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Trends in tuberculosis

K. M. CITRON
M.D., F.R.C.P.

Brompton Hospital, London SW3

One of the major medical advances of the 20th century has been the discovery of anti-tuberculosis drugs capable of curing almost every patient suffering from the disease. The application of chemotherapy in technically advanced countries has resulted in a spectacular decline of tuberculosis. In contrast, in developing countries there has been little improvement since mass chemotherapy has failed because of lack of money, medical and paramedical personnel and inadequate health education.

Trends in tuberculosis have been ones of success and failure, and changing epidemiology. Recent research and progress in tuberculosis has been concerned mainly with the design and application of chemotherapy programmes suitably adapted to the widely differing medical, financial and social needs of different communities.

Epidemiology of tuberculosis

Developing countries

In developing countries there has been an increase in the number of people suffering from tuberculosis since the population has doubled during the last three decades and control measures have been inadequate to deal with the increasing number of patients. Estimates suggest that throughout the world every year 10 million people develop tuberculosis and at least 3 million die of it, most of these being in the developing countries.

Britain

Tuberculosis, previously a major cause of illness and death among young people, is now relatively rare in the young. This has led to the erroneous belief that tuberculosis is almost eradicated in Britain. This is not so and there remain a number of high risk groups in the community, especially the elderly white male and refugees and immigrants coming from Asia and other high prevalence countries (Citron, Raynes and Berrie, 1981). A survey of tuberculosis notifications in England and Wales during 1978/79 revealed great differences in the incidence in various ethnic groups (Medical Research Council, 1980) (Fig. 1). The rates of notification of respiratory tuberculosis in people of Indian subcontinent ethnic origin (Indian, Pakistani and Bangladeshi), were 30 times greater than in the white population. For non-respiratory tuberculosis the rates were 70 times greater. These differences between the ethnic groups may, in part, reflect the high incidence of the disease in the countries from which the immigrants come. However this is unlikely to be the major reason. Chest radiography of Asian immigrants on entry to Britain reveals little pulmonary tuberculosis. Clinically pulmonary tuberculosis appears to occur frequently after the immigrants have been in Britain for some time, the risks being particularly high during the first 5 years of their residence (British Thoracic and Tuberculosis Association, 1975). Factors that have been thought to contribute to the development of tuberculosis after settling in the country include the reduction of host resistance by the stresses and strains of recent immigration, and the effect of vitamin D deficiency which is common among some immigrants. In addition there is the higher risk of infection associated with living in immigrant communities in U.K.

The Indian subcontinent ethnic group comprise less than 2% of the population of England and Wales but contribute almost one third of respiratory and more than one half non-respiratory notifications. However, they have less extensive pulmonary disease and are less infectious than the white ethnic group. For every sputum-smear-positive patient of Indian subcontinent origin there are four among white patients. The main source of infection in U.K. remains the elderly white male. These men were usually infected in youth, the disease remaining quiescent for years, becoming reactivated in middle or old age. Many of these men are smokers and may have cough or sputum, and are therefore thought to be bronchitic. This acceptance of chronic respiratory symptoms may contribute to the late diagnosis of pulmonary tuberculosis at a stage when it is extensively cavitated and highly infectious.

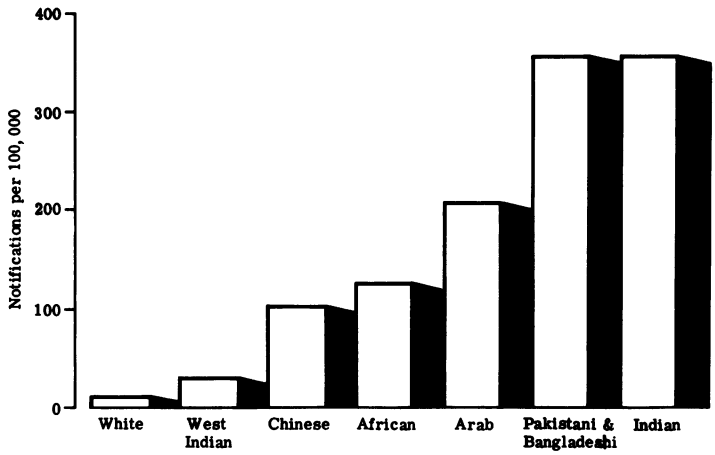

FIG. 1. Tuberculosis notifications among various ethnic groups in England and Wales.

Tuberculosis prevention and control

Case finding

Case finding with effective chemotherapy diminishes the source of infection in a community. In most developing countries case finding is 'passive', and is restricted to diagnosing patients who present with respiratory symptoms. In developed countries active case finding is practised. It concentrates on examining the high risk groups, which in Britain include middle-aged white males, vagrants and Asian immigrants. These immigrants should be examined as soon as possible after they have reached their place of abode. There are considerable variations in the annual notifications in England and Wales where the average rate is 18 per 100,000 but in the Indian subcontinent ethnic group it is 380. There are great regional variations in Britain. In one region a figure of 1,132 per 100,000 was recorded among immigrants. Regional differences are mainly due to the distribution of immigrants and it is important that the priorities for health care staff are varied according to the needs of the community (Medical Research Council, 1982).

Hospitalization and segregation

The only source of tuberculous infection is, for practical purposes, a person with pulmonary tuberculosis in whose sputum tubercle bacilli are present in sufficient numbers to be seen on direct examination of sputum smears (sputum smear positive). Patients whose smears are negative are non-infectious, even though cultures may be positive, and do not require segregation.

Chemotherapy with regimens including rifampicin abolish infectivity rapidly and long before the disappearance of acid-fast bacilli from sputum smears. The number of tubercle bacilli in the sputum which are alive as shown by growth on culture, fall by 99% after the first 2 weeks of chemotherapy (Jindani *et al.*, 1980). Hence patients can be regarded as non-infectious after 2 weeks of effective chemotherapy and segregation need not be continued beyond this time providing chemotherapy is taken regularly.

Home treatment exposes close family contacts to a negligible risk of infection due to the rapid abolition of infectivity by chemotherapy. Controlled studies have shown that home treatment does not submit those contacts to a significant risk of infection once chemotherapy is started (Toman, 1979). The therapeutic results of well-supervised home treatment have been shown to be as good as that obtained by hospital treatment (Fox, 1977). However in spite of convincing evidence that most patients can be effectively and safely treated at home, the majority of patients with pulmonary tuberculosis in England and Wales are admitted to hospital for the purposes of diagnosis, treatment, segregation or for social reasons.

BCG vaccination

In Britain BCG vaccination is provided for school children aged 10–14 years. Recent epidemiological studies have shown this to be highly effective in preventing tuberculosis (British Thoracic Association, 1980a.) There are regions which currently have a low prevalence of tuberculosis but BCG should not be abandoned for children living in these regions, because they may subsequently visit or work in regions where there is a much higher prevalence of tuberculosis such as London and the industrial cities of the Midlands where the risk of infection is much greater than in the place of their schooling. BCG

vaccination is also recommended for infants whose parents are of Indian subcontinent ethnic origin, and for children of this ethnic group as soon as possible after their arrival in U.K. The reason for this recommendation is that the incidence of tuberculosis in children of this ethnic group compared with that of white children is 50 times greater if they are born abroad and 20 times greater if born in Britain. Although a study in India failed to demonstrate the value of BCG in that country, there is no good reason to doubt the efficacy of BCG given in U.K. to immigrants from India (World Health Organization, 1980).

Anti-tuberculosis chemotherapy

The practice of chemotherapy is currently undergoing considerable change and there are wide variations in drug regimens used depending upon the needs of different communities and of individual patients. For many years there was almost universal use of so called standard chemotherapy. This consists of isoniazid with a companion drug to prevent the emergence of drug resistance, this companion drug being either ethambutol, PAS or thiacetazone. Streptomycin was given as a third drug for the first 2 or 3 months of treatment (Table 1). The total duration of chemotherapy had to be 18 months if relapse was to be minimized. Although the success of this regimen under the conditions of meticulously controlled clinical trials could be shown to be 100%, in contrast observations under service programme conditions showed it to be much less satisfactory. In several developing countries more than 50% of patients defaulted before the end of the regimen. In developed countries, including Scotland and U.S.A., long-term surveillance showed that there was an appreciable failure rate (Fox, 1983a). These observations stressed the importance of studying chemotherapy regimens in two ways. Firstly by meticulously conducted controlled trials to show the potential of the regimen. Secondly by testing it under service programme conditions in the different circumstances of different countries to evaluate its efficacy in the varied social, medical and financial conditions of the community being investigated.

There are two main causes of failure of standard chemotherapy. One is irregular daily self medication. To overcome this problem programmes of totally supervised intermittent medication are now available. Another cause of failure is default before the end of the full course of chemotherapy. Short course chemotherapy offers special advantages here. The advantages of both fully supervised and short course chemotherapy may be combined. Much research has been devoted to designing programmes suitable for the differing needs of various communities and the individual needs of patients with special problems likely to lead to poor compliance such as alcoholism, vagrancy or a nomadic life style (Citron and Girling, 1983).

Short course chemotherapy

In standard duration chemotherapy, combinations of bactericidal and bacteriostatic drugs are continued until the bacterial population is effectively eliminated, a process which requires at least 18 months. Short course chemotherapy depends upon the use of special drugs which have sterilizing properties that kill the persisting organisms responsible for relapse after the end of chemotherapy. In addition bactericidal drugs are used to kill the rapidly dividing organisms, together with bacteriostatic drugs whose main role is to prevent the emergence of drug resistance. The cardinal drugs in short-course chemotherapy are isoniazid (H) rifampicin (R) and pyrazinamide (Z) (Fox, 1981). Isoniazid is the most bactericidal and is continued throughout the regimen. Rifampicin is less bactericidal but its bactericidal action is very rapid so that it is able to kill dormant bacilli that start to metabolize for only brief periods of time, thus helping to remove the persisters. Pyrazinamide has a low bactericidal action but is important because it probably acts on persisting organisms living intracellularly inside macrophages, or in the walls of tuberculous cavities and acts as an important sterilizing drug. It has a low activity in

TABLE 1. Long-course regimens

Initial intensive phase			
Drugs	Duration	Continuation phase	Total duration of regimen (months)
Daily regimens			
SHE (P or T)	2–3 months	HE (P or T)	18
RHE (P or T)	2–3 months	HE (P or T)	18
Intermittent regimens			
SHE (P or T)	2–3 months	HS twice weekly	18
SHR	2 weeks	HR twice weekly	12

Drugs in Table 1 and 2: H = isoniazid; R = rifampicin; Z = pyrazinamide; S = streptomycin; E = ethambutol; P = PAS; T = thiacetazone.

preventing drug resistance. Recent studies suggest its use is maximized when given for the first 2 months of a regimen, and there is little value in continuing the drug longer. Streptomycin (S) is bactericidal and ethambutol (E) is bacteriostatic. Neither are likely to contribute much to short course chemotherapy, although they may have a role where initial resistance to isoniazid or streptomycin exists.

A landmark in the history of tuberculosis chemotherapy research was attained when the East African/British Medical Research Council reported their study of daily SHR given for 6 months to hospitalized patients. This report and subsequent ones have shown that in terms of bacteriological quiescence and relapse rate in the subsequent 5-year follow-up, the 6-month regimen proved as good as anything attained by standard 18-month chemotherapy. This pioneer study showed the practicability of short-course chemotherapy and prompted many other studies.

Nine-month daily regimen

In 1973 the British Thoracic Association launched a national multicentre study in which HR was given daily for durations of 6, 9, 12 or 18 months together with an initial third drug for the first 2 months, either streptomycin (S) or ethambutol (E). Drugs were given according to the normal practise of the many participating physicians with no special instructions for monitoring self medication. The study was therefore undertaken in the normal service programme conditions. The 9-month regimen was found to be highly satisfactory and in a 4-year post-chemotherapy follow-up the results were as good as any that had been previously studied. Ethambutol was as satisfactory as streptomycin, as the third drug in the initial intensive phase, so that the difficulties of using streptomycin can be avoided. The currently recommended regimen by the British Thoracic Society is HR for 9 months with E for the first 2 months. Daily drug doses are H 300 mg, R 600 mg for patients weighing over 50 kg and 450 mg for those weighing less and E 25 mg/kg for the first 2 months only (British Thoracic Association, 1980b) (Table 2).

Six-month daily regimen

In a British Thoracic Association multicentre study, 6-month regimens were given using HR daily for 6 months and during the 2-month initial intensive phase, pyrazinamide was used together with a fourth drug which was either streptomycin or ethambutol (SHRZ2/HR, EHRZ2/HR). These were compared with the standard 9-month regimen EHR/HR (Table 2). Both 6-month regimens were as successful as the 9-month. The 6-month regimen had the advantage that it was shorter and cheaper and caused more rapid sputum conversion, than the 9-month regimen. It was not associated with more hepatotoxicity than the control regimen and is more likely to cure patients who abscond early because it contains pyrazinamide, a valuable sterilizing drug (British Thoracic Association, 1982).

The dose of pyrazinamide is 1·5 g daily if the patient weighs less than 50 kg, 2 g daily if the patient weighs 50–74 kg and 2·5 g daily if the patient weighs 75 kg or more. The dose of streptomycin is 1 g daily but for patients over 40 years or under 50 kg is reduced to 0·75 g.

Further shortening of regimens

Much research is now concerned with investigating regimens shorter than 6 months. So far none of them

TABLE 2. Short-course regimens

Initial intensive phase		Continuation phase	Total duration of regimen (months)
Drugs and frequency	Duration (months)	Drugs and frequency	
Daily Regimens			
EHR daily	2	HR daily	9
SHR daily	2	HR daily	9
SHRZ daily	2	HR daily	6
EHRZ daily	2	HR daily	6
SHRZ daily	2	H daily	8
Intermittent Regimens			
SHRZ 3 times weekly	6	—	6
EHRZ 3 times weekly	6	—	6
SHRZ 3 times weekly	2	HR 3 times weekly	6
SHRZ daily	2	HR 2 times weekly	6

Drugs in Table 1 and 2: H = isoniazid; R = rifampicin; Z = pyrazinamide; S = streptomycin; E = ethambutol; P = PAS; T = thiacetazone.

have proved as effective as the 6-month regimen. Nevertheless remarkable results are obtained with daily SHRZ given for 3 months in advanced pulmonary tuberculosis curing 85%. However to ensure 100% success, a duration of about 6 months seems to be necessary even for sputum smear negative cases (Fox, 1981). The results of further research in which both microbial drugs and host resistance are manipulated may provide exciting advances.

Fully supervised intermittent therapy

Chemotherapy is likely to fail if the patient does not take the drugs regularly as prescribed. Giving every dose under full supervision ensures compliance and becomes practical when given intermittently. Fully supervised intermittent regimens are usually easy to arrange in urban communities where patients can attend for their drugs 2 or 3 times weekly.

Isoniazid and streptomycin given twice weekly for 18 months have been widely used (Table 1). When isoniazid is given intermittently, it is essential that a high dose of isoniazid 15 mg/kg is used with pyridoxine 5 mg per dose to prevent isoniazid toxicity. The advantages of intermittency and short course can be combined (Table 2). A particularly useful regimen is SHRZ or EHRZ 3 times weekly supervised for 6 months, successfully used in Hong Kong (Hong Kong/BMRC, 1981). Another useful regimen is SHRZ 3 times weekly for 2 months followed by HR 3 times weekly, the regimen totalling 6 months. Alternatively SHRZ daily for the first 2 months with HR twice weekly, the regimen totalling 6 months (Table 2).

Special aspects of chemotherapy

Cost

Severe lack of finance for tuberculosis control and treatment is a major problem in many developing countries. Mass chemotherapy can only be undertaken with the cheapest regimens (Aquinas and Todd, 1983). Standard long-course chemotherapy (isoniazid with PAS or thiacetazone for 18 months with streptomycin for the first few weeks) is cheap but efficacy is low because of lack of patient co-operation. Short-course chemotherapy is more effective but more expensive, but the cost-efficacy is likely to be high. SHRZ daily for 2 months followed by H daily for another 6 months is cheap and effective. SHRZ 3 times a week for 2 months followed by HR 3 times weekly for a total duration of 6 months is also a good cheap regimen.

It is unrealistic to use 100% regimens which are generally unacceptable and have a high default rate. A shorter but potentially less effective regimen may cure more patients. Thus SHRZ daily for 2 months is likely to cure 80% of patients, and be very acceptable. Relapses occur with sensitive organisms and can be retreated with the same regimen.

Administrative aspects of mass chemotherapy

However effective a chemotherapy regimen may be it will fail if it is not taken correctly by the patient. Mass chemotherapy is as much an exercise in administration as it is in medicine. The use of properly trained administrators and paramedical workers is essential in attaining successful mass chemotherapy. The use of paramedical staff working in remote rural situations dealing with basic medical care including tuberculosis, has proved to be highly successful in some communities, hence the importance of training appropriate staff for this type of work.

The cure of tuberculosis is more than the prescription of drugs. It requires careful outpatient monitoring both by interrogation during outpatient attendances and checking urine for presence of drugs by either red colour for rifampicin or by paper strip test for isoniazid. Sputum cultures taken towards the end of chemotherapy should be negative. Serial drug sensitivity testing and chest X-rays are of little value in the routine management of patients with pulmonary tuberculosis during chemotherapy.

Patients likely to be uncooperative

Patients who are alcoholic, psychiatrically disturbed, or lead a vagrant or nomadic life, are unlikely to be reliable in self-medication. They need careful supervision and usually require fully supervised intermittent medication for as short a period as possible. SHRZ or EHRZ given 3 times weekly for 6 months is often acceptable for these people. It is often wise to use SHRZ daily initially for as long as the patient will co-operate, since this ensures the highest percentage of cure should the patient abscond before the end of 6 months, this regimen being curative in about 80% of patients when given for only 2 months.

Toxicity

Early studies of pyrazinamide using doses higher than those now recommended revealed much hepatotoxicity. However a study in which it was given in a dose of 30–40 mg/kg daily for 2 months compared with a similar regimen without pyrazinamide, showed no increased hepatotoxicity which could be attributed to pyrazinamide (British Thoracic Association, 1981). Pyrazinamide appears to be relatively well tolerated by most alcoholics. Rifampicin compared with isoniazid is remarkably free from side effects and although a proportion of patients will show elevation of liver enzymes during chemotherapy, clinical symptoms and signs of liver disease

are very rare. Early studies of intermittent rifampicin showed frequent febrile reactions, but later studies using lower doses of 600 or 900 mg given twice or three times weekly caused few and mild reactions. If reactions occur they can usually be overcome by giving rifampicin more frequently. Rifampicin is a powerful hepatic microsomal liver enzyme inducer, resulting in important drug interaction. Oestrogens are more rapidly metabolized hence rendering ineffective oestrogen-containing oral contraceptives. The dosage of corticosteroids needs to be doubled in patients receiving rifampicin in order to compensate for the more rapid hepatic metabolization of corticosteroids.

Renal failure

Rifampicin and isoniazid are metabolized by the liver and can be given in normal doses to patients in renal failure with safety. In contrast ethambutol and streptomycin are eliminated mainly by the kidneys and must be avoided in patients with renal failure.

Pregnancy

Ethambutol and rifampicin given in large doses in animals are teratogenic. However in woman there is no good evidence that teratogenicity has occurred. If there is a risk it would be during the first trimester of pregnancy and hence the drugs are best avoided at this time. However if pregnancy occurs whilst a woman is receiving anti-tuberculosis chemotherapy, the pregnancy is unlikely to be diagnosed much before the 12th week, and if the pregnancy is advanced beyond this time there is little risk of continuing the drug. Patients who are more than 12 weeks pregnant can be given the usual anti-tuberculosis drugs with the exception of streptomycin, which can cause 8th nerve damage in the foetus, and PAS which may cause foetal goitre.

Non-pulmonary tuberculosis

The duration of chemotherapy for non-pulmonary tuberculosis should usually be 18 months since there is as yet insufficient evidence from studies of short-course chemotherapy to judge the efficacy of short-course chemotherapy in these conditions.

Lymph node tuberculosis is notoriously unpredictable in its response to chemotherapy. Lymph node enlargement or abscess formation is not uncommon during chemotherapy which appears otherwise satisfactory. Pus from lymph nodes which break down during chemotherapy almost never yield living tubercle bacilli. Caseation and abscess formation may be due to immunological response to tuberculo-protein contained within the lymph node. Because of inability to clear dead tubercle bacilli from lymph nodes, immunologically reactive products from the bacilli may persist in the nodes for a prolonged period. The situation is very different from that found in the lung where dead tubercle bacilli are cleared by expectoration in sputum and by other means. This fact possibly accounts for the more favourable response of pulmonary tuberculosis. However with prolonged chemotherapy the final outcome in lymph node tuberculosis is usually entirely satisfactory (Campbell and Dyson, 1979).

Tuberculous meningitis

This remains a very dangerous condition. All the drugs which give good levels in the cerebrospinal fluid should be given. The drugs of choice are pyrazinamide, rifampicin, isoniazid and ethambutol given in maximum doses. The role of intrathecal streptomycin is contentious but it is probably advisable in the more advanced cases. Corticosteroids are probably valuable for advanced cases, although the evidence for this is anecdotal, since no controlled studies have been made.

Conclusion

A wide variety of effective chemotherapy programmes is now available to suit the different requirements of various communities and of individual patients. In the world as a whole however, the number of cases of tuberculosis continues to increase especially in some developing countries. In developing countries efforts are needed to apply new regimens of chemotherapy, including short-course and fully supervised programmes, in order to improve the often unsatisfactory results of mass chemotherapy. Research is needed to explore the use of established drugs in new regimens, and to discover new drugs which act either on the tubercle bacillus or upon host resistance. It is important that the results of research are widely and effectively disseminated so influencing practising clinicians worldwide to bring the treatment of patients up to date. (Fox, 1983b). Programmes for administering BCG to the new-born in high risk communities need to be intensified.

In the developed countries, unfamiliarity with tuberculosis may result in the disease being diagnosed too little or too late. It is important to maintain medical expertise for prevention and treatment of tuberculosis in these countries, as well as to strengthen efforts to combat the disease in certain high risk groups in the community.

References

AQUINAS, M. & TODD, D. (1983) *Particular problems of tuberculosis in developing countries. Oxford Textbook of Medicine. S.212* (Ed. D.J. Weatherall, J.G.G. Ledingham and D.A. Warrell). Oxford University Press, London.

BRITISH THORACIC AND TUBERCULOSIS ASSOCIATION (1975) Tuberculosis among immigrants related to length of residence in England and Wales. *British Medical Journal,* **3,** 698.

BRITISH THORACIC ASSOCIATION (1980a) Effectiveness of BCG vaccination in Great Britain. *British Journal of Diseases of the Chest,* **74,** 215.

BRITISH THORACIC ASSOCIATION (1980b) Short course chemotherapy in pulmonary tuberculosis. Third report. *Lancet,* **i,** 1182.

BRITISH THORACIC ASSOCIATION (1981) A controlled trial of six months chemotherapy in pulmonary tuberculosis. First report. *British Journal of Diseases of the Chest,* **75,** 141.

BRITISH THORACIC ASSOCIATION (1982) A controlled trial of six months chemotherapy in pulmonary tuberculosis. Second report. *American Review of Respiratory Disease,* **126,** 460.

CAMPBELL, I.A. & DYSON, A.J. (1979) Lymph node tuberculosis: a study of treatment 18 months after completion of chemotherapy. *Tubercle,* **60,** 95.

CITRON, K.D. & GIRLING, D.J. (1983) *Tuberculosis. Oxford Textbook of Medicine 5.237.* (Ed. D.J. Weatherall, J.G.G. Ledingham and D.A. Warrell). Oxford University Press, London.

CITRON, K.M., RAYNES, R.H. & BERRIE J.R.H. (1981) *Topics of our time. 3. Tuberculosis today.* Her Majesty's Stationery Office, London.

FOX, W. (1977) The modern management of pulmonary tuberculosis. *Proceeding of Royal Society of Medicine,* **70,** 4.

FOX, W. (1981) Whither short-course chemotherapy? *British Journal of Diseases of the Chest,* **75,** 331.

FOX, W. (1983a) Compliance of patient and physician: experience and lessons from tuberculosis—1. *British Medical Journal,* **287,** 33.

FOX, W. (1983b) Compliance of patient and physician: experience and lessons from tuberculosis—2. *British Medical Journal,* **287,** 101.

HONG KONG. CHEST SERVICES/BRITISH MEDICAL RESEARCH COUNCIL (1981) Controlled trial of four thrice-weekly regimens and a daily regimen, all given for 6 months for pulmonary tuberculosis. *Lancet,* **i,** 171.

JINDANI, A., ABER, V.R., EDWARDS, E.A. & MITCHISON, D.A. (1980) The early bactericidal activity of drugs in patients with pulmonary tuberculosis. *American Review of Respiratory Disease,* **121,** 939.

MEDICAL RESEARCH COUNCIL (1980) National survey of tuberculosis notifications in England and Wales 1978–79. *British Medical Journal,* **281,** 895.

MEDICAL RESEARCH COUNCIL (1982) The geographical distribution of tuberculosis notifications in a national survey of England and Wales (1978–1979). *Tubercle,* **63,** 75.

TOMAN K. (1979) *Tuberculosis case-finding and chemotherapy. Questions and answers.* Geneva: World Health Organisation. No. 219.

WORLD HEALTH ORGANIZATION (1980) Vaccination against tuberculosis. *World Health Organization Technical Report Service, Geneva.*