

PostScript.....

LETTERS TO THE EDITOR

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DOT for all patients with smear-positive pulmonary TB in London?

Supervised drug taking is frequently seen as the answer to rising levels of tuberculosis. Djuretic *et al* advocate directly observed therapy (DOT) for all patients with smear-positive pulmonary tuberculosis in London.¹ At first sight the experience of instituting DOT in New York City appears especially impressive, with a 21% reduction in case rates and 39% decrease in drug resistant isolates. However, these reductions occurred at the same time as close attention was paid to drug regimens, the use of drug combinations, increased staffing levels, and the payment of incentives combined with the threat of imprisonment for persistent defaulters. The cost was phenomenal.²

The proportion of cases of tuberculosis in London that have recently been transmitted has been estimated at 14.4%.³ This is very low compared with 48% in New York City.⁴ The decreased incidence of tuberculosis in New York City was achieved entirely within groups where recent transmission was suspected. Over the same time period there was a 22% increased incidence among foreign born persons. Such people have contributed most to the recent increased incidence of tuberculosis in London.⁵

Randomised controlled trials have shown that direct observation either by a healthcare worker or family member does not improve treatment completion rates when compared with self-administered treatment.⁶⁻⁸ Furthermore, even with supervised drug taking, patients can still fail to complete treatment. In one study in Denver, 18% missed two consecutive weeks of treatment, continued treatment for more than 30 days beyond the expected date of completion because of defaulting, or were imprisoned as a threat to public health.⁹ In a review of randomised controlled trials to promote adherence, monetary incentives, home visits and attentive staff were important elements of successful programmes.^{10 11}

The situation in London clearly requires action. The data, however, suggest different approaches to those taken in New York City (table 1). New entrant screening deserves greater attention, and a heightened awareness of tuberculosis in primary care could

Table 1 Epidemiology and treatment of TB in London (UK) and New York (USA)

	London (current)	New York (1992-4)
Incidence of TB	35/100 000 (Newham 110/100 000)	46 per 100/000 (Central Harlem 222/100 000)
Cost of TB services	£8 million ¹⁴ (£34.2 million) ^{15*}	>\$400 million ²
DOT strategy	Selective	Universal†
Completed treatment	87%‡	<50% ²
Relapsed TB	6-8%‡	51% ²
HIV co-infection	14% ¹⁶	38% ^{2§}
Multidrug resistant TB	1.7% ¹	19% ¹⁷
Recent transmission (estimate from molecular epidemiology)	14.4% ³	48% ⁴
Cause of increase in TB	New entrants (foreign born), elderly women, HIV (11%) ¹⁶	HIV, ² nosocomial, homeless, foreign born

*Estimated as £6k per TB patient and £60k per MDRTB treated.

†Actually around 30% were receiving DOT.

‡Unpublished data, North East London TB Network, London TB Group and King's College Hospital, South East London.

§38% of all, 72% of those tested.

complement the current system.¹² The tuberculin skin test has a poor specificity and sensitivity and we should investigate newer methods of diagnosing those patients with latent tuberculosis who have a high probability of progressing to disease.¹³ We should maintain our vigilance to prevent active transmission by treating those with infectious, smear positive pulmonary tuberculosis rapidly and effectively. This can be complemented with well targeted contact tracing. Selective DOT is a part of this programme, but we would emphasise that each patient should be treated as an individual and treatment should be tailored to his or her needs.

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Guidelines on prevention of venous thromboembolism during long haul flights

The guidelines¹ drawn up on prevention of venous thromboembolism and long haul flights should be welcomed, though seen in the light of incomplete evidence. We would like to draw attention to several points.

Scurr *et al*² looked prospectively at a group aged over 50 years undergoing long haul travel from which anyone with recognised risk factors was excluded, putting such individuals into a low risk group for venous thromboembolism. Twelve of 116 people who were randomised to the "no stocking" group were diagnosed with symptomless calf deep vein thrombosis after their long haul travel. None of the group randomised to wear compression stockings developed deep vein thrombosis. Even if we take this surprising finding at face value, we are left with the

question: what is the clinical significance of asymptomatic calf deep vein thrombosis in a low risk population? It is far from clear in such a low risk group that we need to treat such events, which weakens any guideline aimed at prevention. Unlike a postoperative patient, the traveller is mobile before and after flight as well as potentially during it.

Furthermore, considering the uncertainty of the evidence, it would be wise to advise passengers of potential side effects from our recommendation. Superficial thrombophlebitis occurred in four individuals (3%) wearing compression stockings in the study by Scurr *et al.*, indicating some morbidity with their use.

As far as we are aware, no study has looked at the preventative effect of long socks or support tights recommended for low risk passengers. It is also a shame that no study has looked at the effect of lifestyle measures such as mobility and hydration or, indeed, compared these to intervention with stockings or socks. Until further evidence emerges, can we promote the use of support tights or long socks in low risk passengers compared with the non-invasive measures of mobility and hydration? If we are to recommend intervention, it should reflect Scurr's evidence and be compression stockings with warnings for thrombophlebitis.

In the passenger with a moderate to high risk of venous thromboembolism, the recommendations are for compression stockings and aspirin or anticoagulation. This is based on extrapolation from studies of postoperative patients,³ but it is not clear that passengers fall into the same category. While it may be prudent to make unsubstantiated guidelines for high risk individuals, are we really going to recommend pre-flight aspirin and use of compression stockings for every individual on hormone replacement therapy and the oral contraceptive pill? What will be the morbidity associated with aspirin use?

While we await further studies to answer our questions, we agree that all at risk patients should be strongly recommended to take lifestyle measures. This information should be dispersed by airlines and public health agencies. There is no evidence for the use of knee socks in any group, and this recommendation should be dropped. Patients with low to moderate risk factors should be advised that compression stockings have reduced venous thromboembolism in other situations, but that superficial thrombophlebitis can occur as a side effect. Any further intervention with aspirin or low molecular weight heparin can be offered to moderate to high risk individuals only on the basis that direct evidence is lacking and side effects are possible.

Finally, when making the recommendations, patients should be warned that case studies found an increased risk of thromboembolism in long distance travel, not just long haul flights.⁴

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Author's reply

We appreciate the interest expressed by Drs Campbell and Rayner in the BTS fitness to fly guidelines and welcome their valuable comments. We would like to clarify the issues they raised.

Firstly, we agree that the clinical significance of asymptomatic calf deep vein thrombosis in a low risk population is as yet unclear, and for this reason we avoided didactic advice while awaiting further evidence. Our recommendations were that physicians may wish to recommend support stockings or non-elasticated long socks in patients at increased risk of venous thromboembolism. The physician's decision will depend on individual circumstances, including patient preference.

Secondly, Drs Campbell and Rayner raise the issue of superficial thrombophlebitis which developed in 3% of passengers who wore below knee elastic compression stockings. The significance of this result, as indicated by the confidence intervals, is unclear, and our recommendations did not include such stockings. Rather, we suggested the possible use of non-elasticated long socks which are less likely to compress varicose veins in the knee region.

Thirdly, we agree that further studies are required to examine the effects of lifestyle measures such as mobility and hydration, and our guidelines recommended further research into this area. With regard to the possible morbidity associated with a single tablet of low dose aspirin, we consider that this is likely to be very small.

Finally, regarding passengers on oral contraception, we have made it clear that the risk is not equal with all forms of contraception, and physicians and passengers will have to make their own decisions in the light of available evidence and individual circumstances.

The process of producing these guidelines has highlighted the fact that there are a considerable number of unknowns regarding flying with respiratory disease, and more research is clearly required.

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Endotoxin: does it have a role in prevention of lung cancer

The paper by Drs Douwes, Pearce and Heederik provides an interesting overview of how endotoxin may interact in atopy and asthma. It discusses issues as to whether endotoxin plays a role in prevention of atopy and asthma or may, in fact, be a contributor to these respiratory diseases. However, readers should be aware that there is another important issue, although controversial, related to endotoxin and the lung—that is, does endotoxin exposure in some occupational groups result in reduced lung cancer rates?

There have been a number of reports^{2–8} suggesting that endotoxin exposure, mostly in

organic dusts, results in reduced lung cancer rates. This reduced lung cancer rate was first identified in textile workers^{2,3} and later in agricultural^{4,5} and other groups^{6,7} exposed to endotoxin. Experimental studies^{9,10} have supported epidemiological findings and clinical trials^{11,12} have been undertaken to evaluate this agent and the effectiveness of its immunomodulators in cancer treatments. Although the concept of a beneficial effect from occupational exposure is novel,⁵ it has been reported in at least one other occupational epidemiological investigation of reduced lung cancer rates for a potentially better recognised anticancer agent (selenium).^{13,14} Most investigators disagree with any benefit from occupational exposure and attribute these findings to various forms of selection bias (healthy worker effect) and lower rates of smokers in study populations (compared with controls).^{4,5,7}

Certainly exposure to organic dusts and endotoxin does not occur without risk. There are numerous reports of the detrimental outcomes associated with such exposures.⁸ However, when various forms of bias are evaluated, there appears to be in some studies an inability to explain the reduced lung cancer rates.^{2,4,7}

It is encouraged that scientists accept the concept that there is an alternative view for lower lung cancer rates in some study populations. Even though this challenges prevailing thought and conventional thinking, we must remember that tradition dies hard and the birth of a new idea requires a creative and innovative spirit.¹⁵

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High incidence of cystic fibrosis in children born in Italy to Albanian immigrants

The incidence of cystic fibrosis (CF) can vary significantly among different racial groups; within white populations it has been reported to vary from 1/3419 in the USA to 1/2500 in the UK and 1/4700 in Italy. According to Lewis,¹ the highest incidence that can be reliably expected in white populations is 1/2500, although a value as high as 1/936 has been reported in a well defined community.²

Italy and other European countries have experienced a heavy influx of immigrants from Albania in the last 10 years following political and economic upheaval occurring in that country. Although precise numbers are not available, since 1989 some tens of thousands of Albanian immigrants have settled in Tuscany, a region of central Italy populated by 3.5 million people in an area of 23 000 sq km. There are no data on the incidence of CF in Albanians, so we have calculated the incidence of CF in newborn infants of the Albanian community residing in Tuscany.

We analysed the records for the period from 1 July 1991 to 31 December 2001 contained in the database of the Tuscan regional neonatal screening programme for CF which was carried out using the immunoreactive trypsin assay with lactase meconium complementary test, and which covered 99.99% of the newborn infants in the region.³ During the observation period 275 520 newborn infants were screened for CF in Tuscany. On the basis of the information contained in the forms completed at birth by the obstetricians at the maternity wards or at home and checked by the CF Regional Centre, 1803 children were born to both ethnic Albanian parents during this period. The number of Albanian newborns was not constant over the years of the study, but it has grown steadily from 15 in 1991 to 474 in 2001.

During the observation period four cases of CF were diagnosed (by two positive sweat tests) among children born to both Albanian parents (incidence 1/450 (95% confidence intervals (95%CI) 1/176 to 1/1653)) and 60 cases were diagnosed among the 273 717 non-Albanian newborn infants in the region (incidence 1/4592 (95% CI 1/3543 to 1/5977); point estimate ratio 10.12 (95% CI 2.67 to 27.28); $p=0.0009$). The four Albanian infants with CF were born to parents who were unrelated and who came from different geographical zones of Albania.

To define the incidence of CF correctly it is important that the study is based on a well defined, large population belonging to a precise geographical area and that it covers a sufficiently long period of time.¹ We are confident that we have analysed an entire population of immigrants in a well defined geographical zone over a period of 10 years. The CF cases were diagnosed using an appropriate screening programme with good sensitivity.

We are not aware of any factor that could account for the increased incidence of CF in the population studied. There is no evidence to suggest the selection of CFTR mutation carriers among Albanian immigrants to our region. We did not note any selection bias in the cases we observed based on parentage or geographical provenance of immigrants from Albania, since couples were unrelated and came from different regions of the country. The suggestion that parents of Albanian newborn infants with CF emigrated because of the knowledge of being a carrier or because of a prenatal diagnosis can be excluded both on the basis of patients' anamnesis and considering the poor status of the Albanian health system.

Available publications on Albanian emigration following the political and social upheaval of the early 1990s do not provide any information relating to migratory patterns based on certain geographical zones, familial origins, or cultural level,⁴ and show a weak correlation between intention to emigrate and income.⁵

The absence of factors which could have biased the results of our study allow us to hypothesise that there is a high incidence of CF in Albanian people. For a long time Albania had no external migratory fluctuations and had closed social structures with a high incidence of endogamy, remaining politically and socially isolated from the rest of the world.⁴ These factors may have contributed to a high prevalence of carriers of the CFTR gene in the Albanian population.

Our data call attention to the necessity of studying the incidence of CF among Albanians in their own country. While awaiting these results, physicians should give particular attention to the possibility of CF when caring for ethnic Albanian children.

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Urokinase in the treatment of childhood empyema

Thomson *et al* reported the first double blind placebo controlled study of intrapleural urokinase for the treatment of childhood empyema.¹ They found a statistically significant reduction in hospital stay in the treatment group and concluded that "urokinase is a successful adjunct to the management of parapneumonic empyema".

The primary management of childhood empyema is controversial with some groups advocating open decortication.² However, because of reports of wound infection, air leaks and bleeding in open decortication, there has been an increase in the potential for video assisted thorascopic surgery (VATS) as primary treatment for childhood empyema.³ We have recently reported our experience in 21 children undergoing primary VATS for empyema between September 2000 and September 2001.⁴ The mean (SE) length of stay in hospital was 7.6 (1.2) days, which is comparable to that in the study by Thomson *et al* (7.4 days). Importantly, no child went on to open decortication; in Thomson's study five of 58 patients went on to surgery. This reflects our own experience of a failure rate with urokinase treatment approximating 10–15%. We have recently undertaken VATS in six children referred to our centre for further management following the failure of urokinase treatment. Five were successfully treated with VATS but one proceeded to open decortication. Urokinase causes the intrapleural loculations to become very adhesive and increases the difficulty of the VATS procedure. Thus, urokinase is likely to increase the chances of a child undergoing open decortication in those who fail medical treatment.

There may be a role for urokinase in early empyema (although this was not specifically studied by Thomson *et al*), and it is likely that VATS is more useful in stages 2 and 3. We call for studies to examine prospectively the primary treatment of choice in childhood empyema and, to this end, we have recently embarked on a randomised prospective study to compare primary VATS with urokinase and chest drain in childhood empyema.

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Authors' reply

We are pleased that Sit *et al* are interested in our controlled trial. We do not doubt that

video assisted thoracoscopic surgery (VATS) will have a role in a limited number of patients with empyema, but do not consider it first line treatment. The major limitation of VATS is that it is highly dependent on the skill of the operator and poor results in some centres were reported at the recent American Thoracic Society meeting. Good paediatric practitioners will be limited to a few major centres in the UK.

One of the strengths of our study was that we obtained excellent results using urokinase in a multicentre trial with very variable previous experience of the technique. Sit and colleagues should note that, of the five patients who had surgery in our study, three were in the control group; the need for surgery in the urokinase group was therefore only 6.6%. Our single centre experience (Oxford) of 69 consecutive patients with empyema treated with urokinase is a median post intervention length of hospital stay of 5 days (range 3–13) with only one patient needing surgical intervention (1.5%). These data should be useful in the power calculations needed before a comparative randomised trial of VATS versus urokinase is commenced.

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BOOK REVIEWS

Childhood Respiratory Infections

Scientific Editor: Rosalind L Smyth. UK: Oxford University Press, 2002. £42.50. ISBN 0 1985 1624 X

When opening a new book, a logical first place to start is the Table of Contents. Here one is immediately struck by the lack of logical order of the chapters. The topics covered

suggest they were chosen by the authors to match their interests rather than in a concerted effort to cover subjects of importance or of recent interest in the field. Some newer topics appear to be missing—for example, there is no obvious treatment of metapneumovirus. Some “specialist” areas are covered—for example, “Respiratory infections following haematopoietic stem cell transplantation in children”—whereas others that might be expected such as mycobacterial infections appear to be missing. In fact, most of the important areas in childhood respiratory infections are covered in this book; it is just a challenge to find some of them.

The chapters themselves are generally easy to read and informative. I particularly liked the simple and separate descriptions of the roles of the innate and adaptive immune systems, together with non-immune factors in host defence that were included in the early chapters. The “Key points for clinical practice” included at the end of most chapters are likely to be particularly useful for most readers. The information in the chapters is up to date and strikes a nice balance between providing sufficiently detailed information to satisfy the informed reader and presenting important concepts simply enough to be understandable to the less well informed. The references are extensive and up to date.

Overall, this is an easy to read and informative book that should be of great interest to practising physicians, paediatricians, respiratory trainees, and medical undergraduates.

P D Sly

Clinicians' Guide to Sleep Medicine

N J Douglas. UK: Arnold, 2002. £29.99, paperback. ISBN 0 340 74205 4

Those unfamiliar with the subject might be forgiven for thinking that sleep medicine is synonymous with obstructive sleep

apnoea. However, in his excellent new book Professor Douglas demonstrates that disordered sleep can be caused by a surprisingly diverse range of diseases and environmental factors.

The book is well laid out, attractive, and not too thick! The material is covered comprehensively, in a style that is easily readable, using language that is clear and concise. The text is broken up into “bite size” chunks with numerous figures and illustrations interspersed throughout. Each topic is extensively referenced and suggestions for further reading have been included at various points for those interested in delving deeper.

Broadly speaking, the book is divided into two main sections. The first half concentrates on the causes of excessive daytime sleepiness with OSA and narcolepsy being addressed in great detail. The chapter on investigation of the sleepy patient is very useful and examines the role and scope of different tests. Management protocols are suggested and the author includes tips from his own clinical practice.

The second part of the book looks at many disparate issues in sleep. Topics discussed in this section include insomnia, circadian rhythms disorders (including jet lag and shift work), snoring, and miscellaneous causes of sleep disturbance. There is a particular emphasis on COPD and nocturnal asthma. The final chapter briefly reviews a selection of other medical conditions, the more noteworthy ones being neuromuscular disease, obesity hypoventilation syndrome, and Cheyne-Stokes respiration in heart failure.

I enjoyed reading this book and wholeheartedly recommend it to anyone (especially respiratory trainees) wishing to acquire a practical up to date understanding of the rapidly developing specialty of sleep medicine. Even those with years of experience in the field are likely to derive benefit and the later sections are relevant to all doctors.

M Chandri