Editorials

Carrots, sticks and tuberculosis

Richard J Coker

Public health authorities have long had at their disposal the authority to impose coercive measures to protect the public from perceived threats. Tuberculosis is a global emergency and the spectre of widespread drug resistance resulting from inadequate treatment is perhaps the most feared vision by those involved in control programmes. To improve treatment completion rates and reduce the development of drug resistance, the World Health Organisation (WHO) and others are advocating the broad use of observed therapy as a central plank in their tuberculosis control programme. Directly observed therapy (DOT) has been shown to be effective in several settings, perhaps most dramatically in New York City.¹ The success of this particular programme has received widespread recognition, but what has perhaps received less international attention is the use of some measures to support this approach.

In addition to a broad array of incentives, including cash payments, food coupons, shelter, and assistance with travel, the city underpinned the expansion of its DOT programme by amending its health codes and authorising the Commissioner of Health to detain both infectious and non-infectious individuals “where there is a substantial likelihood, based on such person’s past or present behaviour, that he or she can not (sic) be relied upon to participate in and/or to complete an appropriate prescribed course of medication for tuberculosis and/or, if necessary, to follow required contagion precautions for tuberculosis.”² This represented a fundamental shift in officials’ authority to include measures directed towards the non-infectious recalcitrant patient. At the time the amended regulations were adopted, concern both from civil libertarians and city officials was focused upon “due process” protections with an emphasis on the use of less restrictive alternatives to detention. Both sides accepted the constitutional and ethical principles underlying the justification for detention of “recalcitrant” individuals and little distinction was made between whether they were infectious or non-infectious.³ Although the primary goal was reduction of threat to public health, little attention was paid to the uncertainty regarding the risk of relapse or the actual magnitude of the threat posed by non-infectious poorly compliant individuals, particularly by those opposing the regulatory changes. The Health Department officials simply suggested that “over time, it is likely that they (poorly compliant, non-infectious individuals) will pose a very serious threat to large segments of the public.”⁴ Since 1993, when the amended regulations were adopted, more than 200 non-infectious individuals have been detained, most for prolonged periods, some for more than two years.

Although patients with acid fast bacillus smear positive pulmonary tuberculosis pose a public health threat, much

of what is accepted dogmatically with regard to the transmissibility of tuberculosis is, in fact, uncertain and it is far from clear what threat smear negative individuals who are non-compliant pose to the public.⁵ When treatment is erratic, when only some drugs but not others are taken, and when there is primary or acquired drug resistance at the commencement of treatment, estimating the risk of relapse and the possibility that further drug resistance has developed (even when the clinical history is reliable) is, in practice, almost impossible. So, if the risks posed to the public health by any individual smear negative poorly compliant patient are small but uncertain, and probably unquantifiable, how should society respond? How might the perception of risk have influenced the response in New York City, and what can we learn from this when considering the adoption or implementation of coercive public health measures?

Societies respond to risk in a value laden manner.⁶ It was widely perceived that tuberculosis in New York City during the 1980s and early 1990s affected principally homeless, alcoholic, drug dependent, and HIV infected individuals. Was the perception of risk from poorly compliant individuals in New York City heightened, for example, by an unspoken fear of these individuals who populate the margins of society, and by certain cases, such as that of the immunocompromised prison guard with cancer acquiring multidrug resistant tuberculosis (MDRTB),⁷ or other nosocomial outbreaks,⁸ including those involving health care workers?^{9–11} Although there was no “signal” event prompting the authorities to respond to the epidemic,¹² some cases certainly generated considerable publicity.¹³

In the USA, unlike in the UK, the “police powers” which provide for and protect the public health are not held centrally but locally (with the Mayor’s appointee, the Commissioner of Health, in the case of New York City) and this system, it could be argued, increases local political awareness, accountability, and responsiveness in the public health arena. Moreover, in the case of tuberculosis where restriction fragment length polymorphism (RFLP) typing provides a mechanism to support the epidemiological linking of cases (and highlights failures in control), concerns over litigation may encourage health officials to respond more assertively in the USA (although, interestingly, cases resulting in litigation from nosocomial hospital spread of MDRTB have been seen in the UK but not in New York City).

Broadly speaking, however, although there are some differences, national responses to threats—whether they are environmental hazards or new pathogens—are similar on both sides of the Atlantic. For example, when one looks at the public, professional, and media responses to the risk of occupational transmission of HIV from health care

workers, the response to asbestos or cigarette smoking, or homicides resulting from the mentally ill, one sees many similarities. Coercive public health measures have not, however, been a major feature in tuberculosis control programmes outside the USA. In the UK, for example, legislation allows for the detention of an individual with a notifiable disease who is a threat to others, but this legislation is rarely used. Moreover, there is no legislation to detain an individual who may become a threat in the future. Whether this will remain so if rates of tuberculosis, and particularly rates of drug resistance, continue to rise is unclear.

How can public health policy directed towards tuberculosis control, which includes coercive measures and which, by necessity, focuses on a disenfranchised group of individuals whose voice may not be heard in policy debates, be as equitable and as fair as possible? What is clear is that the burden of proof that individuals pose a threat to the public should be more demanding when the consequences of regulation include detention than when economic encumbrances are created.¹⁴ Furthermore, we need to recognise that, when people feel threatened, they focus inappropriately on external sources such as stereotyped minorities and blame them, rather than assessing other threats which are perhaps closer to home.¹⁵

We must further recognise that public health decision making, particularly in a crisis, may be prone to errors, and we must be clear of the goals we are trying to attain. When coercion was used in the South Asia smallpox campaign the goal was different—it was eradication, not control. Although the campaign was successful, concerns have been raised that some of the measures used may hinder future public health campaigns, and that ultimately the use of coercion may be counterproductive.¹⁶

Despite the WHO's assertion that "everyone who breathes air, from Wall Street to the Great Wall of China, needs to worry about this risk", it is clear that the risks to all from tuberculosis are not equal. For example, in New York City, those using homeless shelters in which beds were spaced 18 inches apart and HIV prevalence was high were obviously at greater risk of exposure than those in the leafy suburbs. But the perception was high in New York that all were at risk, and undoubtedly encouraged the response seen.

As new information regarding tuberculosis transmission becomes available, as circumstances alter, and as our understanding of the perceived threats improves or changes, we must alter appropriately our view of the probabilities of potential given events occurring. Policy decisions should involve assessments that are both individualised and weighted to account for expert views on probabilities (and perhaps further weighted on the basis of past predictive success), upon economic calculations, and upon ethical analysis. Furthermore, one should be able to evaluate whether the consequences of policy decisions are similar to or different from those predicted.

An approach to our understanding of risk with regard to tuberculosis must therefore attempt to define the risk of an

event occurring (for example, the transmission of tuberculosis from a smear negative poorly compliant individual), determine the gravity of that event, weight different available measures to be taken, and alter the perception of risk with time both as our understanding improves and as circumstances change. In addition, with the changing perception of that risk, the legislative and regulatory approach to coercive public health measures should be responsive and encourage swift modifications of public health measures. The anxiety over MDRTB in New York has largely abated. It will be interesting to see if either the regulations, or the application of them, is modified in response.

Perhaps more important than any of the above, however, the use of coercive measures to support strategies which improve treatment compliance must be sensitive to national and cultural differences and not simply be based upon perceived successes elsewhere. The global control of tuberculosis may be harmed more than it is assisted by inappropriate, ill judged, culturally insensitive coercive public health measures.

This work was supported by The Commonwealth Fund, a New York City based private foundation. The views presented here are those of the author and are not necessarily those of the Commonwealth Fund, its directors, officers, or staff.

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More carrot or more stick or both?

Richard Coker describes how a system, with a substantial coercive component even for non-infectious patients, evolved in New York based on a perception of risk which was perhaps fuelled by media hype.¹ The reasons why such a system came about can, however, be appreciated from the

state of tuberculosis control—or perhaps non-control—in New York in the early 1990s.

Due to a series of cuts in health funding, routine drug sensitivity testing had been stopped, support systems were slashed, and in some areas only about 10% of patients com-

pleted treatment.² By 1992 33% of isolates were drug resistant, including 26% to isoniazid, and the rate of multidrug-resistant tuberculosis (MDRTB) was 19%.³ The expenditure in New York alone of \$750 million (£500 million) with an extensive directly observed therapy (DOT) programme had reduced the MDRTB rate to 13% in 1994.⁴

In England and Wales tuberculosis notifications fell progressively until 1987, with a rise between 1987 and 1992 of some 20%⁵ to around 6000 cases a year. Drug resistance levels had remained low between 1981 and 1992⁶ with a stable MDRTB rate of 0.6%. There has, however, been a rise in the MDRTB rate since 1993 up to 1.6%,⁷ with HIV positivity, ethnic minority groups, prior treatment, and residence in Greater London all being significant associations. Tuberculosis in the United Kingdom, as in many developed countries, is increasingly a disease which is localised to certain areas and population groups.^{8,9} The problems of tuberculosis control are largely limited to such high prevalence areas which make up some 20% of districts, with Greater London having the greatest number of such districts.⁹

The key elements of tuberculosis control in order of importance are (1) detection and treatment of cases, particularly those with sputum smear positive disease; (2) case holding which could be defined as maintaining treatment to completion; and (3) preventive measures such as chemoprophylaxis and BCG vaccination. There also needs to be adequate staffing levels of doctors and, in particular, of tuberculosis nurses/health visitors to deliver a service with those elements.¹⁰

The philosophical or ethical dilemma that Dr Coker raises is where the "balance point" between the libertarian and coercive strategies in tuberculosis management lies or, alternatively, where the rights of society in general outweigh the rights of an individual or vice versa. This varies according to the society and situation, and with the public perception of risk rather than the actual risk. In England and Wales currently, as a last resort, sections 37 and 38 of the Public Health Act allow for compulsory detention of a person with infectious tuberculosis of the respiratory tract. Compulsory treatment is not allowed so that compulsory admission is only sought in extreme circumstances to safeguard the public health. When such compulsory admission is sought, there are also the practical problems of maintaining such detention and of determining when "infectivity" ceases. Legally compulsory detention is only allowed for "infectious" tuberculosis of the respiratory tract, but how should this be defined—sputum smear positivity or sputum culture negativity? If a compulsorily detained person with fully sensitive smear positive disease accepts standard short course chemotherapy,¹⁰ trial evidence shows that >90% should become smear and culture negative by two months and 98% culture negative by three months.¹¹ However, infectivity requiring segregation (if in hospital) is generally only required for two weeks because the infectivity of smear positive individuals declines rapidly.^{12,13} Therefore, even applying culture negativity, detention legally would be for a maximum of three months, only half the duration required for full treatment.¹⁰

The dilemma is even more complicated for HIV positive individuals or those with MDRTB. HIV positive individuals are much more susceptible to disease progression, perhaps 170 times that of HIV negative individuals,¹⁴ and in acquiring infection, so that even smear negative culture positive disease may be significantly infectious for this group. With MDRTB, because of the loss of the main killing drug (isoniazid) and the main sterilising drug

(rifampicin), the usual rapid reduction in infectivity is no longer possible,^{12,13} and such individuals can remain infectious, however defined, for prolonged periods, sometimes lasting up to months.

The Government in its recent moves on Care in the Community for mental health announced alterations to the Mental Health Act to permit compliance orders which will force psychiatric patients to take their medication, and "assertive outreach teams" to police this with the right to compulsorily readmit non-compliant patients. Whilst a person with smear positive tuberculosis not taking treatment, or taking it only intermittently, is not as immediately dangerous as an acute paranoid schizophrenic, such persons are infectious, transmit such infections readily to the unvaccinated and immunocompromised, if poorly compliant are at increased risk of developing and then transmitting drug resistance, tuberculosis still carries a significant morbidity and mortality even in immunocompetent cases (5859 cases in 1997, 392 deaths attributable to tuberculosis and 55 due to late effects; P Van Buynder, personal communication), and MDRTB carries a very much higher morbidity and mortality even in immunocompetent cases.¹⁵

A review of the powers for communicable disease control has been promised over the next few years when such issues will need to be debated by doctors and allied professions, patient representatives, lawyers and politicians representing the "public interest". A possible pragmatic solution would be to increase the incentives to compliance, free drugs with practical help—food, housing, social support for disadvantaged groups such as the homeless and refugees (more carrot), but to strengthen or at least define clearly if and when compulsory detention (and treatment?) should be used for cases where the collaborative approach has failed (more stick). Such a system would be predicated on having minimum staffing levels to monitor and deliver treatment to recommended standards.¹⁰

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Bronchiolitis obliterans organising pneumonia associated with the use of nitrofurantoin

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Abstract

The spectrum of nitrofurantoin lung injury continues to widen. The case histories are presented of two patients who developed lung disease associated with the use of nitrofurantoin with histological features of bronchiolitis obliterans organising pneumonia (BOOP), a rare but recognised form of drug induced injury. The two middle aged women presented with respiratory symptoms after prolonged treatment with nitrofurantoin. Both had impaired lung function and abnormal computed tomographic scans, and their condition improved when nitrofurantoin was withdrawn and corticosteroid treatment commenced. The favourable outcome in these two patients contrasts with the fatal outcome of the two other reported cases of nitrofurantoin induced BOOP. We suggest that the previous classification of nitrofurantoin induced lung injury into "acute" and "chronic" injury is an oversimplification in view of the wide variety of pathological entities that have subsequently emerged.

(Thorax 2000;55:249-251)

Keywords: bronchiolitis obliterans organising pneumonia; drug induced pulmonary disease; nitrofurantoin

An increasing number of drugs are recognised as causing lung injury and the spectrum of their adverse effects is widening. A recognised but uncommon form of drug induced lung disease is bronchiolitis obliterans organising pneumonia (BOOP).¹ We report two cases of nitrofurantoin induced pulmonary disease with histological features of BOOP.

Case 1

A 34 year old female non-smoker with recurrent urinary tract infections presented with increasing dyspnoea and cough over several months. She had been taking nitrofurantoin 50 mg at night for more than two years. She had no other significant exposures and was on no other medications. Examination was normal. The chest radiograph showed diffuse bi-basal reticulonodular shadowing. Baseline blood tests were normal, except for ANA 1:1280, with a diffuse staining pattern. Lung function tests showed forced expiratory volume in one second (FEV₁) of 2.09 l with forced vital capacity (FVC) of 2.33 l (predicted 3.18/4.04). Carbon monoxide transfer factor (TLCO) was reduced to 67% predicted. High resolution computed tomographic (HRCT) scans of the thorax showed patchy peribronchial interstitial

thickening, especially of the medium and small sized bronchi, with very little fibrosis. Open lung biopsy specimens showed that many respiratory bronchioles were distorted and largely occluded by fibroblastic tissue with associated mucus plugging and outgrowth of respiratory epithelium into surrounding alveolar tissue, consistent with BOOP. In the absence of other factors a diagnosis of nitrofurantoin induced pulmonary disease was made and the drug was discontinued. Prednisone 30 mg per day, gradually reducing over nine months, resulted in significant symptomatic improvement, significant improvement in lung function (FEV₁ 3.56 l, FVC 4.20 l, TLCO 82% predicted), and considerable but incomplete clearance of interstitial changes on the HRCT scan.

Case 2

A 50 year old female non-smoker with recurrent urinary tract infections gave a two month history of worsening dyspnoea, fatigue, anorexia, and cough with fevers and night sweats for three weeks. There was no history to suggest an underlying connective tissue disorder. She had been taking nitrofurantoin 50 mg at night regularly for one year. On examination she was tachypnoeic and tachycardic with bi-basal "velcro" crackles. Arterial blood gas measurements showed hypoxia (Pao₂ 6.5 kPa) with a wide alveolar-arterial gradient (9.1 kPa). Blood count and renal and liver function were normal, erythrocyte sedimentation rate (ESR) was 81 mm/h, and the ANA was 1:1640 with anti dsDNA negative. Lung function tests showed FEV₁ of 0.82 l and FVC of 0.84 l (predicted 2.87 and 3.77 l, respectively). TLCO could not be measured because of breathlessness. An HRCT scan of the thorax showed patches of "ground glass" opacity, interstitial fibrosis with traction bronchiectasis, and scattered areas of dense consolidation (fig 1). Transbronchial biopsy specimens showed loose immature fibrous tissue within air spaces and incorporated into the interstitium, a patchy interstitial infiltrate of mixed inflammatory cells including lymphocytes, plasma cells, and a few eosinophils, and prominent hyperplasia of type II pneumocytes. Pieces of airway wall showed inflammation with peri-airway fibrous and outgrowth of respiratory epithelium into fibrotic lung tissue. The appearance was consistent with BOOP/diffuse alveolar damage. The diagnosis of nitrofurantoin induced pulmonary disease was made; the drug was withdrawn and prednisone 40 mg daily reducing slowly to baseline 10 mg daily was given over three months. At three months a repeat

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Received 25 November 1997
Returned to authors
19 January 1998
Revised manuscript received
2 June 1998
Accepted for publication
10 July 1998

Figure 1 (A) Mid thoracic HRCT scan in case 2 showing small residual areas of normal lung, extensive interstitial fibrosis with traction bronchiectasis most marked in the right middle lobe, patchy ground glass opacity, and areas of dense consolidation. (B) Equivalent HRCT scan three months after withdrawal of nitrofurantoin and commencement of treatment with prednisone showing extensive but incomplete clearance of abnormalities.

HRCT scan showed marked reduction of the ground glass opacities and areas of consolidation, but with persistent interstitial fibrosis. Repeat lung function tests showed FEV₁ had improved to 2.88 l (100% predicted) with FVC 2.89 l (77% predicted) and TLC 66% predicted. The patient was subsequently weaned off oral steroids with no clinical, radiological, or physiological evidence of relapse.

Discussion

We conclude that both patients had nitrofurantoin induced pulmonary disease on the grounds that there was a lack of an alternative explanation for their lung disease and a good response to drug withdrawal and treatment with an oral corticosteroid. We acknowledge that BOOP of other causes may respond well to

corticosteroid treatment, but there was no disease recrudescence on steroid reduction and withdrawal. The establishment of a firm aetiological relationship would require re-challenge with nitrofurantoin. This was considered inappropriate in view of the severity of pulmonary impairment on presentation and the residual and irreversible changes on the HRCT scan.

Relatively few pharmaceutical agents have been associated with BOOP. These include amiodarone, acebutalol, nilutamide, cephalosporins, barbiturates, and cocaine.² There are only two previously reported cases of BOOP attributable to nitrofurantoin use.³ Both patients were elderly ex-smokers with symptoms of 3–4 weeks duration and both responded well to initial corticosteroid treatment, but rapid tapering led to an irreversible decline and death after failure to respond to increased steroid dosage. Details of drug treatment were not included in the report.

The course of the disease in our patients was rather different. Both were maintained on medium to high dose prednisone initially, gradually reducing over months, and the duration of treatment may have been important in terms of the improved outcome. They were weaned off oral steroids without clinical, radiological, or physiological evidence of relapse.

Nitrofurantoin induced pulmonary disease may present in many forms including BOOP, diffuse alveolar damage, vasculitis, interstitial fibrosis, pleural and airways disease, and pulmonary haemorrhage.¹ A final common toxic pathway has not been postulated. Nitrofurantoin induced pulmonary disease may result from immune mediated injury^{3,4} or via hydroxyl radical generation with subsequent free oxidant damage.⁵ The reduced incidence with the addition of the antioxidant ascorbic acid to nitrofurantoin preparations⁵ and results of *in vitro* studies⁶ suggest that this and other antioxidants may significantly reduce toxicity.

Initial reports suggested that the duration of nitrofurantoin treatment dictated the disease pattern. The “acute” reaction was characterised by marked constitutional symptoms including rash, fever, arthralgia, fatigue, together with pulmonary symptoms of dry cough and dyspnoea.^{3–5} The “subacute” and “chronic” forms were more insidious, with increased eosinophil count, raised ESR, and vasculitis and interstitial inflammation on histological examination, consistent with a type III immune response.^{3,4} Increased immunoglobulin levels, hepatic transaminases and ANA titres (the so called “drug induced lupus syndrome”^{7,8}) was associated with a degree of irreversible fibrosis. Some early reports of biopsy specimens from a patient with nitrofurantoin induced lung disease⁵ which predate the recognition of idiopathic BOOP as an independent entity are suggestive of a BOOP-like pattern. Cohen³ suggested that BOOP may be a precursor to chronic lung fibrosis, an early and potentially reversible phase in the spectrum of fibrosing lung disease. However, both patients in this report had residual radiological abnormalities although the remaining functional abnormalities were minor. The subsequent variety of

pathological entities now shown to be caused by nitrofurantoin suggests that these early categorisations are an oversimplification.

The initial interest in nitrofurantoin induced lung disease has waned as more suitable less toxic agents have been found for chronic urinary infections. However, the drug remains generally available in spite of its high toxic profile and clinicians need to be aware of the spectrum of associated lung disease.

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LETTERS TO THE EDITOR

Systematic review of antistaphylococcal antibiotic therapy in cystic fibrosis

McCaffery *et al*¹ conclude that "antistaphylococcal treatment achieves sputum clearance of *Staphylococcus aureus* in patients with cystic fibrosis . . ." and that prophylactic treatment in young children is "... likely to be of clinical benefit". These positive conclusions are based on the results of a study which has important methodological problems. Neither the introduction nor the methods section of this review state what hypotheses the review set out to test, the criteria used to decide whether a study was suitable for inclusion, outcomes to be studied in the review, or methods used to assess the methodological quality of included studies. Systematic reviews differ from narrative reviews in that they test hypotheses using a methodology which is well described.² The authors have described their search strategy, which is based on that developed by the Cochrane Collaboration, to identify randomised controlled trials. The authors have, however, included a number of studies in their review which are not randomised controlled trials. It is not clear from the information provided whether their search strategy is sensitive enough to identify all possible relevant studies.

The authors base their conclusions on the results of just two randomised controlled trials, involving only 66 children, with a maximum follow up of two years.^{3,4} All of these children were under seven years of age (most under two years) and had upper respiratory samples taken, not sputum. Of the other studies described as randomised, one used alternate allocation (and so was not randomised)⁵ and one reported further outcomes in patients included in one of the randomised controlled trials.⁶ Only two randomised controlled trials actually reported the prevalence of *S aureus* in respiratory secretions. The larger study by Weaver *et al*⁶ reported that the prevalence of *S aureus* was reduced with prophylaxis but

"clearance" was not achieved from nose and throat swabs.

The important issues for cystic fibrosis patients and their families are not eradication of an organism but fewer symptoms, improved lung function, and prolonged survival. None of the studies described in the review addressed these issues nor, indeed, the concern that prophylactic antibiotics may encourage chronic pulmonary infection with organisms such as *Pseudomonas aeruginosa* or multiply resistant *S aureus*. A Cochrane review addressing this intervention is currently being undertaken by two of us (AS and SW) and this will have the advantage that it will be regularly updated to incorporate new studies. Only when further properly designed studies have been completed and included in an up to date systematic review will we be able to evaluate whether antistaphylococcal antibiotic prophylaxis is "... likely to be of clinical benefit".

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AUTHORS' REPLY Smyth *et al* have listed a number of features that they regard as being essential to systematic reviews. In particular, they suggest that systematic reviews should always test hypotheses. However, a clear understanding of the existing evidence is necessary for the generation of valid hypo-

theses and, in our view, this is best achieved by systematic reviewing. Indeed, many important systematic reviews published in major clinical journals do not specifically test hypotheses, but study the current evidence in order to identify the state of existing knowledge and to define areas for further research.^{1,2} This objective is consistent with the view of the authors of the Cochrane Collaboration Handbook who recognise that systematic reviews can have different motivations, one of which is the resolution of conflicting evidence.³ Indeed, it is probably difficult to define systematic reviews as formally as Smyth *et al* (and others) have proposed as the science of systematic reviewing is undergoing continuous development. More systematic reviews are being performed now than ever before (a Medline search looking for "systematic review" in titles and abstracts presents 4158 citations in the last 10 years, 1538 (37%) of which are in the last two), with reviewers defining their methods according to the problem in question.

Again, because of the nature of the field being studied, we had purposely not defined stricter criteria for study selection or drawn up a preselected list of outcomes of interest. As the area under investigation was largely unknown, we felt such criteria could limit our search. Also, in the absence of any significant background information, we were uncertain if such a choice of outcomes could be made objectively. Indeed, if we had arbitrarily drawn up a list of outcomes that were of interest to us, we would have missed a number of outcomes that others had used and which could be of potential interest to readers when designing clinical trials in the future. We did not use quality scores because there is little objective evidence to support the use of quality scoring in systematic reviews.⁴ Many of the scoring systems have not been developed with sufficient rigour⁴ and could add the analyst's bias to the results.⁵ A recent review of a random sample of 240 meta-analyses showed that less than half assessed trial quality.⁶ However, we note that newer techniques such as meta-regression may provide better alternatives in the future.

As we were principally interested in randomised controlled trials (RCTs), we used a search strategy that has been well validated for the recall of such trials. However, as before,⁷ we wanted to present an analysis of outcomes of both RCTs and non-RCTs because we felt this would make our conclusions more objective. Again, this approach is supported by the authors of the Cochrane Collaboration Handbook.⁸ Smyth *et al* state quite rightly that the important issues for cystic fibrosis patients and their families are not eradication of an organism but fewer

symptoms, improved lung function, and prolonged survival. However, this should not inhibit the use of laboratory based outcomes which could influence clinical decision making until appropriate clinical data are available. Indeed, given the high predictive value of oropharyngeal cultures in children for identifying pathogens in bronchoalveolar lavage fluid (sensitivity and specificity of 90%),⁸ we feel the evidence we have defined in support of clearance of *Staphylococcus aureus* from the upper or lower respiratory tract with anti-staphylococcal antibiotics does suggest that this therapeutic intervention is likely to be of clinical benefit, although we strongly support their argument that properly designed studies are needed to confirm this hypothesis.

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Therapeutic ratio of inhaled fluticasone

I read with interest the recent article by Meijer and colleagues on the effects of inhaled fluticasone and prednisolone on clinical and inflammatory parameters in patients with asthma.¹ Rather than focusing on the differences between oral and inhaled corticosteroid, I believe that a more important finding is the effect of a fourfold increase in the dose of fluticasone on the therapeutic ratio. For airway parameters there were no significant differences in the effects on bronchial hyperresponsiveness to methacholine and adenosine monophosphate or on sputum eosinophils between fluticasone in doses of 500 µg and 2000 µg per day. However, for systemic bioactivity markers there were significant differences between the two doses of fluticasone on serum cortisol levels and blood eosinophils. Taken together these findings suggest that, at least for effects on airway hyperresponsiveness and inflammation, the therapeutic ratio for fluticasone declines sharply above a watershed dose of 500 µg per day. This result is perhaps not surprising, given the high glucocorticoid

topical potency for in vitro anti-inflammatory activity with fluticasone.²

It is also important to point out that the study by Meijer *et al* was performed using fluticasone delivered via a Diskhaler dry powder inhaler device, which delivers a twofold lower respirable fine particle dose than a fluticasone propionate pressurized metered dose inhaler.³ This is due to the larger particle size from the fluticasone dry powder inhaler. Hence, increasing the nominal dose of fluticasone dry powder may result in a proportionately greater delivery of larger particles to the central airways and consequently to a less than expected impact on small airway inflammation. The lower fine particle dose of fluticasone dry powder will also result in reduced lung bioavailability, as shown by a fivefold lower degree of adrenal suppression compared with the same nominal dose of fluticasone delivered via a pressurized metered dose inhaler with spacer device.⁴ The use of fluticasone in a dose of 500 µg/day via a dry powder inhaler would therefore explain the absence of any significant suppression of blood eosinophils or serum cortisol in their study. This does not mean that fluticasone propionate dry powder in a dose of 500 µg/day is not systemically bioavailable, as recently published data with this dose of fluticasone given via a Diskhaler reported significant suppression of 24 hour urinary cortisol excretion (33% reduction) and peripheral blood lymphocyte glucocorticoid receptor mRNA expression (71% reduction) during steady state dosing in asthmatic patients.⁵

Another finding in the study by Meijer *et al* was the relatively greater effect on bronchial hyperresponsiveness to adenosine monophosphate than to methacholine challenge with both oral and inhaled corticosteroid after two weeks. Similar findings have been reported after two weeks of treatment with inhaled budesonide powder in a dose of 1600 µg/day.⁶ The authors not unreasonably suggested that adenosine monophosphate responsiveness might be more sensitive to changes in airway inflammation than methacholine. However, the treatment period was relatively short and one cannot exclude the possibility that the effects on methacholine hyperresponsiveness might have been proportionately greater with a longer duration of treatment, as has been reported in previous studies.^{7,8} It is also conceivable that differences in bronchial hyperresponsiveness between the doses of inhaled fluticasone may have become apparent with a longer duration of treatment.

Finally, it is important not to extrapolate the results of the study by Meijer *et al* on patients with relatively mild asthma to more severe asthmatic patients in whom altered airway geometry may cause a reduction in lung delivery and lung bioavailability from narrowed peripheral small airways. Also, their results may be specific to the unique drug/device interaction of fluticasone propionate given via the dry powder inhaler, and further studies are needed to look at the dose-response relationship for the therapeutic ratio using more efficient delivery systems such as a pressurized metered dose inhaler with spacer.

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- 1 Meijer RJ, Kerstjens HAM, Arends LR, *et al.* Effects of inhaled fluticasone and oral prednisolone on clinical and inflammatory parameters in patients with asthma. *Thorax* 1999;**54**:894–9.
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AUTHORS' REPLY We thank Dr Lipworth for his interest in our article.¹ Although we found no significant dose difference in PC₂₀ adenosine monophosphate and methacholine or in sputum eosinophils over a two week period between the two doses of fluticasone, the trends suggested a favourable effect of 2000 µg compared with 500 µg per day for every parameter measured, and there was, indeed, a significant dose response effect on sputum levels of ECP. It is well known that the dose response curve for inhaled steroids in general is very shallow at conventional and higher doses, and we agree that from our data this seems to apply to fluticasone also. From our study, in which only two doses of fluticasone were used, we are careful not to overinterpret where the decline in the therapeutic ratio starts with this drug.

We are aware that the respirable fraction of fluticasone in the dry powder formulation is lower than in the pressurized metered dose inhaler, although the suggested magnitude of the difference is debatable using data from Dr Lipworth's own group.² Unfortunately, in humans we still have considerable problems in separating the effects of common drugs on the large and the small airways, and the remarks by Dr Lipworth on the site of delivery are intuitively correct but, we believe, unproven as far as the clinical effects are concerned. There is no doubt that the dry powder formulation has systemic bioavailability and we clearly demonstrate this. We accept the notion that, with more sensitive markers of bioavailability, an effect might have been demonstrable also with the dose of 500 µg per day. The clinical relevance of this still needs to be determined even after so many years of using inhaled steroids.

We agree that the improvement in hyperresponsiveness with steroid treatment can continue for much longer than the improvement in forced expiratory volume in one second (FEV₁).³ The concept that the improvement in methacholine hyperresponsiveness might continue for a longer period than that of

adenosine is interesting, but we are unaware of any data to substantiate this. In fact, in a study by Weersink and colleagues, the same difference between the two bronchoconstrictor agents held true for six weeks instead of the two weeks of fluticasone treatment in the current study.⁴

It is interesting to debate whether the insufficient effect of inhaled steroids in patients with severe asthma is due to lower availability in the peripheral airways, as Dr Lipworth suggests, or, for instance, to a decreased sensitivity to steroids—either *per se* or as a result of increased inflammation and associated cytokine load.⁵ The suggestion by Dr Lipworth should result in a relatively better effect of systemic steroids compared with inhaled steroids, especially in the more obstructed patients, but this does not agree with our clinical impression. In fact, the finding of a superior effect of the inhaled corticosteroid over oral prednisolone (30 mg for two weeks) in our study rather suggests a contrary mechanism, perhaps compatible with a higher effectiveness of the lipophilic compound fluticasone at the level of the epithelium and (sub)mucosa than of systemic prednisolone, even if only in the larger airways. Nevertheless, we are careful not to extrapolate our findings beyond the devices and population studied. There are, however, in addition to ours, a few other studies which suggest that inhaled corticosteroids may have an effect at least as great as prednisolone in asthma exacerbations.^{6,7}

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- 1 Meijer RJ, Kerstjens HA, Arends LR, *et al.* Effects of inhaled fluticasone and oral prednisolone on clinical and inflammatory parameters in patients with asthma. *Thorax* 1999;54:894–9.
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“Systematic review” of asthma education studies

We were disappointed that Sudre *et al.*¹ felt there was insufficient documentation and excessive variability in studies of education programmes for adults with asthma published between 1979 and 1998. We feel that their conclusion is largely because they did

not perform a rigorous systematic review of papers in this area.

Systematic reviews of research evidence are undoubtedly invaluable scientific activities. They establish whether scientific findings are consistent and can be generalised across populations, settings, and other variations. Systematic reviews should be based on the “gold standard” of published randomised clinical trials. However, in the 77 trials reported Sudre *et al.* included 35 studies which were not randomised controlled trials. They also give no information about which interventions were found to have statistically significant effects. They include a study which simply asked patients whether they preferred audiovisual information or written information and did not have any intervention,² a study which has not been published,³ and interventions assessing the use of psychotherapy⁴ and yoga⁵ for asthma patients, which seem outside the criteria for inclusion in the review. Another four studies they include are excluded from the Cochrane reviews of patient education^{6,7} on the grounds that they are not educational intervention studies. It is therefore not surprising that in 81% of projects assessed the background educational theory was not mentioned and few projects had a patient’s needs assessment performed.

While we accept that many of the studies reviewed had missing information on the form and duration of education, we are concerned that some of these studies may be being misquoted. As an example, our own randomised controlled trial on personalised patient education for asthma delivered in four booklets over three months (reference 65) is incorrectly quoted as consisting of “a 10 minute encounter with a physician”.⁸ We are concerned that other studies referenced may also have been incorrectly classified.

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- 1 Sudre P, Jacquemet S, Uldry C, *et al.* Objectives, methods and content of patient education programmes for adults with asthma: systematic review of studies published between 1979 and 1998. *Thorax* 1999;54:681–7.
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AUTHORS’ REPLY Drs Douglas and Osman correctly state that we did not perform a systematic review of the efficacy of education

programmes, but neither did we claim to do so. Our goal, clearly stated in the title, was to describe the objectives, methods, and content of education programmes. In fact, we renounced conducting a meta-analysis of the effectiveness of programmes when we realised the extent of the variability of educational interventions. Averaging the proverbial apples and oranges did not make much sense. Our study suggests that, not only is the number of fruit species greater than anticipated (variability between programmes), but you cannot always tell one from the other (insufficient description of programmes). The latter finding implies that even a systematic review aimed at identifying features associated with greater effectiveness is not feasible. Such an endeavour would be further complicated by the fact that variables used to assess efficacy vary from one evaluation study to the next. In our opinion, standardisation of both programme descriptions and evaluation methods would foster progress in patient education.

While randomised controlled trials are the gold standard for assessing efficacy, *all* studies reporting an educational intervention should describe in sufficient detail what that intervention consisted of. We therefore included in our review all studies that had an educational component, regardless of the evaluation design.

We admit that we used a broad definition of education as “any attempt to provide the patient with knowledge or personal skills to reduce the impact of asthma on health”. The educational content varied among programmes (this is one of our main points) and could include drug management, environmental control, relaxation, yoga, etc. The paper by Partridge¹ provides an interesting description of an education programme in an asthma clinic, its weaknesses, and attempts at correcting these. As for including work published only as a dissertation, this may be considered an advantage rather than a drawback by some meta-analysts. We maintain that all studies that we reviewed included an explicit educational component and doubt that changing eligibility criteria to exclude a small subset of studies would much alter our general conclusions.

We stand corrected about the incomplete reference to the Grassic intervention in the discussion section of our paper.² In our database this programme was described more accurately as follows (partial data): number of training sessions: 4 (counting one 10 minute session in person and three mailed booklets); duration of training period: 3 months; delivery of education by: *physician and self-help*; educational setting: *individual*; training tools: *booklet*; training method: *lecture/vertical teaching*. Had we conducted an effectiveness review we would have no doubt singled out this study as by far the largest trial of asthma education, and one that did achieve clinical benefits for its patients. More such research studies are needed.

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- 1 Partridge MR. Asthma education: more reading or more viewing? *J R Soc Med* 1986;79.
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BOOK REVIEWS

Case Presentations in Clinical Tuberculosis Davies PDO, Ormerod LP. (Pp 320; £29.99). Edward Arnold. ISBN 0 340741 597.

This text is a thorough but concise overview of clinical tuberculosis presented as a well structured series of cases with clearly reproduced radiographs, computed tomographic scans, and slides. Each case is complemented by a short pertinent discussion clarifying any points of interest or debate. A carefully chosen chapter layout sequentially introduces the reader to the most challenging and interesting aspects of the disease and also provides an easy reference framework.

The authors' obvious wealth of experience allows readers with a more limited exposure to learn something of the more unusual manifestations of infection, including an extensive range of extrapulmonary and multisystem disease. The complex matter of antituberculous treatment in the emergent group with drug resistant mycobacterial infection, comorbidity, or compliance problems is tackled in some depth, highlighting potential pitfalls and explaining, in a real clinical context, the reasons behind the decisions made.

The difficulties associated with the diagnosis and management of tuberculosis in patients with human immunodeficiency virus are well illustrated, but not exhaustively covered, in a chapter whose commentary sections are particularly full and instructive.

Most of the 120 featured case presentations have a short list of affiliated references aimed to guide, rather than delineate in detail, further research of the points of interest raised.

The format of the book ensures an enjoyable and pragmatic approach to learning about tuberculosis, thus making it directly relevant to all those involved in the medical care of patients with the condition, especially at a training level. It would be an ideal accompaniment to existing formal textbooks.—ILJ

Anti-Inflammatory Drugs in Asthma. Sampson AP, Church MK, eds. (Pp 288, hardback). Switzerland: Birkhauser, 1999. ISBN 3 7643 5873 4

This is one of a series of publications under the collective heading "Progress in Inflammation Research" to which some of the European heavyweights in asthma research have contributed chapters. All the asthma drugs are included with the notable exception of the anticholinergic agents, although I found the title a little misleading as the in vivo

anti-inflammatory effects of some of the drugs discussed remains contentious. However, from the opening chapter it becomes apparent that investigations into the pathophysiology of, and the effects of treatment on, asthma have played an important part in defining the inflammatory mechanisms. The "commonly" used asthma medications are discussed initially with Peter Barnes giving an erudite synopsis of the anti-inflammatory effects of corticosteroids. The next two chapters deal with the putative anti-inflammatory effects of phosphodiesterase inhibitors and β_2 adrenoceptor agonists, although the chapter on phosphodiesterase inhibitors concentrated on the different isoenzymes and thus was heavy going with little discussion of their anti-inflammatory effects and no concluding summary. Despite theophylline being available for at least 40 years, I was struck by the paucity of clinical data available regarding its efficacy and in vivo anti-inflammatory effect (if at all). This is presumably because it is not profitable for pharmaceutical companies to investigate the drug further. The mast cell stabilisers are considered next, and the last third of the book deals with leukotriene antagonists and discusses other novel potential anti-inflammatory agents including anti-IgE agents, cytokines and adhesion molecule antagonists.

Several of the chapters are interesting and well written with well laid out tables and graphs, although some have several annoying typographical errors. The book does provide a good summary of the anti-inflammatory effects of present and potential future asthma medications and would act as a good reference source for departments or individuals with an interest in this field.—JB

NOTICES

Cardiovascular Disease Prevention V

A conference entitled "Cardiovascular Disease Prevention V" will be held on 4–7 April 2000 at the Conference Centre, Kensington Town Hall, London. For further information contact The Secretariat, Hampton Medical Conferences Ltd, 127 High Street, Teddington, Middlesex TW11 8HH, UK. Telephone +44 (0)181 977 0011. Fax +44 (0)181 977 0055. email hmc@hamptonmedical.com

British Association for Lung Research

The British Association for Lung Research (BALR) Spring Meeting entitled "Inflammation Control: A Goal for the Millennium" will

be held on 18 April 2000 at the Wills Hall, University of Bristol. For further information contact Dr Lynne Armstrong, The Lung Research Group, University of Bristol Medical School Unit, Southmead Hospital, Westbury on Trym, Bristol BS10 5NB, UK. Telephone +44 (0)117 959 5348. Fax +44 (0)117 959 5018. email Lynne.Armstrong@bristol.ac.uk

CORRECTIONS

UK Pulmonary Vascular Units

In the list of UK Pulmonary Vascular Units given at the end of the review article on "Primary pulmonary hypertension" by A J Peacock which appeared in the December issue of *Thorax* (1999;54:1107–18), the address for Dr Simon Gibbs should have included the Imperial College School of Medicine which includes Hammersmith, Brompton and Harefield hospitals.

Atrial septostomy in pulmonary vascular disease

In the editorial entitled "Role of atrial septostomy in the treatment of pulmonary vascular disease" by R J Barst which appeared on pp 95–6 of the February issue of *Thorax*, there was an error in figure 1. The correct version is reproduced below, showing that in "non-responders" the PAP is *increased* or unchanged. The publishers apologise for this error.