PostScript

LETTERS TO THE EDITOR

If you have a burning desire to respond to a paper published in *Thorax*, why not make use of our "rapid response" option?

Log on to our website (www.thoraxjnl.com), find the paper that interests you, and send your response via email by clicking on the "eLetters" option in the box at the top right hand corner.

Providing it isn't libellous or obscene, it will be posted within seven days. You can retrieve it by clicking on "read eLetters" on our homepage.

The editors will decide as before whether to also publish it in a future paper issue.

Revision of BTS guidelines for treatment of asthma

The paper by Ward *et al*[1] confirms the findings of Laitinen *et al*[2] showing that airways inflammation is present even in patients with mild asthma. This emphasises the importance of using anti-inflammatory drugs (steroids) as soon as the diagnosis of asthma has been confirmed, even in patients thought to have only "mild asthma". Without anti-inflammatory treatment, symptoms resulting from bronchial hyperresponsiveness are never controlled and optimal lung function is never attained. Over time, structural changes (remodelling) occur leading to a progressive decline in lung function[3] and the risk of fixed obstruction (chronic obstructive pulmonary disease).

The present widespread dependence on bronchodilators in the UK may contribute to the fact that we have one of the highest respiratory death rates in Europe.[4] The use of bronchodilators alone as in step 1 of the BTS guidelines should be discouraged, and treatment started at step 2 with regular inhaled corticosteroids to control symptoms and maximise peak flow rate. Bronchodilators should be used only as necessary for breakthrough wheezing. These principles have been used in Finland since 1994 with remarkable success in treating asthma.[5] The new BTS guidelines would do well to follow their example.

George Strube
33 Goffs Park Road, Crawley,
West Sussex RH11 8AX, UK;
Gstrube@btinternet.com

References

1 **Ward C**, Pais M. Bish R, *et al*. Airway inflammation, basement membrane thickening and bronchial hyperresponsiveness in asthma. *Thorax* 2002;**57**:309–16.
2 **Laitinen LA**, Laitinen A, Haatela T. Airway mucosal inflammation even in patients with newly diagnosed asthma. *Am Rev Respir Dis* 1993;**147**:697–704
3 **Haatela T**, Jarvinen M, Kava T, *et al*. Effects of reducing or discontinuing inhaled budesonide in patients with mild asthma. *N Engl J Med* 1994;**331**:700–5
4 **British Thoracic Society**. *The burden of lung disease*. London: British Thoracic Society, 1991.
5 **Haatela T**, Klaukka T, Koskela K, *et al*. Asthma programme in Finland: a community problem needs community solutions. *Thorax* 2001;**56**:806–14.

Authors' reply

We would like to thank Dr Strube for his interest in our recent paper[1] and his stimulating letter which is topical given that the new BTS guidelines on asthma management are currently in preparation.

Our study was an attempt to investigate the interrelationships between airway inflammation, airway structural change (remodelling), lung function, and bronchial hyperreactivity to methacholine in patients with mild to moderate symptomatic asthma. This included a longitudinal limb characterising the temporal effects of inhaled corticosteroid (ICS) treatment using a high proof of concept dosage (750 µg fluticasone propionate twice daily). The physiology, airway inflammation, and remodelling in asthma were found to be interrelated and improved by ICS, but the changes were not temporally concordant, with prolonged treatment necessary for maximal benefit in remodelling and bronchial hyperresponsiveness (BHR). We felt that the results support early and long term intervention with ICS, even in relatively mild asthmatics. This is a view shared by some and, arguably, provides a complementary pathophysiological and mechanistic context to recent clinical studies such as the OPTIMA trial.[2] This year long study found that ICS treatment, even in mild asthmatics who had not previously been treated with corticosteroids, was associated with a significant effect on clinical exacerbations.

In his letter Dr Strube states that "without anti-inflammatory treatment, symptoms resulting from bronchial hyperresponsiveness are never controlled and optimal lung function is never attained". Our interpretation of the current BTS guidelines[3] is that guidelines not only provide for—but also, indeed, indicate—regular ICS medication in such circumstances, with no prescriptive requirement to work linearly through the stages. This is because the outcome of the escalatory stepwise management is to attain control of symptoms and lung function: "The importance of gaining control of asthma is reemphasised . . . by starting treatment at a level likely to achieve this".[3] It also seemed appropriate to consult the pre-publication draft of the 2002 update of the guidelines which have been available at the BTS website for comment.[4] These state at step 2: "The threshold for introduction of inhaled steroids has never been firmly established" and that "patients with lower inhaler requirements (short acting β_2 agonist less than 2–3 times a day) may benefit". Hence, the latest available guidelines further emphasise the importance of anti-inflammatory treatment with scope for early intervention based on clinical judgement. It would appear to us that Dr Strube's valid concerns about the potential of undertreatment in some asthmatics, also apparent in studies such as OPTIMA,[2] is also articulated in the BTS guidelines, but expressed slightly differently.

Our paper is supportive of a further point, adding to work from others,[5] which we feel is potentially substantive, of possible importance to future guideline considerations, and perhaps relates to some of Dr Strube's concerns. The potential paradigm shift is that determining appropriate treatment only by reference to symptoms and lung function, as in current international and draft BTS guidelines, or even against indices of inflammation, may be oversimplistic, with prolonged treatment necessary to benefit airway remodelling reflected by improvement in BHR. It should be recognised that this remains a hypothesis and, pragmatically, it is of interest that the inclusion of BHR as an asthma management tool in the UK is not resourced and is not currently practicable.[6 7]

We also realise that the demanding and detailed preparation of the BTS asthma guidelines has followed a due process, reliant on the available evidence base with "levels of evidence" leading to "grades of recommendation" and, in turn, to "recommended best practice". If appropriate pathophysiological research relevant to the clinical questions does not exist, it cannot be included. We feel that longitudinal data that seek to integrate information on airway inflammation, airway remodelling, lung function, and bronchial hyperreactivity and the effects of treatment are required. Such work, though demanding, is possible and would require multidisciplinary cooperation, dialogue, and appropriate support.

Chris Ward is a European Respiratory Society long term research fellow. The work was also supported by Australian NHMRC and a grant in aid from Glaxo Smith Kline.

C Ward
Lung Biology and Transplant Group, University of Newcastle upon Tyne and The Freeman Hospital, Newcastle upon Tyne, UK
chris.ward@ncl.ac.uk

D Reid, E H Walters
Clinical Sciences,
University of Tasmania, Australia

References

1 **Ward C**, Pais M, Bish R, *et al*. Airway inflammation, basement membrane thickening and bronchial hyperresponsiveness in asthma. *Thorax* 2002;**57**:309–16.
2 **O'Byrne PM**, Barnes PJ, Rodriguez-Roisin R, *et al*. Low dose inhaled budesonide and formoterol in mild persistent asthma. The OPTIMA randomised trial. *Am J Respir Crit Care Med* 2001; **164**: 1392–7.
3 **British Thoracic Society**, National Asthma Campaign, Royal College of Physicians of London, *et al*. The British guidelines on asthma management: 1995 review and position statement. *Thorax* 1997;**52**(Suppl 1):S1–21.
4 http://www.brit-thoracic.org.uk/guide/guidelines.html
5 **Sont JK**, Willems LN, Bel EH, *et al*. Clinical control and histopathologic outcome of asthma when using airway hyperresponsiveness as an additional guide to long-term treatment. The AMPUL Study Group. *Am J Respir Crit Care Med* 1999;**159**:1043–51.
6 **Butterfield AK**, Cushley MJ. Bronchial provocation testing with histamine and methacholine: current UK practice. *Thorax* 2001;**56**(Suppl III):iii66, abstract P68 (cited in Richardson CM, Medford AR, Green RH.

British Thoracic Society Winter Meeting 2001. *Thorax* 2002;**57**:286–8).
7 **Ward RJ**, Ward C, Johns DP, *et al.* European Community Respiratory Health Survey calibration project of dosimeter driving pressures. *Eur Respir J* 2002;**19**:252–6.

Chronic respiratory failure

The recent case report by Smyth and Riley[1] describes an extremely uncommon chronic respiratory failure due to hypoventilation secondary to brainstem stroke, and documents a new treatment option with medroxyprogesterone acetate.

We recently saw two patients also with central hypoventilation resulting in chronic type II respiratory failure and treated both with, among other things, medroxyprogesterone acetate (30 mg twice daily) with good results. The first patient, a 69 year old man with a medical history of glomus caroticum resection due to malignancy with postoperative radiotherapy in 1979, presented to our outpatient clinic with polyglobulia. Arterial blood gas analysis revealed marked hypoxaemia (Pa_{O_2} 4.8 kPa) and hypercapnia (Pa_{CO_2} 6.9 kPa). An intensive search for the cause showed no abnormalities; his lung function indicated only marginal chronic obstructive pulmonary disease (FEV_1/VC 68%) but his hypoxic ventilatory response was markedly decreased and his hypercapnic ventilatory response was absent. The patient was treated with acetazolamide, theophylline, and medroxyprogesterone acetate and his blood gas tensions improved within days to normal values (Pa_{O_2} 10.3 kPa, Pa_{CO_2} 5.1 kPa).

The second patient, a 38 year old woman, was known from birth to have a hypothalamic pituitary gland deficiency with (stable) adipositas (quetelet index 53). She had complained of dizziness, general malaise, and dyspnoea on several occasions before being sent to our department. Arterial blood gas analysis revealed hypoxaemia and marked hypercapnia (Pa_{O_2} 8.0 kPa, Pa_{CO_2} 7.2 kPa). She probably suffers from Pickwick syndrome and formal polysomnographic measurements will be performed shortly, but she also has a complete absence of hypoxic and hypercapnic ventilatory responses. Again, treatment with theophylline, acetazolamide, and medroxyprogesterone acetate normalised her arterial blood gas tensions within days. Furthermore, she now follows an intense weight reduction programme and has lost more than 10 kg in weeks.

Acetazolamide has been shown to augment both the hypoxic and hypercapnic ventilatory response and to decrease Pa_{CO_2} levels significantly in patients with chronic obstructive pulmonary disease (COPD).[2 3] The mechanism of the effect is possibly due to a direct effect on the peripheral chemoreceptors (carotid bodies) as well as to an effect on cerebral blood flow regulation.[2 4]

It has been shown that medroxyprosterone acetate also acts on the peripheral chemoreceptors (directly) as well as on the central chemoreceptors (indirectly) and progesterone receptors in the hypothalamus in cats.[5] This was also found in hypercapnic COPD patients, indicating that medroxyprogesterone acetate acts centrally on the respiratory centres.[3] This supports the use of medroxyprogesterone acetate in central hypoventilation. Furthermore, the combined treatment of acetazolamide and medroxyprogesterone acetate increases ventilation and improves arterial blood gas values—that is, it decreases Pa_{CO_2} to normocapnic values and increases Pa_{O_2} to almost normoxic values in hypercapnic and hypoxic patients with COPD.[3]

In conclusion, we agree with Smyth and Riley that medroxyprogesterone acetate can be used in patients with central hypoventilation disorders.

G P Bootsma, Y Heijdra, M Wagenaar
P O Box 9101, Nijmegen 6500 HB, The Netherlands;
g.bootsma@long.umcn.nl

References
1 **Smyth A**, Riley M. Chronic respiratory failure: an unusual cause and treatment. *Thorax* 2002;**57**:835–6.
2 **Vos PJ**, Folgering HT, de Boo TM, *et al.* Effects of chlormadinone acetate, acetazolamide and oxygen on awake and asleep gas exchange in patients with chronic obstructive pulmonary disease (COPD). *Eur Respir J* 1994;**7**:850–5.
3 **Wagenaar M**, Vos PJ, Heijdra YF, *et al.* Combined treatment with acetazolamide and medroxyprogesterone acetate in COPD patients. *Eur Respir J* 2003 (in press).
4 **Wagenaar M**, Teppema L, Berkenbosch A, *et al.* Effect of low-dose acetazolamide on the ventilatory CO_2 response during hypoxia in the anaesthetized cat. *Eur Respir J* 1998;**12**:1271–7.
5 **Wagenaar M**, Teppema LJ, Berkenbosch A, *et al.* Medroxyprogesterone acetate with acetazolamide stimulates breathing in cats. *Respir Physiol* 2000;**119**:19–29.

Caffeine and exhaled nitric oxide

We read with interest the paper by Bruce *et al*[1] which reported a significant decrease in exhaled nitric oxide (NO) levels 1 hour after caffeine consumption. However, we do not believe that this study has fully clarified the relationship between caffeine consumption and exhaled NO levels.

When ascertaining the normal ranges for offline exhaled NO measurements we observed that some individuals had raised exhaled NO levels after caffeine consumption. To further clarify this effect, exhaled NO (parts per billion (ppb)) levels were measured at baseline and 0.5 and 1 hour after drinking a hot cup of coffee in 18 healthy non-asthmatic adults (five men) aged 17–56 years. Exhaled NO was measured by chemiluminescence (NOA 280, Sievers Instruments Inc, Boulder, CO, USA) using an offline technique in which subjects performed a slow vital capacity manoeuvre into a mylar balloon against a resistance of 5 cm H_2O which corresponded to a flow rate of 50 ml/s. In order to minimise NO contamination from the upper airways and dead space, the first portion of the exhalation was not collected. Median (interquartile range) levels of exhaled NO were significantly increased from baseline values 0.5 hour after caffeine consumption (8.3 (4.5–21.8) ppb *v* 5.4 (3.2–8.5) ppb, difference between medians 2.9 ppb (95% CI 1.4 to 12.4), p=0.007). There was no significant difference between baseline levels and the levels 1 hour after caffeine consumption (4.7 (2.6–6) ppb, p=0.4).

We conclude that levels of exhaled NO are significantly increased compared with baseline values 0.5 hour after caffeine consumption and have returned to baseline levels by 1 hour. The mechanism for this remains unclear. These results may need to be taken into consideration alongside the results of the previously mentioned study[1] when designing studies and interpreting exhaled NO levels in adults.

T J Warke, M D Shields
Department of Child Health, The Queen's University of Belfast, Belfast BT12 6BJ, UK

J Finnegan, M D Shields
Royal Belfast Hospital for Sick Children, Belfast, UK

Correspondence to: Dr M D Shields, Department of Child Health, The Queen's University of Belfast, Belfast BT12 6BJ, UK; m.shields@qub.ac.uk

References
1 **Bruce C**, Yates DH, Thomas PS. Caffeine decreases exhaled nitric oxide. *Thorax* 2002;**57**:361–3.

Authors' reply

We thank Warke *et al* for their interest in our paper and for publicising their results. This disparity in the effect of coffee between the two studies is not easy to explain. Although the sex ratio was similar, our study differed in the following ways: it was measured online, it was placebo controlled, showed that caffeine alone was the active ingredient, and our subjects had less heterogeneity in baseline levels of exhaled NO than those of Warke *et al*.[1] In addition, we used freshly brewed coffee, measuring both the caffeine content and the serum plasma caffeine levels. Warke *et al* did not estimate the caffeine content of their coffee which would have been important, especially as instant coffee can have very low levels.[2] We eschew instant coffee, and this may account for the difference. Whatever the cause of such a difference, it appears that coffee consumption can affect exhaled NO levels at either of the antipodes, perhaps in opposite directions.

P S Thomas, D H Yates, C Bruce
Faculty of Medicine, University of New South Wales, NSW 2052, Australia;
paul.thomas@unsw.edu.au

References
1 **Bruce C**, Yates DH, Thomas PS. Caffeine decreases exhaled nitric oxide. *Thorax* 2002; **57**: 361–3.
2 **Garattini S**. *Caffeine, coffee and health*. New York: Raven Press, 1993.

Morbid obesity and hypersomnolence in several members of an ancient royal family

Recent studies have described an inherited basis for the sleep apnoea syndrome, as suggested by reports of families with multiple affected members.[1] We present evidence indicating that several members of the Ptolemys, the royal family that ruled Egypt from 305 to 30 BC, suffered from obesity and sleep disordered breathing. Most of the information was reported by the Greek philosopher and historian Athenaeos (170–230 BC).

The family's pedigree with all affected members (shaded) is shown in fig 1. Magas I (case 1) was morbidly obese. Athenaeos reported that Magas "was weighted down with monstrous masses of flesh in his last days; in fact he choked himself to death".[2] Ptolemy II (case 2) and his sister Arsinoe III were extremely obese. Ptolemy II was not an energetic man and he disliked physical exertion. Although he lived to the age of 62, he was troubled by ill health throughout most of his life.[3] Ptolemy IV, the Philopater (case 3),

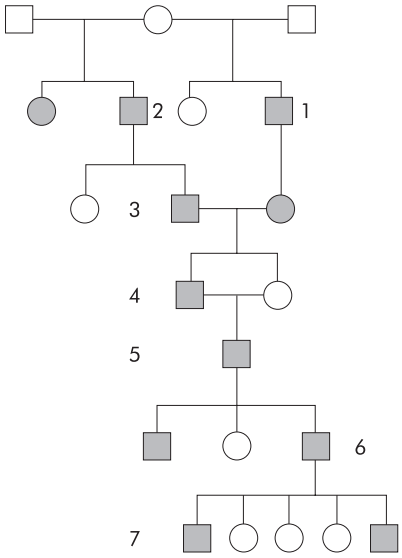

Figure 1 The pedigree of the Ptolemaic dynasty (shading indicates affected members).

was described as licentious even by the standards of his contemporaries. Calvin Wells reported that he was obese and he languished in habitual lethargy, perhaps because of chronic illness.[4] Ptolemy V Epiphanes (case 4) also developed extreme obesity and used to fall asleep during social and political events. Athenaeos wrote: "One day, Aristomenes, his Prime Minister and chief advisor, had the effrontery to nudge the king awake when he dozed off during a diplomatic reception".[2] Ptolemy VI Philometor (case 5) was portrayed by historian Polybios[5] as "good and kind" and "apt to be lethargic and inert". Justinus added that he was extremely obese and sluggish.[3] Ptolemy VIII Evergetes II (case 6) was morbidly obese.[6] Apart from naming him Evergetes (benefactor), Alexandrians labelled him Kakergetes (malefactor) and—because of his obesity and large belly—"Physcon" (large bubble). Ptolemy VIII's belly was so large that its circumference was wider than two arms extended. In order to cover his belly he wore a long tunic that extended down to his ankles with sleeves up to his wrists. Because of his obesity he was unable to walk, apart from an occasion when he went to meet the Roman Consul Skipion, the African.[6] In a poem entitled "Ptolemy VIII Evergetes II or Kakergetes" the Greek poet Constantine Cavafy wrote:

"Most obese, slothful Ptolemy
Physkon, and due to gluttony somnolent
observed: wise poet
your verses are somewhat exaggerated.....
And from obesity heavy as a stone,
and from voracity somnolent
the unalloyed Macedonian
could scarcely keep his eyes open."

Ptolemy X Alexander I (case 7) was so grossly obese that he had a man on either side to help him walk.[7] He was idle, drunken, and extravagant in his lifestyle.

From these descriptions it is clear that obesity was present in all of them and, in at least four of the seven kings, there were reports of daytime somnolence. This dynasty was probably the first reported family with sleep disordered breathing that had a familial predisposition.

A Michalopoulos
Henry Dunant Hospital, Athens, Greece

G Tzelepis
Wayne State University Detroit, MI, USA

S Geroulanos
Onassis Cardiac Center and University of Ioannina, Greece

Correspondence to: Dr A Michalopoulos, Henry Dunant Hospital, Athens, Greece; amichalopoulos@hol.gr

References

1 **Redline S**, Tishler P, Tosteson T, *et al*. The familiar aggregation of obstructive sleep apnea. *Am J Respir Crit Care Med* 1995;**151**:682–7.
2 **Athenaeos**. *The Deipnosophists*. Translated by Gulick CB. Cambridge, Mass: Harvard University Press, 1863: 497.
3 **Strabo**. **XVII**: 1.5.
4 **Calvin Wells**. The Ptolemaic jaw. *Appl Ther* 1967;**9**:768–71.
5 **Polybius**. **XXXIX**: 7.
6 **Posidonius**. Athens, **XII**: 549c.
7 **Davis N**, Krag CM. *The Hellenistic kingdom portrait, coins and history*. London: Thames and Hudson, 1973: 169.

BOOK REVIEW

Clinical Management of Chronic Obstructive Pulmonary Disease

T Similowski, W A Whitelaw, J-P Derenne, Editors. Lung Biology in Health and Disease, Volume 165. New York: Marcel Dekker, 2002. $250.00. ISBN 0 8247 0610 2

According to the publishers, this book is a comprehensive review of recent evaluative and management strategies aimed at practising clinicians. In the past, most of the volumes from this epic series have concentrated on selective aspects of the scientific basis of respiratory disease and therefore attracted the interested specialist. As on previous occasions, the format follows the pattern of a series of reviews written by acknowledged scientific experts. As usual the book is expensive, and is wide in scope with over 90 collaborators and more than 1000 pages. Unlike a textbook, however, the content lacks strong editorial control and it is effectively a collection of individual reviews. The quality of the chapters is therefore inconsistent. Some authors have clearly accepted their brief and produced excellent reviews. In particular, the chapters on radiology, dyspnoea, genetics, and trial methodology are outstanding. However, many other chapters fall short and there is evident "resting on laurels" in some areas. The book does cover many other interesting facets of COPD but clinicians who purchase this book will also be aware of substantial omissions in clinical areas of COPD care that are currently being developed. There is, for example, very little on rehabilitation or the organisation of services. There is nothing at all on nursing intervention, terminal care, travel, or self-management. There is, however, a welcome attempt to cover the global issues surrounding COPD.

This is an expensive book which contains some excellent chapters. However, the overall volume is slightly disappointing and would compare badly with a thoughtfully structured comprehensive textbook. In the past this series has worked well where it examines the leading edge of research. In this instance the more general reader may find better value in a textbook but could still profit from borrowing a copy from the library.

M D L Morgan
mike.morgan@uhl-tr.nhs.uk