College lectures

Tuberculosis—out of control?

The Mitchell Lecture 1995

The aim of tuberculosis control is to eradicate the disease from the community, as has been achieved for several other major infectious diseases. Since Robert Koch discovered the tubercle bacillus in 1882, the development of effective vaccines and drugs has given us the tools for tuberculosis control. In spite of this, over 100 years later in 1993, the World Health Organisation (WHO) declared tuberculosis a global emergency. Every year 8 million new cases arise and 2.9 million people die, nearly all in developing countries where tuberculosis is still responsible for 25% of all avoidable adult deaths. Although the HIV (human immunodeficiency virus) epidemic is one of the major reasons for today's problems, many other factors have threatened and still threaten tuberculosis control and have prevented our attempts to eradicate the disease, even in countries that have not yet felt the full effect of HIV.

The size of the tuberculosis problem in a country today depends on the stage of the epidemic, the efficacy of the control programme and the impact of the HIV epidemic [1]. The tuberculosis epidemic reached its peak in Western Europe and the white population of North America in the late 18th to early 19th century and in Asia in the late 19th century, but in sub-Saharan Africa the peak did not occur until the early 20th century [1]. Much of the tuberculosis disease in Africa is therefore still in the younger age groups, with major implications for the overlap with the HIV epidemic.

Even before effective chemotherapy was available, mortality and morbidity from tuberculosis was declining in the UK and other Western countries. The reasons for this 'natural decline' of 1–2% per year are unknown but have been variously attributed to:

- Increase in resistance in the population
- Isolation of infectious cases
- Improved socioeconomic conditions, particularly nutrition and the reduction of overcrowding.

The absence of a similar decline in many developing countries suggests that the last factor may be the most important. In 1899 Sir Herman Weber wrote in the first edition of Tuberculosis, the journal of the National Association for the Prevention of Consumption and other forms of tuberculosis [2], that 'the most important factors in producing tuberculosis are:

- Air contaminated by the so-called tubercle bacillus
- Food inadequate in purity, quality and quantity
- Confined and overcrowded dwellings with absence of sun, light and ventilation, especially when situated on damp and impure soil
- A low state of general health and resisting power of the body'.

This led to the establishment of sanatoria and open-air homes.

The natural decline in tuberculosis in the UK and several other countries was interrupted by World Wars I and II. The Medical Research Council (MRC) Committee on tuberculosis in war-time reported in 1942 [3] that factors that led to an increase in both mortality and morbidity were likely to include:

- Evacuation of the sanatoria to make way for casualties, resulting in infectious cases returning to the community
- Overcrowding because of the destruction of homes and the evacuation of individuals to the country
- Increased consumption of raw milk by children who were evacuated. One of the great successes of tuberculosis control in the UK has, however, been the eradication of bovine tuberculosis, although this owes more to vets than to doctors
- Increased industrialisation resulting in increased contact at work
- Lowered host resistance for various reasons, including long hours being worked by people unused to heavy work and disturbed nights
- Poor nutrition.

The impact of World War Two was primarily on morbidity and mortality associated with reactivation of infection. However, the increase in the number of cases because of reactivation may well have increased transmission. Indeed, the greatest increase in morbidity during World War Two was in tuberculous meningitis in children and young adults. A recent small study from El Salvador suggests that increased transmission has occurred in a small community displaced in the civil war between 1980 and 1992 [4]. A tuberculin survey of 700 people aged 1 to 30 years showed that among those who had not had BCG (bacille Calmette-Guérin) vaccination the estimated annual risk of infection had declined from 3.1% for

This article is based on the Mitchell Lecture given at the Royal College of Physicians on 12 June 1995 by Janet Darbyshire, Head of MRC HIV Clinical Trials Centre, University College London Medical School, London.
those born between 1963 and 1968 to 1.25% for those born between 1980 and 1986, but the risk had increased to 2.5% for those born after 1986. Clearly, wars are a continuing threat to tuberculosis control.

Tuberculosis control

The development of effective drugs and vaccines provided us with three approaches to tuberculosis control:

- Case finding and treatment
- Chemoprophylaxis
- Vaccination.

Vaccination might appear to be the most attractive option as it should prevent disease and has been successful in many other infections. In tuberculosis, however, it has been very disappointing as a control measure. One reason for this is the wide variation in its efficacy in different populations, as demonstrated in both clinical trials and epidemiological studies [5]. Further, contrary to popular theory, prevention is not better than cure [6]. First, whereas the outcome of chemotherapy should be cure, BCG vaccination allows infection to occur, limiting the extent and progression of the infection but leaving the risk that tuberculosis might develop subsequently. Many issues remain unresolved in relation to BCG vaccination. The apparent decrease in protection over time may be due to waning potency of the vaccine or to increased immunity in the unvaccinated. The benefits of revaccination, which is still carried out extensively in some populations, have never been adequately evaluated. Second, chemotherapy acts rapidly to prevent infections in contacts and the infections it prevents would probably have occurred over the next year or so. In contrast, those infections prevented by BCG vaccination might have occurred over more than 10 years. Third, chemotherapy can be given to a high proportion of tuberculosis cases, whereas it is impossible effectively to cover the whole population with BCG; in particular, many people are probably already infected. Further evidence that BCG vaccination plays no role in tuberculosis control comes from the similarities in mortality and morbidity between countries that adopted policies of vaccination and those that did not, the classic example being the UK and the Netherlands.

Although BCG vaccination is disappointing as a control measure, its value in preventing the severe forms of childhood disease justifies its inclusion in the expanded programme of immunisation. Research efforts to develop better vaccines continue, but even if a promising vaccine is found, evaluation will be a long and difficult process. As Paul Fine has pointed out 'as BCG is used widely in most populations at high risk of tuberculosis, any new vaccines will have to contend with BCG’s influences, whatever they may be ... the recognition that BCG vaccines can provide good protection in one population, but not in another, will haunt any effort to evaluate and to extrapolate the effects of new vaccine products' [5].

Chemoprophylaxis

Chemoprophylaxis has been used on a wide scale in some countries, such as the US, which have not adopted BCG vaccination, but it too is a disappointing control measure even though its aim is also to prevent disease. There is general agreement that chemoprophylaxis is of value in infected people who have a high risk of developing the disease, for example young children and recent immigrants, and also to prevent infection in infants of mothers with a positive sputum smear. Its role, particularly in developing countries, is limited because of the costs and difficulties of organising a successful programme and the risk that resources may be diverted from treatment services. There is also a risk of hepatotoxicity, particularly in the older age groups, which is important if only 10% are likely to develop tuberculous disease.

HIV may be the most potent risk factor for breakdown of tuberculosis. There is now evidence from several studies that chemoprophylaxis may reduce the risk, certainly in the short term, but its longer term effects are less certain, particularly in populations with a high frequency of tuberculosis where apparent failure may be due to reinfection. However, the role of chemoprophylaxis, even in HIV infection, may be limited, particularly in developing countries, because of the cost and feasibility. There may also be a risk of selection for resistance if chemoprophylaxis with a single drug is given to HIV-positive people in whom active disease cannot be excluded. The risks of developing resistance if isoniazid is given as monotherapy to someone with active disease, and which may be aggravated by the increased risk of toxicity in HIV-infected individuals, must be considered. Shorter regimes than the standard six months of isoniazid would be a major advantage and it may be preferable to give more than one drug to reduce the risk of resistance. A study in Hong Kong in patients with silicosis showed that three months’ prophylaxis with rifampicin alone was as effective as six months with isoniazid (and indeed as three months with both drugs) in preventing the development of active tuberculous disease [7]. However, regimens based on rifampicin are expensive and in some developing countries there are major concerns about making it widely available.

People with HIV infection are likely to be more susceptible to new infection with tuberculosis. A short course of chemoprophylaxis cannot totally prevent disease and life-long prophylaxis may need to be considered. A policy of chemoprophylaxis therefore needs careful evaluation. Although it may be of great value in reducing morbidity and mortality from tuberculosis in association with HIV, and may also reduce the rate of progression of the HIV infection, the risks and practical difficulties cannot be ignored.
Case finding and effective treatment

In low prevalence countries active case-finding programmes have largely been abandoned, except in population groups with a higher risk. In high prevalence countries such programmes are not appropriate until a high proportion of cases presenting spontaneously can be diagnosed, treated and cured.

Tuberculosis control programmes mainly concentrate on pulmonary cases with positive sputum smears. Although smear examination is relatively simple, a high-quality smear service requires considerable organisation, including training and supervision, quality control procedures and maintenance of equipment (particularly microscopes) and adequate supplies of slides and stains. Smear examination detects the most infectious cases, as demonstrated in a study carried out in the 1960s [8] where there was greater risk of both infection and disease in the household contacts of cases with positive smears than in those who had negative smears, whether culture positive or negative. In this study 6.5% of household contacts of smear-positive cases had active disease and 45% were infected, the corresponding figures for the smear-negative but culture-positive cases were 1.3% and 26% respectively, and for those who had negative smears and cultures the results were 1.1% and 26%, respectively [8]. However, this and other studies have also shown that by the time smear-positive cases are detected they have probably already infected many of their close contacts. Therefore, concentrating only on smear-positive cases cannot prevent all transmission.

In a study in Hong Kong of patients with clinically and radiographically ‘active’ tuberculosis but with three negative sputum smears and cultures, 71 (41%) of 173 patients who were not treated developed bacteriologically confirmed tuberculosis over five years compared with only 3% of 161 randomised to a three-month regimen of isoniazid, rifampicin, pyrazinamide and streptomycin [9]. Although the breakdown rate depends on the accuracy of diagnosis of bacteriologically negative disease, and therefore may vary considerably in different populations, treatment of such cases will reduce the number of potentially infectious cases and therefore transmission. Until there are cheap and simple alternative diagnostic methods that are both sensitive and specific, sputum-smear examination remains the most widely used tool. However, important groups will remain undiagnosed and untreated if diagnosis is restricted to smear examination, not just the smear-negative pulmonary cases but also patients with disease at non-respiratory sites.

Attempts to improve case finding in developing countries by exploring active case-finding methods in the community may be appropriate when control programmes are achieving acceptable levels of success. A programme of studies in Kenya assessed several methods of case finding designed to be feasible and appropriate to the community. The first stage was a house-to-house survey in the community to identify all ‘suspects’, defined as individuals with a cough for four weeks or more or haemoptysis. Next, village elders were interviewed on one or more occasions and asked to identify suspects in their community [10]. It rapidly became clear that most of the people identified as suspects had already attended one or more health units because of their symptoms, often on several occasions. Therefore the programme moved to screening outpatients attending peripheral health units and, later, district hospitals and maternal and child welfare clinics. When a register was set up in the peripheral health units in which suspects’ details were to be entered so that they could be seen by the survey team, only 9% of those suspects who claimed they had attended the health units in a year were entered [11]. Reasons for the failure to register the suspects included lack of training and supervision, considerable workload and, perhaps most important, more urgent demands of acute medical and surgical priorities in the peripheral health units. Thus it is clearly inappropriate to develop more active case-finding programmes before diagnostic and, even more important, treatment services are available for all cases presenting with symptoms.

Treatment

The primary aim of treatment is to cure infectious cases and so reduce the transmission of infection. The development of effective chemotherapy owes much to the British Medical Research Council (MRC) group and its collaborators in many countries throughout the world.

It soon became clear that monotherapy rapidly led to the development of resistance, a finding that has been mirrored in leprosy and more recently in the HIV epidemic. Two drugs were soon shown to be more effective, and a third drug was then included in the initial phase, both to prevent the emergence of resistance and to improve the treatment of patients with initial resistance.

The early standard regimens based on streptomycin, isoniazid and para-aminosalicylate (PAS) were effective but had major disadvantages. Streptomycin had to be given by injection, PAS was very unpleasant to take, all the drugs had side effects and, perhaps most important, at least two drugs had to be taken for not less than 12 months, often longer.

The MRC group explored thiacetazone as an alternative to PAS; it was cheap and easy to take as a combined tablet with isoniazid. An important finding was the marked variation between different populations in the proportion developing toxicity, particularly cutaneous [12,13]. In many countries, however, it was well tolerated and was adopted as the basis of national control programmes.

An important series of studies from the Tuberculosis Research Centre in Madras showed that ambulatory
chemotherapy was just as effective as bed rest and sanatorium treatment [14]. This raised new issues, in particular compliance with the prolonged chemotherapy regimens, and education of patients and their families became a crucial part of tuberculosis control. Patient compliance with regimens of 12 months or longer was a major problem, although they formed the basis of all tuberculosis control programmes in the 1960s and 1970s and are still the only regimens that some countries can afford for some, if not all, patients. Surveys conducted at that time by the British and East African Medical Research Councils in Kenya and Tanzania showed that only between a quarter and a third of patients collected even 12 months of chemotherapy from outpatient clinics, and may well have actually taken much less [15,16].

In 1983, Radhakrishna produced estimates of the success of the National Tuberculosis Programme in India. At that time it was estimated that only 30% of cases were being found, only 35% of them completed treatment and that the regimen used was only 75% effective [17], resulting in an overall level of success of only 8%. He demonstrated that by improving only one of the three aspects of control, for example by introducing regimens of 95% efficacy, there would be very little improvement. It was only by greatly improving all three that an overall level of success of over 50% could be achieved.

In assessing the level of success of control programmes, it is important to consider the outcome of tuberculosis without effective chemotherapy. A study from the National Tuberculosis Institute in India showed that without chemotherapy about half the patients who had died by five years, about a third had recovered and about a fifth remained as chronic infectious cases [18]. The risks of poor control programmes are that, although survival may be improved, inadequately treated patients may increase the number of infectious cases in the community and also increase the risk of drug resistance.

Two approaches were developed to improve compliance. First, intermittent therapy regimens were developed with the aim of full supervision of every dose. The first studies in the early 1970s demonstrated that, in a 12-month regimen, twice weekly streptomycin and isoniazid was as effective as daily PAS and isoniazid. The importance of making fully supervised, or directly observed therapy as it is now known, acceptable to the patient by exploring all possible ways of reducing travel to a minimum, was appreciated and discussed in the ninth report of the WHO Expert Committee on Tuberculosis [19].

The development of short-course regimens represented the second major step forward in the control of tuberculosis. The MRC group was instrumental in demonstrating the role of the three key drugs, isoniazid, rifampicin and pyrazinamide (which had previously been restricted to second-line therapy because of its toxicity, particularly at higher doses).

Regimens of six months duration based on isoniazid and rifampicin throughout, plus pyrazinamide for the first two months, together with streptomycin or ethambutol initially in patients thought to be at higher risk of initial resistance, are now widely accepted as the new standard regimens [20-22]. A further advantage of these regimens is that they can be given intermittently either three times a week throughout, as developed and widely used in Hong Kong [23], or twice or three times a week in the continuation phase. This important development was for many years denied to those countries that most needed it because of the cost, in particular of rifampicin. This means that many developing countries still cannot use such short-course regimens in the continuation phase even if given intermittently. An alternative eight-month regimen developed in East Africa in which thiacetzone plus isoniazid are given in the continuation phase, is much cheaper and therefore has been widely adopted in countries unable to afford rifampicin for six months. However, this regimen has a number of disadvantages: eight months is still too long and supervision over the first two months has often required hospital admission, partly because of the streptomycin injections but also because of the perceived need to restrict access to rifampicin in those countries where it has a black-market value, particularly for the treatment of sexually transmitted diseases. The logistic problems of streptomycin, such as supplies of sterile needles and syringes, remain and are a particular concern in countries afflicted by the HIV epidemic. The regimen is not as effective in the presence of initial isoniazid resistance. Thiacetzone toxicity limits its use in some populations and this has been aggravated by the HIV epidemic.

Perhaps the most disappointing finding from the short-course chemotherapy trials was that, even with the best drugs available, reducing the duration below six months, certainly in smear-positive pulmonary disease, led to less effective regimens. However, there is an alternative way to look at this that is that even with only three months of streptomycin, isoniazid, rifampicin and pyrazinamide treatment, over 80% of patients are cured and it is likely that an appreciable proportion are cured even before this [24], a major advantage of short-course regimens.

**Drug supplies**

There is now a wide choice of highly effective short-course regimens but their efficacy may be jeopardised by inadequate drug supplies. If inadequate quantities of drugs are available, patient compliance may be threatened by the lack of continuity of supplies. The need to obtain supplies as cheaply as possible has led to poor quality supplies which occasionally contain dangerous contaminants. Combining drugs in a single preparation, such as rifampicin, pyrazinamide and isoniazid, reduces the risk of resistance by avoiding
monotherapy and also improves compliance by reducing the number of tablets. These advantages are threatened by the poor bioavailability of rifampicin in some of these preparations [25]. Tuberculosis control may be seriously jeopardised by drugs of poor quality, which may lead to inadequate doses of drugs and so potentially to the development of resistance.

Compliance

Although a wide choice of regimens is now available for use in differing circumstances, the problem of compliance continues to threaten their success. Compliance, both of patients and of physicians, was the theme of Wallace Fox’s Mitchell Lecture in 1982 [26,27]. Many private physicians in both technically advanced and developing countries use inadequate regimens, with the associated risks of failure and resistance; even in England and Wales, physicians have been slow to adopt new approaches. The introduction of major advances in therapy into clinical practice may be delayed and resources may be wasted by continuing with less effective regimens of longer duration. In a survey of the treatment of pulmonary tuberculosis in England and Wales in 1978–79, few physicians were using pyrazinamide even though there was already evidence of its role in short-course chemotherapy. In 1988, more than two-thirds of patients were treated with regimens based on isoniazid, rifampicin and pyrazinamide, but many were treated with other regimens and an appreciable proportion were treated for more than six months. The involvement of experienced clinicians in the management of all forms of tuberculosis is crucial. In some countries it may be feasible to limit the prescribing of antituberculosis drugs to the tuberculosis service. Educating the patient and the patient’s family remains important, as even short-course regimens are still too long.

Tuberculosis control today

In most technically advanced countries, the rate of decline of tuberculosis increased with the introduction of effective chemotherapy. Indeed, in 1971 at a conference on tuberculosis in the 1970s, Bignall predicted its continuing decline in England and Wales [28]. ‘Extrapolation suggests that there will only be about 1,200 notifications in 1980; by 1990 it is probable that the disease will be no more common than non-tuberculous meningitis is now (1.6 per 100,000 population) and by 2010 it should be of interest to the medical historian only.’

The rate of decline in England and Wales began to slow in the early 1970s as a result of immigration from high-prevalence countries, although surveys conducted in 1965 and 1971 by the British Thoracic Association and in 1978–79, 1983 and 1988 by the MRC and in 1993 by the PHLS/DoH/BTS showed that the rate of decline in the indigenous white population continued at much the same rate [29]. More recently, however, there has been an increase in tuberculosis in several European countries, including the UK, and in the US where the increase began in 1985. The possible reasons for this increase include immigration, the HIV epidemic, socioeconomic deprivation and the fragmentation of control programmes. Some of the increase may be an artefact as a result of, for example, greater case-finding activities or the improvement in notification procedures and practices that have resulted from the detailed surveillance of tuberculosis in England and Wales. The reasons for the increases will probably vary between and within countries. In England and Wales the apparent increase between 1988 and 1993 has been particularly in non-respiratory tuberculosis and in areas with large conurbations [30]. Overall, increases occurred in men aged 15 to 34 years and women aged 35 to 64 years. It is not possible from the statutory notification system to assess the contribution of immigration and HIV. However, preliminary results from the 1995 survey show that, since 1988, there has been an increase in the number of notifications in the Indian subcontinent (Indian, Pakistani and Bangladeshi ethnic group) and the other ethnic groups combined, but not in the white group [John Watson, personal communication]. Within the other ethnic groups a marked increase was seen in the black Africans but decreases in both the black Caribbean and Chinese groups. The contribution of HIV appears as yet to be of minor importance in the UK, in contrast to the US, largely because of the limited overlap between the risk groups for these two infections in the UK. The prevalence of HIV among adults aged 16 to 54 years in the 1993 tuberculosis survey was about 2%, but there was evidence of undernotification of patients with both infections. There is certainly no cause for complacency as the greatest rise in tuberculosis notifications has been in the black African ethnic group which is likely to be also at increased risk of HIV. The recent increase in HIV infection in India may also have an impact in view of the major contribution to tuberculosis notifications from the ethnic groups from the Indian subcontinent.

The association of the increase in tuberculosis in the UK with socioeconomic deprivation has recently been demonstrated in several studies. The relationship between the tuberculosis notification rate and the Jarman index of socioeconomic deprivation (which includes ten factors from the 1991 census, such as overcrowding, poor housing and the proportion of ethnic minority residents) was investigated in the 403 local authorities in England and Wales. In 1992, 29% of cases notified came from the tenth of the population with the highest index and between 1988 and 1992 the rate had increased by 35% in this group and had not changed in the 70% with the lowest index [31]. It is clearly difficult to disentangle the effects of immigration and poverty.
The particular problem of tuberculosis in the single homeless was highlighted by surveys carried out by the charity Crisis in their Christmas shelters in 1992 and 1993 and in cold-weather shelters, hostels and day centres in 1994. The rates of active tuberculosis were of the order of 2%, around 200 times the overall rate in England and Wales in 1993 [32]. The cases of tuberculosis were largely in older men, and the absence of active cases of tuberculosis in the cold-weather shelters was thought to be related to the younger age of the people surveyed. However, only about half of those attending volunteered to be screened and the increase in the numbers of young homeless in the community remains a cause for concern.

HIV and tuberculosis control

The increase in tuberculosis in the US preceded that in the UK, and although much of it was attributed to HIV, the effects of the fragmentation of control programmes and of socioeconomic deprivation are clearly demonstrated by the New York experience [33]. Tuberculosis control became a low priority, budgets were cut and by 1988 only 11% of cases in Harlem completed their treatment, a worse situation than in many developing countries. By 1990 over 30% of cases were HIV positive and by 1991 nearly 33% were resistant to at least one drug, nearly 20% to both isoniazid and rifampicin. An increase in the budget, a considerable strengthening of the tuberculosis control services and the introduction of supervised (‘directly observed’) therapy led to a reduction in cases between 1992 and 1993.

The impact of HIV on tuberculosis has been even greater in African countries and is likely to become increasingly important in Asia as HIV spreads there. Before the HIV epidemic, effective tuberculosis control programmes were developed in several countries in Africa in the early 1980s, largely due to the efforts of the International Union Against Tuberculosis and Lung Disease (IUATLD) assisted programmes, and an impact on the disease could be demonstrated.

The first programme was developed in Tanzania in the late 1970s. By the late 1980s its success was demonstrated by a marked increase in the proportion of patients cured and corresponding reductions in the chronic cases and defaulters. IUATLD assisted programmes were developed in several African and South American countries and similar programmes in other countries with WHO assistance. There is a marked contrast between the success rates in those areas using short-course chemotherapy where nearly all achieved cure rates of over 80%, and those still using standard regimens, where in most cases cure rates were less than 60% [33]. Effective control programmes need a political commitment from the government, regular supplies of high-quality drugs and good diagnostic facilities [34]. The main risks of inadequate control programmes are an increase in infectious cases and drug resistance in the country, so that ‘tuberculosis programmes in such countries have achieved the humanitarian end of saving lives and lessening suffering but have failed in the public health aim of reducing the size of the problem of tuberculosis’ [1].

In 1994 it was estimated that at least a third of the world population was infected by tuberculosis, 14 million by HIV and 5.6 million by both [33]. HIV threatens tuberculosis control in a number of ways. It is a potent risk factor for the breakdown of tuberculosis in those already infected and hence increases the risk of new infection, both in hospital and in the community. The risk of adverse reactions to all tuberculosis drugs is increased but in developing countries the most important is the increase in reactions to thiacetazone which may be severe, such as Stevens-Johnson syndrome. Even before the HIV epidemic, the variability in frequency and severity of adverse reactions to thiacetazone had been clearly established by the MRC studies. In spite of this, it has been the main drug used in many countries in combination with isoniazid, both in long- and short-course regimens because of its low cost and acceptability. The difficulties of replacing thiacetazone in countries that still rely on it for therapy are many as there is no cheap, safe alternative. Ethambutol requires careful dosing because of the risk of ocular toxicity and it is not cheap. Its widespread use in primary therapy may also jeopardise its valuable role in second-line therapy. Rifampicin, which would have the advantage of shortening therapy, remains too expensive for most countries and there are few other options.

The risks of multiple drug resistance in association with HIV may be greater than in the normal population but the causes are the same, namely inadequate regimens and poor compliance. The situation may be further aggravated by the greater toxicity. If combined resistance to isoniazid and rifampicin becomes widespread, control of tuberculosis will be seriously threatened as regimens that do not include these two key drugs are much less effective and often more toxic. The overlap between tuberculosis and HIV infection varies considerably in different countries, and even in different population groups within countries. The prevalence of tuberculosis among AIDS patients is highest in African countries, between 20 and 44% in reported surveys [35], and is around 10% or less in the US and European countries. The high and increasing prevalence of HIV infection among patients with tuberculosis in many African countries is of major concern because of the increased demands on the health services. The increase in HIV in Asia may well lead to even greater problems.

Tuberculosis: out of control?

If tuberculosis is out of control it is not because we do not have the tools to control it, although many could
be improved. Easier and quicker ways of diagnosing and establishing the identity and sensitivity pattern of organisms would be a major advantage. Some of the molecular typing techniques being developed may help in the surveillance and understanding of pathogenesis. At present, such techniques are not sufficiently developed to be applicable on a wide scale but when they are, the cost, particularly if they are exploited by commercial companies, is likely to mean that they will be restricted to the technically advanced countries and will not be available in countries where they are most needed. New drugs are urgently needed to reduce the duration of therapy and the frequency with which it has to be given. Once-weekly, or even less frequent, regimens would have a major advantage and the long-acting rifamycins, some of which have been in development for over 10 years, may make this possible. This delay in development has been, at least in part, due to the lack of interest of the pharmaceutical industry in drugs for treating tuberculosis, as for other tropical diseases. We can only hope that the re-awakened interest in tuberculosis in the West will extend to the pharmaceutical industry. The search for new vaccines continues but it will be many years before their role is clarified. The results of the South African trial of M. vaccae are eagerly awaited.

It will clearly be some time before we have new tools, so what can we do with the tools we have? In Western countries the complacency of the 1970s and 1980s has been replaced by the realisation that tuberculosis is not just a third-world disease and timescales for eradication have had to be revised. Tuberculosis is not out of control in these countries but, while significant immigration from areas of high prevalence continues, adequate national resources for a sufficiently long period will be required to regain and retain control, particularly in the presence of socioeconomic deprivation.

In developing countries, where HIV has not as yet had a major impact, short-course chemotherapy in well-organised control programmes can lead to improvement in tuberculosis, even without improving socioeconomic conditions. The latter might be as, or even more, effective but is a much greater challenge. To maintain success requires sustained national and international resources.

In developing countries where HIV has already had a big impact, HIV itself puts huge demands on the health services and has major effects on the economy of a country by primarily affecting the economically active population. However, tuberculosis is one of the few preventable and treatable infections in HIV-infected people and, more important, is a risk to the non-infected population. It is crucial that sufficient national and international resources are committed to both the use of the available tools and the development of new ones. If not, tuberculosis in these countries will be out of control by the 21st century, if it is not already.

Acknowledgements

I am indebted to my many mentors and colleagues in the world of tuberculosis, in particular Wallace Fox and Denny Mitchison.

I should also like to thank to Don Enarson, Director of Scientific Activities of the IUATLD for providing me with information on the IUATLD tuberculosis control programmes.

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