SARS has knock-on effects on the care of other patients and disrupts the lives of relatives and hospital staff alike. A major SARS outbreak in the UK could effectively close down the health service.

In this issue of *Thorax*, Chan *et al*[5] describe the clinical features of 115 patients (including five doctors and 18 nurses) with SARS admitted to a single hospital in Hong Kong, beginning in March 2003. Their mean age was 41 years, and the crude mortality was 15.7% with one third of deaths occurring more than 3 weeks after onset of symptoms. Intriguingly, Chan *et al* show that diabetes, cardiac disease, and age are strongly predictive of an adverse outcome, mirroring a smaller previous study of patients mainly from the Amoy Gardens housing block. In this other study[4] 40% of those with ARDS (n=15) had chronic hepatitis B infection compared with 5% of the 60 patients who did not develop ARDS.

These observations raise intriguing questions about why some patients become very ill and die while others have mild disease and survive. Certainly, young healthy people infected with SARS CoV rarely become very ill,[6] and those already elderly[7] or in poor health are at increased risk when a viral or bacterial pneumonia develops. However, it is also possible that some of the patients with pre-existing disease may have heightened innate immune responses that augment the immunopathological response to SARS and thus leads to more severe pulmonary infiltration, ARDS, and death. It is also possible that the immunological traits that lead to chronic disease—for example, hepatitis B infection or immune organ damage—also adversely influence the immunopathological response to SARS CoV infection.

Experience with smallpox and polio shows that a highly effective vaccine is essential for global elimination of an infectious disease and that an animal reservoir makes elimination hard or impossible. Vaccine development is a worldwide priority, funded by US Federal support for industrial partners using three distinct approaches. A vaccine would be likely to prevent systemic spread; there are successful vaccines for some veterinary coronavirus infections and it would be possible to test vaccines in non-human primates.[2] However, success is not guaranteed and anti-coronavirus immunity can even increase disease severity—for example, in coronavirus induced feline peritonitis. The existing human coronavirus common cold agents are able to re-infect despite low variability, and prolonged viral shedding in SARS patients (about 70% of patients are still positive at day 21 on stool samples) despite good serological responses (60% seroconversion by day 21 and virtually 100% by day 30[4]) indicates that a specific immune response may not be capable of terminating infection.

The SARS outbreak has important lessons for us all. Epidemics of this type do not respect national borders, have a large impact on tourism, travel and trade, and potentially have devastating effects in poor countries with insufficient infrastructure. The unprecedented speed of international and national collaboration undoubtedly contributed greatly to limiting the impact of SARS, and the WHO and respective governments must be praised for their incisive and energetic leadership. What will happen to SARS during the next 6–9 months is guesswork—a major worldwide epidemic might develop this coming winter or the outbreak could die down. Certainly, there will be more outbreaks of respiratory viral disease in the future, and we need to be well prepared for such events.

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Lung volume reduction surgery

Closing the NETT on lung volume reduction surgery

P M A Calverley

The National Emphysema Treatment Trial (NETT) of lung volume reduction surgery in patients with COPD has shown that surgery can and should be evaluated on a par with other forms of treatment.

Most textbooks and many physicians now use the term "chronic obstructive pulmonary disease" (COPD) to define airflow obstruction that results from a variable combination of small airways disease and loss of elastic recoil due to emphysema. A detailed knowledge of the underlying pathology does not normally influence the treatment prescribed, with one important exception.[1] Patients who have large space occupying bullae visible on their plain chest radiograph can experience significant improvements in lung function and exercise capacity if these lesions are resected, a treatment that is now well established.[2] Initial attempts to extend this approach to include the resection of gross emphysematous areas of lungs were scorned by physiologists as being irrational and were associated with significant perioperative morbidity and mortality.[3] The pressures of a lengthening lung transplantation waiting list led Cooper and colleagues to revisit this approach using modern techniques of intensive care and better surgical methods of strengthening the previously suspect suture lines between friable areas of lung. Their report of significant improvements in spirometry, breathlessness, and 6-minute walking distance after surgery compared with historical controls had a

dramatic effect on thoracic surgical practice in the USA.[4] Their findings were replicated by others using a variety of surgical approaches and techniques and were reported in a series of uncontrolled case studies[5] which suggested variable benefit when meta-analysed.[6] After some debate, this procedure is now known as lung volume reduction surgery (LVRS). Detailed physiological testing before and after surgery showed that there was a significant improvement in resting lung volumes in most cases, together with less dynamic hyperinflation during exercise,[7] improved diaphragmatic mechanics secondary to changes in chest wall configuration,[8] and increased lung elastic recoil in the remaining lung.[9] Theoretical models were developed to explain how lung volume reduction could improve expiratory flow, irrespective of the distribution of emphysema.[10] Finally, several small randomised controlled trials confirmed the efficacy of LVRS in terms of sustained improvements in spirometry, exercise capacity, and health status.[11–13]

Unlike medical treatments which are strictly regulated and must demonstrate sustained benefits without unacceptable risk, surgical treatments have traditionally been introduced on the basis of sustained short term benefit and LVRS was no exception. However, despite the patchy nature of the longer term follow up data, it became clear that the improvement seen after surgery was not permanent and, in some cases, the return to baseline conditions was more rapid than anticipated from the normal decline in lung function known to occur in these patients.[14] More worryingly, the rapid uptake of LVRS was accompanied by a steep increase in the reported 90 day mortality rate, rapidly reaching the alarming figures which had originally led to the procedure being discontinued.[15]

At this point something quite unusual but very appropriate happened. A unique coalition was formed between the NHLBI and the principal healthcare providers in the USA who introduced a moratorium on performing surgery of this kind outside the large prospective randomised controlled clinical trial, which they agreed to fund. This was the National Emphysema Treatment Trial (NETT), the results of which were reported initially as an interim analysis of high risk cases[16] and which have now been reported both as an intention to treat analysis[17] and in a companion paper addressing the cost effectiveness of the procedure.[18]

Of the 3777 patients screened, 1218 were finally randomised, 580 eventually receiving surgery and 562 routine medical care. All patients underwent 6–10 weeks of pulmonary rehabilitation before entry to the study, performed cycle ergometry breathing 30% oxygen and standardised pulmonary function testing, and completed the disease specific St George's Respiratory Questionnaire (SGRQ), a general health questionnaire, and a dyspnoea questionnaire. Emphysema distribution was graded by visual scoring of the high resolution CT scan as being homogeneous or heterogeneous, with or without upper lobe predominance of the disease. Physiological and symptomatic evaluations were conducted at 6 and 12 months and annually thereafter. Primary outcomes were all cause mortality and maximum exercise capacity. Given the risks inherent in the surgery, a higher than usual clinically significant change was established a priori—namely, an increase in maximum exercise capacity of 10 watts and an 8 point change in the SGRQ score.[19] Adherence to treatment and to the pulmonary rehabilitation programme at home was monitored by telephone contact and in the clinic, and all patients were non-smokers when studied.

Patient groups were well matched (mean age 66.6 years, mean FEV_1 26.8% predicted, mean T_{LCO} 28.3% predicted) and were not hypercapnic (Pa_{CO_2} 5.75 kPa). The total SGRQ score was around 53, a value lower than might be expected given the degree of airflow obstruction but compatible with successful pulmonary rehabilitation. The 90 day mortality was 7.9% in those randomised to surgery compared with 1.9% in those undergoing routine medical treatment. Improvements in exercise capacity of more than 10 watts occurred in 28% of surgically treated patients at 6 months and were still present in 15% at 2 years compared with 4% and 3%, respectively, in the medically treated group. Early in the trial a high risk group of patients with homogeneous disease on the CT scan and an FEV_1 and/or T_{LCO} below 20% predicted were identified as having an unacceptably high early mortality and no further patients of this type were recruited. In the remaining 1078 patients surgery was still significantly more hazardous by 90 days (5.2% versus 1.2% mortality in the medical group) but mortality did not differ over the follow up period. Significantly greater changes in FEV_1, health status, and the degree of dyspnoea were seen in the surgically treated patients, all showing an initial improvement with a later deterioration compared with a steady deterioration in these variables in those undergoing medical treatment.

When patients were stratified post hoc for the presence of upper lobe predominant disease and by their initial exercise impairment before randomisation, four subgroups emerged. Patients with upper lobe predominant emphysema and a low exercise capacity showed the greatest and best sustained improvements in all physiological and symptomatic variables and also had a significantly better survival experience than similar patients randomised to medical treatment. In contrast, those without upper lobe predominance of disease and a preserved exercise capacity faired scarcely better than the high risk group previously identified. The remaining two groups lay between these extremes with no benefit in mortality but significant improvements in the degree of health status impairment, spirometry, and exercise capacity.

The companion report[18] examined the healthcare costs associated with this treatment which were substantial, amounting to $190 000 per quality adjusted life year (QALY) at 3 years and $53 000 at 10 years. Unsurprisingly, the most cost effective treatment was directed at those with upper lobe predominant disease and a low exercise capacity ($98 000 per QALY at 3 years and $21 000 per QALY at 10 years). The 10 year data, adjusted for the likely survival in this population, extrapolated the benefits seen at 3 years and assumed that the treatment differences observed were maintained over this time—both rather imponderable issues in patients such as these. By comparison, coronary artery bypass surgery costs $64 000 per QALY gained (2002 prices).

There are many lessons to be learned from the NETT study. Firstly, important improvements in exercise capacity and health status are possible in patients with severe emphysema by reducing the operating lung volume at which these patients breathe. The changes in exercise capacity and well being can be dramatic even when the spirometric improvement is small, an important lesson which is applicable to all COPD treatments. These benefits can be achieved surgically without an unacceptable mortality risk, at least in patients in whom surgery is performed according to the NETT protocols and attention is paid to previous rehabilitation and patient selection. The distribution of disease and prior exercise capacity are important determinants of operative success. This suggests that more comprehensive imaging and exercise studies will be needed if we are to characterise COPD patients properly in future clinical trials and in our clinical practice. An impaired exercise capacity is not just a marker of poor prognosis,[20] but also appears to define the patients with the most to gain from treatment of their underlying disease. However, we should be cautious about all the conclusions drawn in this study as some of the most important are based on a post hoc analysis of predictor variables, a source of concern to statisticians[21] but less worrying to clinicians who are likely to be impressed by the biological plausibility of the conclusions drawn. Inclusion of a comprehensive prospective cost effectiveness

analysis also emphasises the economic impact of advanced COPD and the need to offer surgery only to those patients in whom the benefit can be best justified, given the scarcity of healthcare resources.

Future analysis of this important dataset is likely to provide many new insights and to generate further hypotheses that will need to be tested. Perhaps most importantly of all, the conduct of the NETT study has shown that surgery can and should be evaluated on a par with other forms of treatment. Only when this is done can we be certain that our intervention as doctors helps rather than harms our patients.

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LUNG ALERT

A new test for latent tuberculosis infection?

▲ Ewer K, Deeks J, Alvarez L, *et al*. Comparison of T-cell-based assay with tuberculin skin test for diagnosis of *Mycobacterium tuberculosis* infection in a school tuberculosis outbreak. *Lancet* 2003;**361**:1168–73

This study compared the enzyme linked immunospot assay (ELISPOT) with tuberculin skin testing (TST) for the diagnosis of latent tuberculosis infection (LTBI) in low prevalence settings. The ELISPOT assay measures interferon gamma secretion by blood mononuclear cells to ESAT-6, an antigen present in *Mycobacterium tuberculosis* but not in *M bovis* or environmental mycobacteria. 535 students were tested in a large tuberculosis outbreak in a UK school. Although agreement between the tests was high (89%), ELISPOT correlated significantly more closely with *M tuberculosis* exposure than did TST based on duration of exposure ($p=0.007$) and measures of proximity to the single index case ($p=0.002$). TST was significantly more likely to be positive in BCG vaccinated than in non-vaccinated students. The authors conclude that ELISPOT offers a more accurate approach than TST for the identification of patients with LTBI, and is more precise at targeting preventative treatment.

Interpretation of studies in this area is difficult because of the lack of a gold standard for diagnosing LTBI. There are no comparative studies between ELISPOT and QuantiFERON, an existing assay which measures the interferon response to PPD in whole blood. Although the TST requires a return visit for interpretation, it does not require phlebotomy, analysis within a few hours, laboratory expertise, or expensive equipment like an ELISPOT reader. Studies are required to assess the cost/benefit ratio of ELISPOT and its positive predictive value for the subsequent development of tuberculosis.

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