CORRESPONDENCE

Caucasian race and lung function: time to revisit the racial groups used in reference values

To the Editors:

We would like to comment upon the term “Caucasian”, used in the article by VANDERVOORDE *et al.* [1], and in general upon the racial groups still employed in the modern lung-function reference values.

The term Caucasian originates from J.F. Blumenbach, a German physiologist and anthropologist, born in Gotha, Germany in 1752. He studied medicine at Jena, Germany, and graduated in 1775 with his MD thesis *De generis humani varietate nativa* [On the Natural Varieties of Mankind] [2].

On the basis of his craniometrical research (analysis of human skulls), he divided humanity, *Homo sapiens*, into five races: 1) Caucasian or white; 2) Mongolian or yellow; 3) Malayan or brown; 4) Negro, Ethiopian or black; and 5) American or red.

He thought that the region of origin of white Europeans lay near the Caucasus Mountains, and so started to refer to them as “Caucasian”. The “fairness” and relative high brows of Caucasians were regarded as physical expressions of a loftier mentality and a more generous spirit. This classification, and the scientific concept of human races, was widely accepted for ~200 yrs.

In the late 20th century, *Homo sapiens* were seen as monotypic, *i.e.* not deserving to be divided into races or subspecies.

Modern science uses genetic methods; thus, the concept of race afforded by these techniques is more or less synonymous to ancestry. Studies of mitochondrial DNA [3], the Y chromosome [4], portions of the X chromosome [5] and many autosomal regions [6] support the notion that modern humans first appeared in eastern Africa and then migrated throughout Africa and into the rest of the world [7].

Modern biological evidence contradicts earlier theories and shows that, genetically, humans are all related. Humanity first split into African and Eurasian/Oceanic branches, which share a common origin. The Eurasian branch split further into the Amerindian and major East Asian branches, the latter splitting still further into the Russian and East Asian branches.

The United States Census Bureau still defines races (Public Law 94–171. Redistricting Data File. Updated every 10 yrs). The categories are sociopolitical constructions and should not be interpreted as being scientific or anthropological in nature.

In the UK, police use a classification based on the ethnic background of British society.

We do not know why the term Caucasian is constantly used in modern lung-function testing, although it is solely a historical term in anthropological science. Some ethnic characterisation might be useful to define a certain population for which reference values are given. For instance, in Finland reference values are given for the original Finnish inhabitants. In many other countries, European values are used. However, white people are not “Caucasians”, and it is definitely time to drop J.F. Blumenbach’s racial categorisation.

K. Kiviranta and T. Haahtela

Skin and Allergy Hospital, Helsinki University Central Hospital, Helsinki, Finland.

REFERENCES

- 1 Vandevorode J, Verbanck S, Schuermans D, Kartounian J, Vincken W. Obstructive and restrictive spirometric patterns: fixed cut-offs for FEV₁/FEV₆ and FEV₆. *Eur Respir J* 2006; 27: 378–383.
- 2 Blumenbach J.F. *De generis humani varietate nativa*. Göttingen, University of Göttingen, 1775.
- 3 Ingman M, Kaessmann H, Paabo S, Gyllenstein U. Mitochondrial genome variation and the origin of modern humans. *Nature* 2000; 408: 708–713.
- 4 Underhill PA, Underhill PA, Shen P, *et al.* Y chromosome sequence variation and the history of human populations. *Nat Genet* 2000; 26: 358–361.
- 5 Kaessmann H, Heissig F, von Haeseler A, Paabo S. DNA sequence variation in a non-coding region of low recombination on the human X chromosome. *Nat Genet* 1999; 22: 78–81.
- 6 Harpending H, Rogers A. Genetic perspectives on human origins and differentiation. *Annu Rev Genomics Hum Genet* 2000; 1: 361–385.
- 7 Relethford J. *The Human Species: an Introduction to Biological Anthropology*. 5th Edn. New York, McGraw-Hill, 2003.

DOI: 10.1183/09031936.00097906

Components of airway disease

To the Editors:

“What we think we know already often prevents us from learning”
(Claude Bernard)

I endorse the view of HARGREAVE and PARAMESWARAN [1] that the components of airway disease, inflammation (bronchitis), reversibility (asthma), and chronic airflow limitation (chronic obstructive pulmonary disease (COPD)), are not “mutually exclusive and [...] commonly occur together.” I would like to mention further evidence in support of their position.

I would add the longitudinal (natural history) perspectives of the primary-care practitioner [2] and the epidemiologist [3]. Clinical reports from primary care document that acute bronchitis can precede asthma, which then develops into severe COPD over a few years [4] to decades [2]. Perhaps the best longitudinal evidence derives from a cluster-randomised, population-based 20-yr prospective study finding that asthma was the strongest risk factor for subsequent COPD, both in relative (hazard ratio (HR)=12.5) and absolute (attributable risk (AR)=18.5%) terms compared with tobacco smoking (HR=2.9 for current smoking, AR=6.7% for ever-smoking) [3].

The dogma that asthma and COPD are different diseases (and therefore should be studied separately) appears to have been derived from the mainly cross-sectional perspectives of academic referral lung specialists (adult and paediatric allergists, pulmonologists) who for the most part have not had the opportunity to observe the natural history of lung

disease over a patient's lifetime. I can think of no better explanation for a recent statement by a prominent leader in lung research: “Chronic obstructive pulmonary disease is probably the only chronic disease for which the finger of blame can be pointed at a single risk factor – tobacco smoking” [5].

D.L. Hahn

Dean Medical Center, Madison, Wisconsin, USA.

REFERENCES

- 1 Hargreave FE, Parameswaran K. Asthma, COPD and bronchitis are just components of airway disease. *Eur Respir J* 2006; 28: 264–267.
- 2 Hahn DL. Evaluation and management of acute bronchitis. In: Hueston WJ, ed. 20 Common Problems in Respiratory Disorders. New York, McGraw-Hill, 2002; pp. 141–153.
- 3 Silva GE, Sherrill DL, Guerra S, Barbee RA. Asthma as a risk factor for COPD in a longitudinal study. *Chest* 2004; 126: 59–65.
- 4 Hahn D, Bukstein D, Luskin A, Zeitz H. Evidence for *Chlamydia pneumoniae* infection in steroid-dependent asthma. *Ann Allergy Asthma Immunol* 1998; 80: 45–49.
- 5 Hurd SS, Lenfant C. COPD: good lung health is the key. *Lancet* 2005; 366: 1832–1834.

DOI: 10.1183/09031936.00101806

Three new cases of apparent occupational asthma in swine confinement facility employees

To the Editors:

In a previous issue of the *European Respiratory Journal*, DOSMAN *et al.* [1] reported on four cases of occupational asthma in newly employed workers in the large, recently developed, swine production facilities in Saskatchewan (Canada). All were full-time employees and all developed symptoms suggestive of asthma within a short time of commencing employment. None of the cases had a history of asthma, allergy symptoms or previous exposure to indoor air contaminants of swine confinement facilities. Work in swine buildings has been associated with respiratory symptoms, reductions in mean and across-shift lung function values [2], and increased bronchial responsiveness [3, 4]. Asthma has been reported in swine workers, but this has typically occurred in workers with lengthy employment [5, 6].

Cases 1–3 in our initial report showed some reaction to skin-prick allergy tests. While forced expiratory volume in one

second (FEV₁) for case 1 was relatively stable over time, provocation challenge causing a 20% fall in FEV₁ (PC₂₀) was reduced for several months following resignation from the swine barn. Case 1 also experienced symptoms requiring removal from the barn during a re-entry challenge. It was speculated that these cases might exhibit a type of occupational asthma, described by BROOKS *et al.* [7], as “not-so-sudden onset” nonallergic asthma resulting from irritant exposure over a number of months.

Since the initial study [1], we have encountered three additional cases that have been labelled as cases 5, 6 and 7 (table 1). In contrast to the previous four cases, the cases reported herein are all male. Again, none of the cases had a history of asthma or wheeze and none had reported previous regular occupational exposures in a swine confinement facility. Each of the cases developed symptoms within weeks to months of commencing employment and each has had continued sensitivity to exposures in a swine barn.

TABLE 1 Age, employment and health-history information of the three new cases

	Case 5	Case 6	Case 7
Age yrs	48	47	30
Occupational exposure time months	21	10	12
Time from onset of work to onset of symptoms months	6	Shortly after commencing work	<1 yr
FEV ₁ L	2.47 [#]	3.36 [†]	Not completed
PC ₂₀ mg·mL ⁻¹	Not calculable [#]	1.95 ⁺	Not completed
Wheal size mm [§]	Shellfish (1–2) House dust (1–2) Grain dust (>3)	House dust mite (1–2)	Not completed
Smoking status	Ex-smoker of 11 yrs	Ex-smoker of 1 yr	Unknown

FEV₁: forced expiratory volume in one second; PC₂₀: provocative concentration causing a 20% fall in FEV₁. Cases described herein are designated as cases 5, 6, 7 to continue with cases 1, 2, 3 and 4 from our previous case series [1]. [#]: June 2004; [†]: January 2005; ⁺: May 2005; [§]: notable skin-prick test reactivity.

Case 5 was a 48-yr-old ex-smoker who began working in the swine industry in late 2002. Within 6 months of employment, he began to have respiratory symptoms, which eventually led to a severe episode several months after commencement of work. Pulmonary function showed evidence of mild airways obstruction, but a post-bronchodilator test was not conclusive. He underwent methacholine challenge testing where FEV₁ decreased by 18% at 4 mg·mL⁻¹, compatible with a mild increase in airways responsiveness. However, overall PC₂₀ was not calculable because, at 8 mg·mL⁻¹, the decrease in FEV₁ was 12%. He exhibited mild skin-prick test reactivity to shellfish and house dust, along with strong reactivity to grain dust. He improved while away from work but continues to work part time at the swine facility.

Case 6 was a 47-yr-old ex-smoker. He began working in the swine barns in early 2003. Shortly after commencing work, he developed respiratory symptoms, which improved away from work. After 1 yr, he resigned from work. FEV₁ at the clinic was 3.36 L while PC₂₀ was 1.95 mg·mL⁻¹. He had a mild skin-prick test reaction to house dust mite. Since resigning, he continues to be bothered by cough and wheeze, as well as continuing to use fluticasone propionate *b.i.d.* (GlaxoWellcome Inc., Mississauga, ON, Canada).

We have less information for case 7, a 30-yr old who had spent 1 yr working in a swine barn ~10 yrs ago. He developed cough and wheeze shortly after commencing, which continued after quitting the barn. Allergy skin-prick testing and pulmonary function testing was not completed.

The addition of these new cases to the previous case series [1] leads us to believe that the extent of this condition may be more common than originally suspected, and that some newly employed workers in swine confinement facilities are at risk of developing a form of asthma identified as “not-so-sudden onset asthma” [7]. Pre-employment assessments and frequent early employment monitoring of workers may be important tools in addressing early respiratory effects in workers in this industry. Finally, we believe that studying this population would provide further insight into the mechanisms by which occupational asthma occurs among workers in these facilities.

J.A. Dosman^{*#}, J.A. Lawson, S.P. Kirychuk, Y. Cormier[†], J. Biem and N. Koehncke^{*}

^{*}Institute of Agricultural Rural and Environmental Health (IAREH), and [#]Dept of Medicine, University of Saskatchewan, Saskatoon, Saskatchewan and [†]Hopital and Universite Laval, St Foy, Quebec, Canada.

REFERENCES

- 1 Dosman JA, Lawson JA, Kirychuk S, Cormier Y, Biem J, Koehncke N. Occupational asthma in newly employed workers in intensive swine confinement facilities. *Eur Respir J* 2004; 24: 698–702.
- 2 Zejda J, Hurst T, Rhodes C, Barber E, McDuffie H, Dosman J. Respiratory health of swine producers. Focus on young workers. *Chest* 1993; 103: 702–709.
- 3 Malmberg P, Larsson K. Acute exposure to swine dust causes bronchial hyperresponsiveness in healthy subjects. *Eur Respir J* 1993; 6: 400–404.
- 4 Bessette L, Boulet L, Tremblay G, Cormier Y. Bronchial responsiveness to methacholine in swine confinement building workers. *Arch Environ Health* 1993; 48: 73–77.
- 5 Donham KJ. The concentration of swine production. Effects on swine health, productivity, human health, and the environment. *Vet Clin North Am Food Anim Pract* 2000; 16: 559–597.
- 6 Holness DL, Nethercott JR. What actually happens to the farmers? Clinical results of a follow-up study of hog confinement workers. In: McDuffie H, Dosman J, Semchuk KM, Olenchok SA, Senthilselvan A, eds. *Agricultural Health and Safety. Workplace, Environment, Sustainability*. Boca Raton, CRC Lewis Publishers, 1995; pp. 44–52.
- 7 Brooks SM, Hammad Y, Richards I, Giovenco-Barbas J, Jenkins K. The spectrum of irritant-induced asthma: sudden and not-so-sudden onset and the role of allergy. *Chest* 1998; 113: 42–49.

DOI: 10.1183/09031936.00096006

The specificity of interferon- γ -based blood tests in the identification of latent tuberculosis infection

To the Editors:

I have read with interest several papers describing the use of cellular interferon (IFN)- γ -based blood tests, including the editorial by DAVIES and DROBNIOWSKI [1]. Whilst reviewing the study by LEE *et al.* [2], DAVIES and DROBNIOWSKI [1] indicate that the T-SPOT.TB assay has higher sensitivity than QuantiFERON-TB Gold, but that the QuantiFERON-TB Gold may have better specificity.

I do not agree with this tentative conclusion as the study by LEE *et al.* [2] does not report the true specificity of the two tests, as the control group of 15- and 16-yr-old students used to examine the specificity of the assays, although healthy, had a defined risk of existing tuberculosis (TB) infection. This was acknowledged by LEE *et al.* [2] in the discussion section of their study as follows.

"The present study has several limitations. First, some of the low-risk subjects may actually have been infected with MTB [*Mycobacterium tuberculosis*] and this might lead to an underestimation of the specificity of the IFN- γ assays. According to a South Korean national survey conducted in 1995, the MTB infection rate was ~15% in 15 yr olds, but rose dramatically to about 52–60% in 18–33 yr olds. Accordingly, 15–16-yr-old students were selected as a low-risk group because they have a lower chance of being infected with MTB."

T-SPOT.TB reported a 15.3% infection rate in this healthy control group *versus* 8.4% for QuantiFERON-TB Gold. In the absence of a true gold standard for latent TB infection (LTBI), it is impossible to definitely resolve whether the discrepancy between the T-SPOT.TB and QuantiFERON-TB Gold results in this group was due to the higher specificity of QuantiFERON-TB Gold or the higher sensitivity of T-SPOT.TB. Nonetheless, the available data suggest that it is more likely that the discrepancy is due to the higher sensitivity of the T-SPOT.TB test rather than the higher specificity of QuantiFERON-TB Gold, for the following reasons.

First, LEE *et al.* [2] demonstrated that T-SPOT.TB has higher sensitivity than QuantiFERON-TB Gold in the diagnosis of culture-confirmed active TB disease, and this finding has also been reported by GOLETTI *et al.* [3]. Whilst active TB disease is clearly not the same as LTBI, it might be hypothesised that this difference in sensitivity is also true in LTBI. In the study by FERRARA *et al.* [4], this hypothesis was suggested by head-to-head evidence of the higher sensitivity of T-SPOT.TB over QuantiFERON-TB Gold in LTBI.

Secondly, both QuantiFERON-TB Gold and T-SPOT.TB use the same antigens (ESAT-6 and CFP-10). Therefore, it is hard to argue that T-SPOT.TB is any less specific for MTB infection than QuantiFERON-TB Gold, as both examine the cellular immune response to identical antigens. Furthermore, to my knowledge, there are no published data showing higher specificity for the QuantiFERON-TB Gold assay over the T-SPOT.TB assay. Additionally, four previous studies [5–8]

investigating the specificity of the T-SPOT.TB test (using pre-approval versions of the test) have demonstrated a specificity of 100%, where truly low-risk controls in a low-endemicity country (UK) were studied.

Finally, Lee *et al.* [2] predicted the prevalence of tuberculosis infection in the healthy control cohort to be 15%. The fact that T-SPOT.TB reported a rate of infection of 15.3% provides further evidence that T-SPOT.TB was detecting true latent tuberculosis infection. It is felt that, on the basis of the above arguments, the lower rate of detection by QuantiFERON-TB Gold is more likely to be attributed to the lower sensitivity of this assay, rather than its higher specificity.

C. Granger

Oxford Immunotec, 91 Milton Park, Abingdon, OX14 4RY, UK.

STATEMENT OF INTEREST

C. Granger is the director of professional relations of Oxford Immunotec, which manufactures the T-SPOT.TB assay.

REFERENCES

- 1 Davies PDO, Drobniewski F. The use of interferon- γ -based blood tests for the detection of latent tuberculosis infection. *Eur Respir J* 2006; 28: 1–3.
- 2 Lee JY, Choi HJ, Park I-N, *et al.* Comparison of two commercial interferon- γ assays for diagnosing *Mycobacterium tuberculosis* infection. *Eur Respir J* 2006; 28: 24–30.
- 3 Goletti D, Carrara D, Vincenti D, *et al.* Accuracy of an immune diagnostic assay based on RD1 selected epitopes for active tuberculosis in a clinical setting: a pilot study. *Clin Microbiol Infect* 2006; 12: 544–550.
- 4 Ferrara G, Losi M, D'Amico R, *et al.* Use in routine clinical practice of two commercial blood tests for diagnosis of infection with *Mycobacterium tuberculosis*: a prospective study. *Lancet* 2006; 367: 1328–1334.
- 5 Lalvani A, Pathan AA, McShane H, *et al.* Rapid detection of *Mycobacterium tuberculosis* infection by enumeration of antigen-specific T cells. *Am J Respir Crit Care Med* 2001; 163: 824–828.
- 6 Pathan A, Wilkinson K, Klenerman P, *et al.* Direct *ex vivo* analysis of antigen-specific IFN- γ secreting CD4 T cells in *Mycobacterium tuberculosis*-infected individuals: associations with clinical disease state and effect of treatment. *J Immunol* 2001; 167: 5217–5225.
- 7 Lalvani A, Nagvenkar P, Udawadia Z, *et al.* Enumeration of T cells specific for RD1-encoded antigens suggests a high prevalence of latent *Mycobacterium tuberculosis* infection in healthy urban Indians. *J Infect Dis* 2001; 183: 469–477.
- 8 Chapman A, Munkata M, Wilkinson K, *et al.* Rapid detection of active and latent tuberculosis infection in HIV-positive individuals by enumeration of *Mycobacterium tuberculosis*-specific T cells. *AIDS* 2002; 16: 2285–2293.

DOI: 10.1183/09031936.00107506

Lymphangioliomyomatosis

To the Editors:

We read with great interest the systematic review by JOHNSON [1], regarding lymphangioliomyomatosis (LAM), which concluded that the key to the development of new treatment strategies is the understanding of the cell-type of origin and the signalling methods used to target LAM cells.

Tuberous sclerosis complex-related tumours, such as LAM, exhibit uncontrolled activation of the protein mammalian target of rapamycin (mTOR). Much hope lies in the clinical use of rapamycin as a regulator of the mTOR. Indeed, recent data in animal models and *in vivo* primary cultures of human LAM cells indicate that rapamycin does prevent cell proliferation [2–4]. However, its effect on LAM cell migration is minor [3]. More specifically, LAM cell migration, which correlates with disease severity, is regulated by the TSC2 gene product, tuberlin, through the activation of RhoA GTPase activity [3]. This implies that a combination of rapamycin and a RhoA modulator should be used in order to restrict the disease progression. Additionally, rapamycin was not found to be effective when administered before the onset of the disease, and evidence of drug resistance was found after prolonged therapy in a mouse model [4]. This also implies that rapamycin may not be the panacea for LAM, given the fact that alternative therapies have to be found.

Furthermore, the oestrogen receptors are expressed aberrantly in the lungs of LAM patients [5]. A hypothesis regarding the reason for the finding that hormonal therapy with tamoxifen or progesterone appears to have mixed success is the fact that both drugs, especially tamoxifen, act as oestrogen agonists [6]. Moreover, tamoxifen-resistant LAM cells may occur. mTOR is activated as a result of growth factor signalling through phosphatidylinositol 3-kinase and the protein kinase AKT. In breast cancer cells with aberrant AKT activity, inhibition of mTOR by rapamycin restores tamoxifen response [7]. In human ovarian and breast cancer cells, combined treatment with mTOR inhibitor and tamoxifen *in vitro* exerts additive antitumoural effects [8]. According to the above, a combination of rapamycin and tamoxifen should enhance the results of the treatment. Additionally, in *in vitro* models of breast cancer, dual inhibition of mTOR and oestrogen receptor signalling was found to induce cell death [9].

Another issue, not as significant as the above but still important, is the fact that hormonal therapy may be implicated in the occurrence of chylothorax, since it has been speculated that steroids may increase fluid accumulation and prevent the transport of fluid out of the pleural space [10].

S. Zarogiannis*, C. Hatzoglou*, P.A. Molyvdas* and K. Gourgoulialis[#]

Depts of *Physiology, and [#]Respiratory Medicine, Medical School of Larissa, University of Thessaly, Larissa, Greece.

REFERENCES

- 1 Johnson SR. Lymphangioliomyomatosis. *Eur Respir J* 2006; 27: 1056–1065.
- 2 Goncharova EA, Goncharov DA, Eszterhas AJ, *et al*. Tuberlin regulates p70 S6 kinase activation and ribosomal protein S6 phosphorylation. A role for the TSC2 tumor suppressor gene in pulmonary lymphangioliomyomatosis (LAM). *J Biol Chem* 2002; 277: 30958–30967.
- 3 Goncharova EA, Goncharov DA, Lim PN, Noonan DS, Krymskaya VP. Modulation of cell migration and invasiveness by tumor suppressor TSC2 in lymphangioliomyomatosis. *Am J Respir Cell Mol Biol* 2006; 34: 473–480.
- 4 Kenerson H, Dundon TA, Yeung RS. Effects of rapamycin in the Eker rat model of tuberous sclerosis complex. *Pediatr Res* 2005; 57: 67–75.
- 5 Finlay G. The LAM cell: what is it, where does it come from, and why does it grow? *Am J Physiol Lung Cell Mol Physiol* 2004; 286: L690–L693.
- 6 Yu J, Astrinidis A, Howard S, Henske EP. Estradiol and tamoxifen stimulate LAM-associated angiomyolipoma cell growth and activate both genomic and nongenomic signaling pathways. *Am J Physiol Lung Cell Mol Physiol* 2004; 286: L694–L700.
- 7 de Graffenried LA, Friedrichs WE, Russell DH, *et al*. Inhibition of mTOR activity restores tamoxifen response in breast cancer cells with aberrant Akt activity. *Clin Cancer Res* 2004; 10: 8059–8067.
- 8 Treeck O, Wackwitz B, Haus U, Ortmann O. Effects of a combined treatment with mTOR inhibitor RAD001 and tamoxifen *in vitro* on growth and apoptosis of human cancer cells. *Gynecol Oncol* 2006; 102: 292–299.
- 9 Boulay A, Rudloff J, Ye J, *et al*. Dual inhibition of mTOR and estrogen receptor signaling *in vitro* induces cell death in models of breast cancer. *Clin Cancer Res* 2005; 11: 5319–5328.
- 10 Hatzoglou C, Gourgoulialis KI, Hatzoglou A, Castanas E, Molyvdas PA. Rapid effects of 17 β -estradiol and progesterone on sheep visceral and parietal pleurae *via* a nitric oxide pathway. *J Appl Physiol* 2002; 93: 752–758.

DOI: 10.1183/09031936.00099606

Cost-optimisation of screening for latent tuberculosis in close contacts

To the Editors:

We read with great interest the article by DIEL *et al.* [1] in a recent issue of the *European Respiratory Journal*. We believe that the authors have been successful in modelling and analysing the cost of alternatives for tuberculosis (TB) contact investigation. Nevertheless, we have some hesitation regarding a simplifying assumption that the authors have made in the follow-up of subjects after a positive screening test.

According to the contact investigation protocol modelled by DIEL *et al.* [1], close contacts with positive initial screening should undergo a chest radiograph, and those who do not receive treatment for latent infection may be followed up with two additional chest radiographs. A probability of 1% was assigned for suspicion of active TB in the follow-up of a positive screening test in all screening strategies. Several studies suggest that the sensitivity of QuantiFERON-TB Gold (QFT-G) in detecting latent or active TB is similar to (if not higher than) that of the tuberculin skin test (TST) [2–4], and its specificity is significantly higher, as QFT-G is not affected by previous bacille Calmette–Guérin (BCG) vaccination [2, 5]. This implies that QFT-G must have a remarkably higher positive predictive value in the presence of a high rate of previous BCG vaccination, and therefore that a higher number of subjects should undergo further work-up for the detection of TB after a positive QFT-G test. In the data provided by the authors, the number of positive TST results is 4.4 times as high as the number of positive QFT-G results (137 *versus* 31). Assuming that QFT-G and TST will result in the same rate of active case detection in the long run (an assumption upon which the cost minimisation analysis is justified), the positive predictive value of QFT-G for detection of active TB must be at least quadruple that of TST. The positive predictive value of the combined tests in other branches of the model should even be higher. This is in contrast with the authors' approach in assigning similar probabilities of suspecting TB in all branches of the decision tree.

Fortunately, since subjects suspected of having tuberculosis exit the model immediately, this is a conservative assumption in favour of the tuberculin skin test. Therefore, the overall conclusion of the study that QuantiFERON-TB Gold is less costly than the tuberculin skin test remains valid. Nevertheless, the calculated level of cost savings and also the rank order of the alternative strategies might be affected.

M. Sadatsafavi and M. Najafzadeh

Centre for Clinical Epidemiology and Evaluation, Vancouver General Hospital, Vancouver, Canada.

REFERENCES

- 1 Diel R, Nienhaus A, Lange C, Schaberg T. Cost-optimisation of screening for latent tuberculosis in close contacts. *Eur Respir J* 2006; 28: 35–44.
- 2 Mori T, Sakatani M, Yamagishi F, *et al.* Specific detection of tuberculosis infection: an interferon- γ -based assay using new antigens. *Am J Respir Crit Care Med* 2004; 170: 59–64.
- 3 Ferrara G, Losi M, Meacci M, *et al.* Routine hospital use of a new commercial whole blood interferon- γ assay for the diagnosis of tuberculosis infection. *Am J Respir Crit Care Med* 2005; 172: 631–635.
- 4 Ferrara G, Losi M, D'Amico R, *et al.* Use in routine clinical practice of two commercial blood tests for diagnosis of infection with *Mycobacterium tuberculosis*: a prospective study. *Lancet* 2006; 367: 1328–1334.
- 5 Kang YA, Lee HW, Yoon HI, *et al.* Discrepancy between the tuberculin skin test and the whole-blood interferon γ assay for the diagnosis of latent tuberculosis infection in an intermediate tuberculosis-burden country. *JAMA* 2005; 293: 2756–2761.

DOI: 10.1183/09031936.00094906

From the authors:

I would like to thank M. Sadatsafavi and M. Najafzadeh for raising an interesting concern. First, our cost minimisation analysis [1] was not a cost-effectiveness analysis between the consequences of isoniazid treatment and nontreatment over several decades; it only considered costs that accumulated over the 2 yrs following the last possible moment of exposure of the contact person to the infectious source case.

Secondly, we had to include new tuberculosis (TB) cases that were typically identified in large contact studies in our model. These generally equate to ~1% of the contact persons investigated, and, because they do not result in further investigation costs, must be shown to drop out of the cohort under suspicion. In our model, we distributed this “dropping out” over the entire 2-yr period. The crucial point, however, is simple: previous molecular–epidemiological studies [2–4] have shown that two types of TB cases may be expected in contact investigations of the kind we studied. On the one hand, there are TB cases with no epidemiological connection to the source case in question, *i.e.* they must have been infected by another source case at the same time or even many years prior to their diagnosis. On the other hand, there are secondary cases (re-activations) of infections that are actually acquired from the source case. Only these cases could be directly assigned to contacts that had previously tested positive using the tuberculin skin test or QuantiFERON-gold. Depending on the risk profile of the source case and its contacts, the proportions of the two types will vary and cannot be predicted.

Thus, although we found a number of positive tuberculin skin tests 4.4 times higher than positive QuantiFERON-gold results, we currently do not know whether the positive predictive value of the QuantiFERON-gold is really higher

than that of a tuberculin skin test not confounded by Bacille Calmette–Guérin vaccination or nontuberculous mycobacteria. This must be determined by ongoing prospective restriction fragment length polymorphism studies observing the clinical course of QuantiFERON-gold-positive contact persons. These use “clustering” with the source case and observe who becomes infected with the disease. As QuantiFERON-gold is only just being implemented for routine use in western industrial countries, this question is not sufficiently answered. In our view, it would be speculative to distinguish between the predictive values of the two testing procedures. Therefore, we assigned a uniform probability of re-activation to manifest tuberculosis disease to subjects testing positive to either the tuberculin skin test or the QuantiFERON-gold assay.

R. Diel

Heinrich-Heine-University, Postfach 101007, Düsseldorf 40001, Germany.

REFERENCES

- 1 Diel R, Nienhaw A, Lange C, Schaberg T. Cost-optimisation of screening for latent tuberculosis in close contacts. *Eur Respir J* 2006; 28: 35–44.
- 2 Behr A, Hopewell PC, Paz EA, Kamamura LM, Schecter GF, Small PM. Predictive value of contact investigation for identifying recent transmission of *Mycobacterium tuberculosis*. *Am J Respir Crit Care Med* 1998; 158: 465–469.
- 3 Diel R, Schneider S, Meywald-Walter K, Ruf CM, Rüscher-Gerdes S, Niemann S. Epidemiology of tuberculosis in Hamburg, Germany: long-term population-based analysis applying classical and molecular epidemiological techniques. *J Clin Microbiol* 2002; 40: 532–539.
- 4 Diel R, Meywald-Walter K, Gottschalk R, Rüscher-Gerdes S, Niemann S. Ongoing outbreak of tuberculosis in a low-incidence community: a molecular-epidemiological evaluation. *Int J Tuberc Lung Dis* 2004; 8: 855–861.

DOI: 10.1183/09031936.00113706

Therapy of exophytic bronchial tumorous stenosis by flexible cryoprobe

To the Editors:

We read with interest the article by VERGNON *et al.* [1] in the *European Respiratory Journal*, about the place of cryotherapy, brachytherapy and photodynamic therapy in the therapeutic bronchoscopy of lung cancers. The article describes indications and limitations of cryotherapy. In the opinion of VERGNON *et al.* [1], the effect of cryotherapy is delayed and is, therefore, not useful for the immediate debulking of an obstructive endoluminal bronchial tumour. For these cases, VERGNON *et al.* [1] advise coring of the tumour with the rigid bronchoscope and subsequent laser therapy or electrocautery. The indication for cryotherapy in this setting is seen as a treatment option for any remaining infiltrative parts of the tumour into the bronchial wall, but not as a treatment option of first choice to remove the main part of an exophytic tumour.

In our clinic, we have positive experience in a large number of patients with the application of cryotherapy for the immediate treatment of acute dyspnoea in patients with obstructive malignant bronchial tumours. We use the cryorecanalisation technique with the rigid bronchoscope under general anaesthesia, as well as with a flexible technique during local anaesthesia and sedation. The commercially available flexible cryoprobe (ERBE, Tübingen, Germany) we use is 780 mm in length and 2.3 mm in diameter. The probe's tip is cooled to -89.5°C by sudden gas decompression (nitrous oxide) in the probe's head. The cryoprobe is a closed system, which can be re-sterilised and re-used. In many cases, we use the cryorecanalisation method in combination with argon plasma coagulation for a more immediate treatment of diffuse tumour bleeding after coring with the rigid bronchoscope.

We apply the following technique: 1) the flexible cryoprobe is introduced *via* a flexible bronchoscope in combination with an Ikeda tubus or a rigid bronchoscope; 2) the tip of the cryoprobe is pushed into the protruding exophytic tumour mass and freezing is started for ≤ 5 s with a footpad; 3) the cryoprobe, including the flexible bronchoscope, is abruptly mechanically removed, a tumour mass of 3–5 mm is frozen at the tip of the cryoprobe and can easily be extracted; 4) rapid thawing is induced in a water bath for ≤ 5 s; and 5) the procedure is repeated until the tumour mass has been extracted and the target bronchus is re-opened. If necessary, subsequent stent implantation is performed in the same session without any problems. With this technique, we have seen no severe bleedings if coagulation parameters were within the normal range. Overall, we have a very low complication rate. Severe bleeding during re-canalisation with the cryoprobe is very rare, we have never seen perforations, and the primary success rate of re-canalisation is very high ($>90\%$), even in long-distance stenoses, and in our experience comparable to that of laser beam or electrocautery. The feasibility of this method for the immediate management of acute airway obstruction has already been published [2]. In contrast to the cryotherapy technique described by VERGNON *et al.* [1], which requires a second bronchoscopy after 8–10 days for the removal of necrotic tissue, a second-look bronchoscopy is not mandatory with our technique.

In addition, the specimens obtained by cryorecanalisation for diagnostic purposes are much larger and of excellent tissue quality, without squeezing artefacts, compared with specimens extracted using forceps. In a study with 60 patients, comparing

specimen quality in forceps biopsy and cryobiopsy, we found the cryobiopsy technique to have a superior diagnostic quality [3].

In summary, the use of the flexible cryoprobe for mechanical removal of obstructive exophytic bronchial tumours is a good alternative to laser therapy or electrocautery in planned bronchoscopic interventions as well as in patients with acute dyspnoea and tumorous bronchial obstruction. Cryorecanalisation is safe, cheap and readily applicable with an immediate success and relief of symptoms.

C. Schumann, C. Kropf, T. Wibmer, T. Merk and S. Krüger
Dept of Internal Medicine II, University of Ulm, Ulm, Germany.

REFERENCES

- 1 Vergnon JM, Huber RM, Moghissi K. Place of cryotherapy, brachytherapy and photodynamic therapy in therapeutic bronchoscopy of lung cancers. *Eur Respir J* 2006; 28: 200–218.
- 2 Hetzel M, Hetzel J, Schumann C, Marx N, Babiak A. Cryorecanalization: a new approach for the immediate management of acute airway obstruction. *J Thorac Cardiovasc Surg* 2004; 127: 1427–1431.
- 3 Schumann C, Mattfeldt T, Hetzel M, Hetzel J, Lepper P. Improving the diagnostic yield of endobronchial biopsies by flexible cryoprobe in lung cancer - comparison of forceps and cryoprobe technique. *Eur Respir J* 2004; 24: Suppl. 48, 491s.

DOI: 10.1183/09031936.00095106

From the authors:

I have read with great attention and interest the letter and comments by C. Schumann and co-workers about our review on cryotherapy, brachytherapy and photodynamic therapy, which was recently published in the *European Respiratory Journal* [1].

All studies into the relationships between cold and tissues underline the delayed action of cold: delayed vascular thrombosis then delayed necrosis. This point explains the delayed action of cryotherapy. The unique described immediate interaction between cold and tissue is the glue effect, which allows the extraction of foreign bodies. C. Schumann and co-workers have presented good studies on the use of newly designed flexible cryoprobes for obtaining large biopsies during flexible bronchoscopies. One of these studies was

indicated in our paper [2]. HETZEL *et al.* [3] also used this technique to perform immediate re-canalisation in cases of bulky tumours. We know this technique and its results well, and have shared discussion with the authors on several occasions about their experiences. However, it is true that in our paper we did not speak about this experience, and we would like to thank C. Schumann and co-workers for detailing their technique.

In our paper, these results were not reported for two main reasons. First, the aim of the paper was to review the methods of therapeutic endoscopy of delayed action, which explains why immediate action of these methods, including cryotherapy, was not detailed. The second reason is that the technique proposed by C. Schumann and co-workers is extremely original. In fact, to my knowledge, this method is not currently being used around the world. Therefore, we must consider that this new technique is in progress and further reports are needed. Haemorrhagic risks should be carefully analysed. Vessel thrombosis induced by cold is delayed by ~8 h. With immediate cryo-extraction proposed in this new technique, there is no possible coagulation and this method is closed to simple mechanical resection. Mechanical resection is widely used with a rigid bronchoscope where bleeding is easily controlled, but, with a flexible bronchoscope, this point could be crucial.

I hope that further papers by C. Schumann and co-workers will quickly confirm these preliminary results and give a new impulse for utilising cryotherapy.

J-M. Vergnon

Dept of Chest Diseases and Thoracic Oncology, University Hospital of Saint Etienne, Hôpital Nord, St Etienne, France.

REFERENCES

- 1 Vergnon JM, Huber RM, Moghissi K. Place of cryotherapy brachytherapy and photodynamic therapy in therapeutic bronchoscopy of lung cancers. *Eur Respir J* 2006; 28: 200–218.
- 2 Schumann C, Mattfeldt T, Hetzel M, Hetzel J, Lepper PM. Improving the diagnostic yield of endobronchial biopsies by flexible cryoprobe in lung cancer-comparison of forceps and cryoprobe technique. *Eur Respir J* 2004; 24: Suppl. 48, S491.
- 3 Hetzel M, Hetzel J, Schumann C, Marx N, Babiak A. Cryorecanalization: a new approach for a immediate management of acute airway obstruction. *J Thorac Cardiovasc Surg* 2004; 127: 1427–1431.

DOI: 10.1183/09031936.00114106

Is forced expiratory volume in six seconds a valid alternative to forced vital capacity?

To the Editors:

We have read with interest the article by HANSEN *et al.* [1] in a recent issue of the *European Respiratory Journal*, stating that the use of forced expiratory volume in six seconds (FEV₆) reduces the sensitivity of obstructive lung disease detection. Their study population of 3,515 current smokers, with a 17.5% prevalence of obstruction, found a sensitivity of only 76.8% and a specificity of 98.2% when comparing FEV₁/FEV₆ with FEV₁/forced vital capacity (FVC) below their respective 95% lower limits of normal (LLN). Based on this low sensitivity, HANSEN *et al.* [1] concluded that FEV₁/FEV₆ is less reliable than FEV₁/FVC as a screening parameter for the detection of obstruction.

The lower sensitivity obtained by HANSEN *et al.* [1] with respect to previous studies, in which sensitivity typically ranged between 92–95% [2–5], was attributed to differences in study population. HANSEN *et al.* [1] contended that previous studies comparing the performance of FEV₆ and FVC in detecting obstruction [3–5] had too few mildly obstructive and normal subjects. However, HANSEN *et al.* [1] cite another study, by AKPINAR-ELCI *et al.* [2], which showed 92% sensitivity and 98% specificity for the detection of obstruction; this is despite a prevalence of obstruction of only 14.5% in 1,139 nonpatients in a workplace setting. In general, these participants are healthy, and obviously median spirometry values are closer to the LLN than for groups of symptomatic patients referred to a pulmonary function laboratory.

In the study by HANSEN *et al.* [1], the “minimal obstructed” group represents the largest group (59%) of all subjects considered obstructive. Minimal obstruction was defined as FEV₁/FVC and/or FEV₃/FVC below the 95% LLN, combined with FEV₁ between 80–120% predicted. However, the rationale for using this criterion of possible morbidity only holds in populations with respiratory diseases; for healthy subjects, the meaning of a low FEV₁/FVC with a normal FEV₁ is unclear [6]. The proportion of subjects with respiratory diseases studied by HANSEN *et al.* [1] is not explicitly mentioned, but is likely to be small. Therefore, a substantial proportion of subjects labelled with “minimal obstruction” could be normal. Figure 3 in the paper by HANSEN *et al.* [1] clearly shows that the number of false negatives in the “minimal obstructed” group represents more than half of all false negatives; this could introduce a serious bias to the results.

In previous studies by us and others [2–5], most of the discordant cases had FEV₁/FVC and FEV₁/FEV₆ values close to their respective LLN, *i.e.* in a range where diagnosis of obstruction is questionable. Values close to the LLN can be assumed from table 5 in the paper by HANSEN *et al.* [1], because the mean deviation is only 2.64%. Considering the day-to-day variability of spirometry, the minimally obstructive subjects could easily shift between the normal and obstruction categories on different testing occasions. Therefore, one

could question the clinical relevance of detecting borderline obstruction.

In addition, we should be careful when comparing two diagnostic tests with each other in the absence of a true gold standard. In reality, FEV₁/FVC is more of a “*de facto* standard”, and by using it as a gold standard for the detection of obstruction, FEV₆ can never be shown to outperform FVC in the denominator of this ratio to better reflect true airway obstruction. This is particularly true when studying a population with FEV₁/FVC and FEV₁/FEV₆ values close to their respective LLN.

The increasing difference between FEV₆ and FVC volumes with increasing age and severity of obstruction is probably irrelevant in terms of identifying airway obstruction, because the deficit in airflow will be present long before 6 s. Moreover, spirometric detection of airway obstruction is a matter of categorisation and not of quantitative agreement. As long as FEV₁/FVC and FEV₁/FEV₆ values stay on the same side of their respective cut-off points the absolute values of these ratios are of little clinical importance, because once obstruction is established, the severity of this obstruction will be evaluated using FEV₁ [6].

In conclusion, the main advantage of using forced expiratory volume in six seconds values in primary care is to assist with the quality of testing. Forced expiratory volume in six seconds is more reliable than forced vital capacity, and using the 6 s cut-off eliminates the need for prolonged exhalations, eliminates the need to meet reproducible forced vital capacity values, and is an easier test for patients to perform. In practice, the advantages of using forced expiratory volume in six seconds values may well more than compensate for the small differences in classification of patients' results that are clustered around the lower limits of normal.

J. Vandevorde* and M. Swanney[#]

*Dept General Practice, University of Brussels (Vrije Universiteit Brussel), Brussels, Belgium, and [#]Respiratory Physiology Laboratory, Christchurch Hospital, Christchurch, New Zealand.

REFERENCES

- 1 Hansen JE, Sun X-G, Wasserman K. Should forced expiratory volume in six seconds replace forced vital capacity to detect airway obstruction? *Eur Respir J* 2006; 27: 1244–1250.
- 2 Akpinar-Elci M, Fedan KB, Enright PL. FEV₆ as a surrogate for FVC in detecting airways obstruction and restriction in the workplace. *Eur Respir J* 2006; 27: 374–377.
- 3 Swanney MP, Jensen RL, Crichton DA, Beckert LE, Cardno LA, Crapo RO. FEV₆ is an acceptable surrogate for

FVC in the spirometric diagnosis of airway obstruction and restriction. *Am J Respir Crit Care Med* 2000; 162: 917–919.

- 4 Vandevorde J, Verbanck S, Schuermans D, Kartounian J, Vincken W. FEV₁/FEV₆ and FEV₆ as an alternative for FEV₁/FVC and FVC in the spirometric detection of airway obstruction and restriction. *Chest* 2005; 127: 1560–1564.
- 5 Vandevorde J, Verbanck S, Schuermans D, Kartounian J, Vincken W. Obstructive and restrictive spirometric patterns: fixed cutoffs for FEV₁/FEV₆ and FEV₆. *Eur Respir J* 2006; 27: 378–383.
- 6 Pellegrino R, Viegi G, Brusasco V, *et al.* Interpretative strategies for lung function tests. *Eur Respir J* 2005; 26: 948–968.

DOI: 10.1183/09031936.00100206

From the authors:

We welcome the comments of J. Vandevorde and M. Swanney, who have been at the forefront of advocacy for the substitution of forced expiratory volume in six seconds (FEV₆) and its ratios for forced vital capacity (FVC) and its ratios. While we respect their findings, our study [1] concerned the use of spirometry to detect airway obstruction in a relatively healthy population, the third National Health and Nutrition Evaluation Survey (NHANES-III), rather than its clinical use in following patients with known disease.

We hope we agree that in following patients with known and significant airway obstruction or in assessing responsiveness to inhaled bronchodilators, the absolute values of FEV₁ or FEV₃ are optimal, and ratios such as FEV₁/FEV₆, FEV₁/FVC or mean forced expiratory flow between 25 and 75% of FVC (FEF_{25–75%}) are not. In following these patients, there is no need for repeated lengthy forced manoeuvres, such as FEV₆ or FVC. Unforced vital capacities not only suffice, but may be more informative and less stressful than repeated FEV₆ or FVC manoeuvres.

The question of selecting spirometric values to detect early airway obstruction, especially in primary-care settings, which was our focus, is more complex. For detecting obstruction, adding a measurement that focuses on the proportional increase in long time-constant lung units, *i.e.* the FEV₃/FVC (or 1–FEV₃/FVC), supplements the FEV₁/FVC well. J. Vandevorde and M. Swanney seem to object to us adding the FEV₃/FVC as a measure to detect obstruction in “healthy subjects”, yet the NHANES-III smokers clearly had greater increases of long time-constant lung units (1–FEV₃/FVC) than nonsmokers [1]. This increase may be undetected by the FEV₁/FEV₆ measurement, while the FEF_{25–75%}, using either the FEV₆ or FVC as a denominator, is certainly not sufficient to independently detect airway obstruction in a statistically valid way in a relatively healthy population [2].

One could question the clinical relevance of detecting borderline obstruction, except for epidemiological studies and for the purpose of the early detection of developing disease. In fact, another proponent of the FEV₆ measurement editorialises that the screening for chronic obstructive pulmonary disease by primary-care physicians has the potential to do more harm than good [3]. However, we think that early detection of

airway obstruction and identification of the cause have merit. Committee guidelines from authorities for detecting airway obstruction are useful [4], but not necessarily the last word, as evidenced by recent public correspondence [5, 6] and the conflicts over the Global Initiative for Chronic Obstructive Lung Disease standard of FEV₁/FVC <70% to define airway obstruction [4, 6].

In many, if not all, studies [2, 7–9], the coefficients of variation for the FEV₁/FVC and FEV₃/FVC are much lower than for FEV₁, FEV₃, FVC or FEF_{25–75%}. We contended that airway obstruction was likely to be present if either the FEV₁/FVC and/or FEV₃/FVC before bronchodilator administration were <95% confidence levels, even though the absolute FEV₁ may have been >80% mean predicted. Thus, in detecting, rather than quantifying obstruction, the spirometric curve after 1 s, and even after 6 s, may be important. Ignoring measurements that detect the increase in long time-constant airspaces lessens the ability to detect early disease. Therefore, in detecting airway obstruction, volume ratios such as FEV₁/FVC and FEV₃/FVC should both be useful. In contrast, absolute values, such as FEV₁ and FEV₃, are valuable in quantifying obstruction or assessing response to bronchodilators or to follow the progress of known disease.

Clinically, when spirometric values are borderline, clinical evaluation including a good history and physical examination, bronchodilator testing, and measurement of gas-transfer index may be necessary to diagnose or exclude lung disease. Neither ignoring airway obstruction nor over-diagnosis and over-treatment are desirable. However, let us acknowledge that spirometry has three major uses: 1) detection of airway obstruction; 2) assessment of disease progression; and 3) assessment of therapy. For the first, we showed that values of both the FEV₁/FVC and FEV₃/FVC separated NHANES-III current smokers from never-smokers by ~20 yrs by middle age [2]. We did not assess the similar effectiveness of the FEV₃/FEV₆, the progression of disease and therapy. However, for assessing disease progression or effect of therapy, we stress that the absolute values of FEV₁ and FEV₃ should be more sensitive than any ratios, including FEV₁/FEV₆, FEV₁/FVC or FEF_{25–75%}, because both numerator and denominator may increase or decrease together, thereby obscuring the absolute change in the fast time-constant lung units (those that contribute to the flow during the first second).

We hope that we can find common ground with J. Vandevorde and M. Swanney and their colleagues in recommending that spirometry to detect airway obstruction should be performed on good equipment by dedicated, trained and experienced technicians, under the supervision of physicians experienced and skilled in the interpretation of spirometry. We also believe that optimal spirometry measurements to detect early airway disease should include detection of an abnormal increase in proportion of longer time-constant (diseased) lung units. Conversely, absolute timed volumes, rather than ratios, are useful for following patients with known disease.

J. Hansen, X-G. Sun and K. Wasserman

Harbor-University of California, Medical Center, Torrance, CA, USA.

REFERENCES

- 1 Hansen JE, Sun X-G, Wasserman K. Should forced expiratory volume in six seconds replace forced vital capacity to detect airway obstruction? *Eur Respir J* 2006; 27: 1244–1250.
- 2 Hansen JE, Sun XG, Wasserman K. Discriminating measures and normal values for expiratory obstruction. *Chest* 2006; 129: 369–377.
- 3 Enright P. Does screening for COPD by primary care physicians have potential to cause more harm than good? *Chest* 2006; 129: 833–834.
- 4 Pellegrino R, Viegi G, Brusasco V, *et al.* Interpretative strategies for lung function tests. *Eur Respir J* 2005; 26: 948–968.
- 5 Enright P. Flawed interpretative strategies for lung function tests harm patients. *Eur Respir J* 2006; 27: 1322–1323.
- 6 Pelligrino R, Brusasco V, Crapo RO, *et al.* Flawed interpretative strategies for lung function tests harm patients. *Eur Respir J* 2006; 27: 1323–1324.
- 7 Crapo RO, Morris AH, Gardner RM. Reference spirometric values using techniques and equipment that meet ATS standards. *Am Rev Respir Dis* 1981; 123: 659–664.
- 8 Knudson RJ, Lebowitz MD, Holberg J, Burrows B. Changes in the normal maximal expiratory flow-volume curve with growth and aging. *Am Rev Respir Dis* 1983; 127: 725–734.
- 9 Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general US population. *Am Rev Respir Crit Care Med* 1999; 159: 179–187.

DOI: 10.1183/09031936.00112706

Epidemiology and costs of COPD

To the Editors:

The lead article in the series “The global burden of chronic obstructive pulmonary disease”, on the epidemiology and costs of COPD, touched briefly on the subject of occupational factors in the section on “tobacco and other causes” of the disease [1]. One of the four citations noted in that discussion was in reference to a report on smoking, occupational and demographic characteristics in a population-based sample of >1,000 elderly Finns, carried out in 1990–1991 [2]. This study was cited to support the following statement: “It is likely that the interaction between occupational exposure and other risk factors determines whether an individual develops COPD.” [2]

Having served on the American Thoracic Society (ATS) task force that developed a recent statement on the occupational contribution to the burden of airway disease [3], which was also cited in the *European Respiratory Journal* article, we were intrigued by the Finnish study, since it had not come up in our task force’s review and appeared to be potentially relevant. We subsequently read the study closely. It does include descriptive data on smoking, social class and occupational dust exposure, but it presents no formal statistical testing of the association between occupational dust and chronic obstructive pulmonary disease (COPD).

As the tabular data in the published paper [2] allowed categorisation of all subjects with respect to airflow obstruction (forced expiratory volume in one second $\leq 65\%$ predicted, the study definition of COPD), sex, occupational dust exposure, social class (lowest *versus* middle and higher combined), and smoking status (ever *versus* never), we were able to recreate the data set (limited to these variables) for the purposes of risk modelling.

Occupational dust exposure and lower social class were inter-related ($p=0.02$). In a multiple logistic regression model adjusting for sex and smoking and including three dust-social class exposure variables (dust and low social class (25%), dust and higher social class (50%), and lower social class without dust (7%)), combined dust and lower social class was associated with a significantly increased risk of obstruction

(odds ratio 2.3; 95% confidence interval 1.1–4.8). Neither dust exposure among those of higher social class, nor lower social class without reported dust exposure was a statistically significant risk factor for airflow obstruction in the same model. Out of 82 cases among 1,191 observations, 28 (34%) fell into the lower class-work dust risk category, yielding a population-attributable risk percentage estimated to be 19.6%.

ISOAHO *et al.* [2] acknowledge that their definition of COPD subsumes asthma. Indeed, 20 of the 82 subjects defined in the study as having COPD on the basis of airflow obstruction also had clinical histories of asthma (two with work-related disease). Thus, the re-analysis we report may overestimate the risk of COPD due to dust, to the extent that asthma is even more strongly related to this factor than is COPD. The recent ATS estimate, however, suggests that the occupational burden of both COPD and asthma is similar among adults [3].

Regarding the reference to the Finnish study [2] in the *European Respiratory Journal*, this re-analysis could support the presence of an interaction between occupational dust exposure and social class, or the findings may simply reflect the differing types and amount of dust exposure inherent in job duties and occupations that are linked to categorisation by social class.

P.D. Blanc and J.R. Balmes

Division of Occupational and Environmental Medicine, Dept of Medicine, University of California, San Francisco, CA, USA.

REFERENCES

- 1 Chapman KR, Mannino DM, Soriano JB, *et al.* Epidemiology and costs of chronic obstructive pulmonary disease. *Eur Respir J* 2006; 27: 188–207.
- 2 Isoaho R, Puolijoki H, Huhti E, Kivela S-L, Laippala P, Tala E. Prevalence of chronic obstructive pulmonary disease in elderly Finns. *Respir Med* 1994; 88: 571–580.
- 3 Balmes J, Becklake M, Blanc P, *et al.* American Thoracic Society statement: occupational contribution to the burden of airway disease. *Am J Respir Crit Care Med* 2003; 167: 787–797.

DOI: 10.1183/09031936.00097406

Cryptogenic organising pneumonia

To the Editors:

We have read with interest the paper by CORDIER [1] describing the current understanding of the pathogenesis, aetiology, diagnosis and treatment of cryptogenic organising pneumonia (COP). The author acknowledged that corticosteroids remain the standard treatment of COP, usually resulting in rapid clinical, and slower radiological, improvements. Although the response to corticosteroids is generally good, a proportion of patients can experience early or late relapses. In addition, some patients may be unable to tolerate corticosteroids, or the disease may continue to deteriorate, despite therapy with corticosteroids. Therefore, there is a need for alternative therapies to treat this condition. CORDIER [1] only briefly mentioned the occasional improvement of COP to treatment with antibiotics, especially macrolides [2].

Macrolides have gained increasing use in the management of diffuse panbronchiolitis, asthma and cystic fibrosis [3]. It has been proposed that the activity of macrolides in these conditions is through anti-inflammatory, as well as antimicrobial, action. *In vitro* studies suggest that macrolides may have an immunomodulatory activity, exhibited through: 1) the inhibition of the pulmonary influx of neutrophils; 2) the reduction of inflammatory cytokines, such as interleukin-8; 3) the protection of the epithelium from bioactive phospholipids; and 4) the improvement of the transportability of airway secretions [3]. Some of these activities may affect the underlying mechanisms involved in the pathogenesis of COP, therefore explaining a potential role of macrolides as therapeutic agents to treat this condition.

Recently, there has been increasing evidence of the role of macrolides in the treatment of COP. For example, STOVER *et al.* [4] described their experience using macrolides to treat three patients with COP and three patients with radiation-induced bronchiolitis obliterans organising pneumonia. Over the last few years we have also gained experience in the use of macrolides in the treatment of COP. To date, we have treated three patients with clinical and/or histological confirmation of COP. Two of our patients presented with an acute illness and one had a more gradual presentation. All three patients received clarithromycin 500 mg *b.i.d.* and the duration of therapy ranged between 3–12 months. All of the patients

showed improvement in their symptoms, together with the radiological resolution of pulmonary infiltrates and improvement in inflammatory markers. One of the patients was originally treated with oral corticosteroids but failed to improve, however, once macrolides were introduced his condition improved and within a few weeks the corticosteroids were able to be withdrawn.

Based on our observations, and the report by STOVER *et al.* [4], we believe that the duration of macrolide therapy should be between 3–12 months, although caution should be exhibited. The decision to treat cryptogenic organising pneumonia patients with macrolides should, at present, be made on an individual basis with the proviso that if improvement is not observed, or if a patient's condition worsens, conventional therapy with corticosteroids should be introduced. Macrolides could be considered for use in combination with corticosteroids in patients who fail to respond to corticosteroids or as a corticosteroid sparing agent. We would suggest wider reporting of experience to gain more information on the role of macrolides in cryptogenic organising pneumonia.

J.A. Kastelik, M. Greenstone, D.V. McGivern and A.H. Morice

Dept of Respiratory Medicine, Castle Hill Hospital, Cottingham, Hull, East Yorkshire HU16 5JQ, UK.

REFERENCES

- 1 Cordier J-F. Cryptogenic organising pneumonia. *Eur Respir J* 2006; 28: 422–446.
- 2 Epler GR, Colby TV, McLoud TC, Carrington CB, Gaensler FA. Bronchiolitis obliterans organizing pneumonia. *N Engl J Med* 1985; 312: 152–158.
- 3 Rubin BK, Henke MO. Immunomodulatory activity and effectiveness of macrolides in chronic airway disease. *Chest* 2004; 125: Suppl. 2, 70S–78S.
- 4 Stover DE, Mangino D. Macrolides: a treatment alternative for bronchiolitis obliterans organizing pneumonia? *Chest* 2005; 128: 3611–3617.

DOI: 10.1183/09031936.00100106

ERRATA

“ANGIOTENSIN II BLOCKERS IN OBSTRUCTIVE PULMONARY DISEASE: A RANDOMISED CONTROLLED TRIAL”. S. ANDREAS. *EUR RESPIR J* 2006; 28: 670–671.

Unfortunately, in this letter from the authors, a reference was cited incorrectly in the text. HOPKINS *et al.* [4] should appear as HOPKINSON *et al.* [4].

DOI: 10.1183/09031936.50079106

“PREVALENCE AND SOCIOECONOMIC ASSOCIATIONS OF ASTHMA AND ALLERGIC RHINITIS IN NORTHERN AFRICA”. V. GEORGY, H.I. FAHIM, M. EL GAUFARY AND S. WALTERS. *EUR RESPIR J* 2006; 28: 756–762.

Unfortunately, the title of this paper was printed incorrectly. Nothern should read northern.

DOI: 10.1183/09031936.50089005