causes for hyperventilation, with symptoms and complaints not exclusively associated with hypocapnia". Many refuse to recognise it as a separate entity[13] or regard it as secondary to organic disease and especially to asthma.[14 15] Many would not use the term in the presence of any organic cause of hyperventilation, yet organic and psychiatric factors are usually difficult to separate. Lum[16] regards hyperventilation as a form of conditioned response and avoids use of the term "hyperventilation syndrome". Gardner[3] believes that it is not useful in the clinical context to label a patient with hypocapnia as "hyperventilation syndrome" and that the term should be abandoned. He believes that hyperventilation is often due to a complex interaction between a range of organic, psychogenic, and physiological factors and that, in all cases, the initiating and sustaining cause or causes of the increased respiratory drive causing the hyperventilation should be sought and documented. Use of a label such as "hyperventilation syndrome" tends to preclude further search for underlying aetiological factors and can be dangerous in the context of the emergency room. It is difficult to assess which of the current definitions applies to the patients in the study by Malmberg *et al*. There was no clear evidence of anxiety or organic causes of hyperventilation and the end tidal P_{CO_2} was recorded as being no different from the control value at rest. However, the history suggested hypocapnia at other times although the presence of a low P_{CO_2} at that time was not documented. About the only certain statement that can be made is that these patients do not have chronic hyperventilation.[17]

Hyperventilation occurs in many different specialties including neurology, cardiology, chest medicine, and psychiatry. The patient population to which the term is applied will vary greatly between specialties. Without a clear understanding of the patient population being studied it is difficult to understand the significance of any findings concerning this subject, and the source of the patients and the clinical context from which they were recruited into the study requires particular emphasis in any study about hyperventilation. There is considerable ignorance among physicians about psychiatry and the precise criteria that are used for psychiatric diagnoses. Many physicians in medical specialties assume that the demonstration of a low arterial P_{CO_2} automatically diagnoses hyperventilation syndrome with an assumption that the patient has some unspecified psychiatric condition. Such patients are then considered to be no longer of interest to the physician. This is often unfair to the patient, and ignores the wide range of organic, behavioural and physiological causes of hyperventilation, many of which can and usually do coexist. These uncertainties reflect the complexity of this subject which falls between psychiatry, clinical medicine, and physiology.

It is difficult to determine the significance of the suggestion in the paper by Malmberg *et al* that their findings should be used as the basis for a diagnostic test for hyperventilation syndrome. At a physiological level this finding requires a more detailed physiological study to evaluate mechanisms before its significance can be ascertained. At a clinical level ventilation is difficult to measure and most routine lung function laboratories do not have tilt tables or the facilities for measurement of respiratory control variables, especially while the patient is moving from one position to another. The methodology for diagnosing hyperventilation is even more controversial than the issues surrounding the definition, and it could be argued that diagnostic criteria cannot adequately be defined unless the issue of definition has been clarified. Strict adherence to the physiological definition would require documentation of hypocapnia, but hyperventilation may be sporadic and there are few current techniques for measuring P_{CO_2} over prolonged periods of time outside the laboratory.[18 19] As in the present study, hyperventilation is often diagnosed with, not only no evidence of a low arterial, end tidal or transcutaneous P_{CO_2}, but even with evidence of a normal P_{CO_2} on spot sampling. While it is possible to provide convincing evidence of hyperventilation on behavioural grounds, using the term hyperventilation in the presence of a normal P_{CO_2} puts an onus on the authors to be more meticulous than usual in documenting the criteria by which hyperventilation was diagnosed. Many such descriptions are sadly unconvincing.

Hypocapnia induces a range of symptoms, and symptom checklists such as the Nijmegen questionnaire[20] have often been used for diagnosing the hyperventilation syndrome. However, many would argue that most of these symptoms are non-specific and do not provide an adequate basis for diagnosis when used alone. It could be argued that the only symptoms specific to hypocapnia are paraesthesiae and tetany, possibly combined with symptoms due to cerebral vasoconstriction and hypoxia. In clinical practice the clinical finding of a low arterial or end tidal P_{CO_2} is of little relevance in itself if there are no associated symptoms of hypocapnia, or if the symptoms are of minor importance compared with the symptoms of the disorder causing the hyperventilation. In other situations the symptoms of hyperventilation are pivotal to the clinical presentation of the patients. The reporting of familiar symptoms during voluntary hyperventilation is often used as a basis for diagnosis, but this has been criticised by Hornsveld *et al*[21] in that similar symptoms are also reported when the Pa_{CO_2} is artificially maintained at normal levels during voluntary overbreathing.

The role of anxiety disorders in the paper by Malmberg and colleagues is unclear. No psychiatric disorders were reported but their patients nevertheless had symptoms of "episodic dyspnoea or air hunger" and "palpitations, sweating, trembling, dryness of the mouth or other symptoms of overactivity of the autonomic nervous system . . . suggestive of panic disorder". This definition of panic is imprecise and no formal psychiatric assessment was apparently performed. Contrary to the statement in the introduction to the paper, the association between anxiety and panic is still controversial.[22 23] Although anxiety was a core component in the original description of hyperventilation syndrome, the relation of hyperventilation to anxiety is not simple and hyperventilation can occur without

anxiety[17 24 25] or anxiety may be induced by hyperventilation.[26] Anxiety can be associated with both mild hyperventilation and abnormalities of breathing pattern.[27] Endogenous non-retarded depression can be associated with hyperventilation[28] and phobic patients have a high prevalence of breathing difficulties.[29 30] The predisposition to overbreathe in response to stress may be dependent on biological vulnerability, personality, and cognitive variables[22] as well as individual interpretation of the hyperventilation induced somatic symptoms,[31] and may become a conditioned response.[22] Because of the complexities of this subject, it could be argued that any paper about hyperventilation requires a collaborative input from a psychiatrist or psychologist. At a clinical level such an input is often required for no reason other than to counter the assumptions of the referring clinician that a patient with hyperventilation must automatically have an anxiety state. Often there is a complex interaction between organic and psychiatric factors such as depression and phobic states which require a combined input from a physician and a psychiatrist.

The authors describe their patients as having a history of recurrent or episodic dyspnoea. Howell[11 12] regards disproportionate dyspnoea as being synonymous with hyperventilation syndrome, and he has described the characteristics of these patients. Gardner[3] has argued that the two are not synonymous and that, if a patient is breathless for reasons that are not clear, it is the breathlessness that is the primary condition for which a cause should be sought and that, if hyperventilation is also present, it is usually secondary to the breathlessness and of little clinical importance. Patients are often referred with a label of psychogenic dyspnoea when the degree of distress seems disproportionate to the clinical findings and lung function or blood gas data, but there is almost no literature on this subject.[32 33] Dyspnoea is what the patient reports and it is therefore difficult to dispute. Studies of breathlessness are impeded by uncertainty about the basic mechanisms[34] and there are probably many different forms. Air hunger, or a sensation of inability to take a satisfying breath or to fill the lungs, was reported by patients in the Malmberg study and may indicate a psychogenic component to breathlessness. It was a universal feature of the patients with chronic hyperventilation studied by Gardner and Bass,[17 25] and more recently Gardner has reported patients in whom the primary presentation is air hunger which leads to variable degrees of panic and hyperventilation.[3]

Asthma is a common underlying basis for hyperventilation[15 35 36] and Gardner has argued that many patients with a primary presentation of hyperventilation have very mild and often previously undiagnosed asthma.[37] Malmberg *et al* describe the exclusion of "physician diagnosed" asthma but give no details about how this was achieved, although patients had "histamine provocation tests and pulmonary diffusion capacity if clinically indicated". Asthma is a surprisingly difficult and controversial diagnosis and many physicians would argue that these indications should be clarified.

In summary, it would seem that the patients in the study by Malmberg and colleagues might fit more accurately into a classification of dyspnoea and air hunger with secondary intermittent hyperventilation rather than receiving an automatic label of "hyperventilation syndrome". Such a reclassification may lead to a different interpretation of these clearly interesting results and may suggest lines of enquiry for possible mechanisms of air hunger. The physiological basis for these responses requires investigation and may provide useful insights into mechanisms by which postural changes can influence control of breathing and respiratory sensations. It is probably unhelpful to suggest this as the basis for yet another indirect diagnostic test for hyperventilation syndrome.

WILLIAM GARDNER

Department of Respiratory Medicine & Allergy, Guy's, King's and St Thomas' School of Medicine, London SE5 9PJ, UK

1 Malmberg LP, Tamminen K, Sovijärvi ARA. Orthostatic increase of respiratory gas exchange in hyperventilation syndrome. *Thorax* 2000;**55**:295–301.
2 Folgering H. The hyperventilation syndrome. In: Altose MD, Kawakami Y, eds. *Control of breathing in health and disease*. New York, Basel: Marcel Dekker, 1999: 633–60.
3 Gardner WN. Review: The pathophysiology of hyperventilation disorders. *Chest* 1996;**109**:516–34.
4 Kerr WJ, Gliebe PA, Dalton JW. Physical phenomomena associated with anxiety states: the hyperventilation syndrome. *Calif Western Med* 1938;**48**: 12–6.
5 Lewis BI. Chronic hyperventilation syndrome. *JAMA* 1954;**155**:1204–8.
6 Ames F. The hyperventilation syndrome. *J Mental Sci* 1955;**101**:466–525.
7 Lewis BI. Hyperventilation syndrome: a clinical and physiological evaluation. *Cal Med* 1959;**91**:121–6.
8 Lewis RA, Howell JBL. Definition of the hyperventilation syndrome. *Bull Eur Physiopathol Respir* 1986;**22**:201–5.
9 Stoop A, de Boo T, Lemmens W, *et al*. Hyperventilation syndrome: measurement of objective symptoms and subjective complaints. *Respiration* 1986;**49**:37–44.
10 Folgering H, Colla P. Some anomalies in the control of $Paco_2$ in patients with hyperventilation syndrome. *Bull Eur Physiopathol Respir* 1978;**14**:503–12.
11 Howell JBL. Behavioural breathlessness. *Thorax* 1990;**45**:287–92.
12 Howell JB. The hyperventilation syndrome: a syndrome under threat? *Thorax* 1997;**52**(Suppl 3):S30–4.
13 Hornsveld HK, Garssen B, Fiedeldij Dop MJC, *et al*. Double-blind placebo-controlled study on the hyperventilation provocation test and the validity of the hyperventilation syndrome. *Lancet* 1996;**348**:154–8.
14 Dent R, Yates D, Higenbottam T. Does the hyperventilation syndrome exist. *Thorax* 1983;**38**:223.
15 Demeter SL, Cordasco EM. Hyperventilation syndrome and asthma. *Am J Med* 1986;**81**:989–94.
16 Lum LC. The syndrome of habitual chronic hyperventilation. *Recent Advan Psychosom Med* 1976;**3**:196–229.
17 Gardner WN, Meah MS, Bass C. Controlled study of respiratory responses during prolonged measurement in patients with chronic hyperventilation. *Lancet* 1986;ii:826–30.
18 Hibbert G, Pilsbury D. Hyperventilation in panic attacks. Ambulant monitoring of transcutaneous carbon dioxide. *Br J Psychiatry* 1988;**153**:76–80.
19 Osborne CA, Gardner WN, Varley JS. The range of end-tidal P_{CO_2} measured noninvasively using an ambulatory capnograph in normal subjects. *Eur Respir J* 1997;**10**(Suppl 25):47s.
20 van Dixhoorn J, Duivenvoorden HJ. Efficacy of Nijmegen questionnaire in recognition of the hyperventilation syndrome. *J Psychosom Res* 1985;**29**: 199–206.
21 Hornsveld HK, Garssen B, Dop MJ, *et al*. Double-blind placebo-controlled study of the hyperventilation provocation test and the validity of the hyperventilation syndrome. *Lancet* 1996;**348**:154–8.
22 Bass C, Kartsounis L, Lelliott P. Hyperventilation and its relationship to anxiety and panic. *Integrative Psychiatry* 1987;**5**:274–91.
23 Garssen B, Buikhuisen M, van Dyck R. Hyperventilation and panic attacks. *Am J Psychiatry* 1996;**153**:513–8.
24 Lewis BI. The hyperventilation syndrome. *Ann Intern Med* 1953;**38**:918–27.
25 Bass C, Gardner WN. Respiratory and psychiatric abnormalities in chronic symptomatic hyperventilation. *BMJ* 1985;**290**:1387–90.
26 Lum LC. Hyperventilation syndromes in medicine and psychiatry: a review. *J R Soc Med* 1987;**80**:229–31.
27 Tobin MJ, Chadha TS, Jenouri G, *et al*. Breathing patterns 2. Diseased subjects. *Chest* 1983;**84**:286–94.
28 Damas Mora J, Grant L, Kenyon P, *et al*. Respiratory ventilation and carbon dioxide levels in syndromes of depression. *Br J Psychiatry* 1976;**129**:457–64.
29 Arrindell WA. Dimensional structure and psychopathology correlates of the fear survey schedule (FSS-III) in a phobic population: a factorial definition of agoraphobia. *Behav Res Ther* 1980;**18**:229–42.
30 Hallam RS, Hafner RJ. Fears of phobic patients: factor analysis of self-report data. *Behav Res Ther* 1978;**16**:1–6.
31 Clark DM, Hemsley DR. The effects of hyperventilation: individual variability and its relation to personality. *J Behav Ther Exp Psychiatry* 1982; **13**:41–7.
32 Mahler DA, Harver A, Lentine T, *et al*. Descriptors of breathlessness in cardiorespiratory diseases. *Am J Respir Crit Care Med* 1996;**154**:1357–63.
33 Meek PM, Schwartzenstein RM. American Thoracic Society. Dyspnoea. Mechanisms, assessment and management: a consensus statement. *Am J Respir Crit Care Med* 1999;**159**:321–40.
34 Tobin MJ. Dyspnea. Pathophysiologic basis, clinical presentation, and management. *Arch Intern Med* 1990;**150**:1604–13.
35 McFadden ER, Lyons HA. Arterial blood gas tension in asthma. *N Engl J Med* 1968;**278**:1027–32.
36 Gardner WN, Bass C, Moxham J. Recurrent hyperventilation tetany due to mild asthma. *Respir Med* 1992;**86**:349–51.
37 Saisch SGN, Wessely S, Gardner WN. Patients with acute hyperventilation presenting to an inner-city emergency department. *Chest* 1996;**110**:952–7.