Realistic Chemotherapeutic Policies for Tuberculosis in the Developing Countries*

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During the course of the last 10 years there has been striking progress in the chemotherapy of pulmonary tuberculosis in the technically advanced countries. The developing countries, however, have derived very little benefit from the progress for two main reasons. First, because they have a gross shortage of medical resources. Secondly, relatively little attempt has yet been made to adapt current knowledge to their special problems. In particular, graduates from developing countries employed or studying in technically advanced countries learn an approach to therapy based on facilities which will not be available when they return home, and they receive very little instruction of practical relevance to the conditions they will have to face. In this lecture I intend to discuss the realistic application of chemotherapy in the developing countries. In order to appreciate the problems involved it is necessary, first, to have a clear picture of the gross shortage of medical resources which exists in many developing countries, and, secondly, to know their current chest-clinic practice.

Medical Resources of Developing Countries

Table I sets out the total governmental expenditure per person on health services in 1960 in seven of the eight countries of the South-east Asia Region of the World Health Organization (figures for Outer Mongolia not available), a region with a total population of over 600,000,000, which is more than a fifth of the population of the world. With the exception of Ceylon (population of only 9,750,000) the average expenditure ranged from U.S. $0.41 to $0.62 per person (World Health Organization, 1963) compared with nearly $40 in the United Kingdom. Furthermore, the demands on the available resources are greater because of the more numerous major health problems which exist in many developing countries, such as smallpox, cholera, typhoid, filariasis, leprosy, and malnutrition, in addition to tuberculosis itself. This economic fact underlies the whole of the health services in the developing countries and is responsible for many shortages and deficiencies.

TABLE I.—*Governmental Expenditure on Health Services in Seven Countries in the South-east Asia Region of W.H.O. and in the United Kingdom in* 1960

Country	Expenditure per Head of Population	Equivalent in U.S. Dollars
Afghanistan	12·4 afghanis	0·62
Burma	2·5 kyats	0·52
Ceylon	14·59 rupees	3·06
India	2·2 „	0·46
Indonesia	22·5 rupiahs	0·50
Nepal	2·0 rupees	0·42
Thailand	8·6 baht	0·41
United Kingdom	14·0 pounds sterling	39·20

There is, for example, a major shortage of doctors. The number of inhabitants per doctor in the seven Asian countries ranges from 4,400 in Ceylon to 72,000 in Nepal (Table II) compared with 930 per doctor in the United Kingdom. There are also major shortages of all cadres of paramedical staff such as nurses, health visitors, almoners, social workers, and laboratory technicians.

The tuberculosis beds available in the seven Asian countries (Table III) range from 1 for every 2,750 inhabitants in Ceylon to 1 for every 177,000 inhabitants in Afghanistan. If it is assumed that 1% of the population of these countries has active pulmonary tuberculosis (a conservative estimate) then the number of cases in the community per tuberculosis bed ranges from 27.5 cases in Ceylon to 1,770 in Nepal. In the United Kingdom, in contrast, even though many tuberculosis beds are being closed down, the ratio in 1960 was still 1 for every 2,100 of the population, despite a much lower prevalence of the disease. It is probable that there is one bed for every five active cases in the community, and for all practical purposes every new case can be admitted to hospital immediately on diagnosis.

TABLE II.—*Number of Doctors in Seven Asian Countries and in the United Kingdom in* 1960

Country	Population	No. of Doctors	Approximate No. of Population per Doctor
Afghanistan	13,000,000	349	37,000
Burma	21,250,000	1,962	11,000
Ceylon	9,750,000	2,201	4,400
India	408,000,000	84,492	4,800
Indonesia	87,300,000	1,938	45,000
Nepal	9,200,000	128	72,000
Thailand	26,400,000	3,402	7,800
United Kingdom	52,350,000	56,431	930

TABLE III.—*Tuberculosis Beds in Seven Asian Countries and in the United Kingdom in* 1960

Country	Population	No. of Beds	Approximate No. of Population per Bed
Afghanistan	13,000,000	132	98,000
Burma	21,250,000	300	71,000
Ceylon	9,750,000	3,506	2,750
India	408,000,000	26,445	15,500
Indonesia	87,300,000	1,707	51,000
Nepal	9,200,000	52	177,000
Thailand	26,400,000	300	88,000
United Kingdom	52,350,000	24,916	2,100

* From the Medical Research Council's Tuberculosis Research Unit, Hampstead, London. Based on a lecture delivered at the Postgraduate Medical School of London on 1 February 1963.

Current Chest-clinic Practice in Developing Countries

It is all too common in tuberculosis clinics in developing countries to find that newly diagnosed patients receive no chemotherapy at all because the clinic has no anti-tuberculosis drugs in stock. Then a relatively small supply of drugs may be received and the physician prescribes triple chemotherapy with isoniazid, streptomycin, and P.A.S., attempting to follow the best practice recommended in the technically advanced countries. Within a few weeks the stock is, in all probability, exhausted and again the patients (both old and new) receive no drugs for a further period. A supply of isoniazid may then be received, and this is prescribed by itself, unless the clinician decides to wait until further stocks of companion drugs are delivered. As likely as not, in the same clinic, isoniazid is being given prophylactically to contacts. Further, a mass radiography apparatus may be touring the city radiographing selected population groups at a very considerable expense (the cost of diagnosing a case of active tuberculosis by mass radiography in India, for example, is $85 (P. V. Benjamin, personal communication, 1962)), merely increasing the numbers of patients in the already congested clinics. This picture of combined chemotherapy, no chemotherapy, and single-drug therapy, dictated by the availability of drugs, and the often haphazard use of other measures, underlines the importance of having well-defined priorities and a clear policy for chemotherapy.

A realistic consideration of the tuberculosis problem in the developing countries is possible only if the background of shortages and current practice just described is kept constantly in mind.

Therapy in Technically Advanced Countries

Tuberculosis therapy in the technically advanced countries is based on: (1) antituberculosis drugs, both main (isoniazid, streptomycin, and P.A.S.) and reserve (such as pyrazinamide, cycloserine, and ethionamide), in adequate supplies to provide courses of chemotherapy of up to two years, or even longer; (2) a laboratory service which can undertake large numbers of cultures for tubercle bacilli and also sensitivity tests; (3) frequent radiographic examinations; (4) an extensive sanatorium service; and (5) an extensive chest-clinic service. These facilities are applied in an efficient administrative framework, which includes notification of the disease and the collection of other tuberculosis statistics, as well as the application of preventive measures.

From economic considerations alone it is quite clear that developing countries must be selective in choosing from the above therapeutic facilities, and the rest of this lecture will consider how the limited resources can best be deployed.

Application of Therapy to Developing Countries

Cost of Antituberculosis Drugs

It is surprisingly difficult to give even the approximate cost of treatment with different drug regimens because the prices vary widely from country to country. Even within a country there are often major differences in price from firm to firm—the price of P.A.S. in the U.S. ranges from $2.20 per 1,000 tablets to more than $6 (Chemical Week, 1960)—and, indeed, often from quotation to quotation from the same firm. Further, many developing countries levy both import and local State duties. Vitamin and mineral supplements are commonly added, again increasing the price, although the evidence suggests that such supplements are of little, if any, value (Ramakrishnan *et al.*, 1961c). Also the margin of profit may be unreasonably high (India, Ministry of Health, 1962, p. 422). Thus a combination of isoniazid plus thiacetazone is being sold in one Asian country at 13 times a reasonable price (Andersen, 1962). There is clearly the need, in developing countries, to take administrative measures at governmental level to see that the prices of antituberculous drugs are kept as low as possible.

The approximate cost of the drugs for a year's treatment with several primary and reserve regimens is given in Table IV. The prices, though given in U.S. dollars, are current drug costs in Britain. The standard combinations of isoniazid, streptomycin, and P.A.S. are all very costly when related to the approximate $0.50 per head of population for all health services in many developing countries, and the attraction of chemotherapy with isoniazid alone at $1.25 to $2.35 a year is obvious. The combination of isoniazid plus thiacetazone, currently under investigation in a series of studies in East Africa (East African/British Medical Research Council Thiacetazone/Diphenylthiourea Investigation, 1960; East African/British Medical Research Council Second Thiacetazone Investigation, 1963), as well as in routine clinical use in some areas there, was selected for study because, if effective, it offered a cheap alternative to isoniazid plus P.A.S. The reserve regimens are all very expensive, and one year of chemotherapy for a single patient can equal the sum for the total health services for about 500 of the population of many developing countries.

TABLE IV.—*Approximate Cost of Drugs for One Year's Treatment With Various Primary and Reserve Regimens*

Regimen	Daily Dosage of Drugs	Approximate Cost in U.S. Dollars
Primary	Isoniazid 200 mg. plus P.A.S. sodium 10 g. (cachets)	20·50
	Isoniazid 200 mg. plus streptomycin 1 g.	44·50
	„ 200 „ „ P.A.S. sodium 10 g. (cachets), with streptomycin 1 g. daily for 6 months	42·00
	Isoniazid 200 mg. (1 tablet)	1·25
	„ 300 „ (1 „)	1·85
	„ 400 „ (1 „)	2·35
	„ 300 „ plus thiacetazone 150 mg. (1 tablet)	2·55
Reserve	Cycloserine 0·5 g. plus ethionamide 0·5 g.	170·25
	„ 0·75 „ „ „ 0·75 g.	255·50
	Streptomycin 1 g. plus pyrazinamide 2 g.	198·50
	„ 1 „ „ ethionamide 0·75 g.	145·25

There is a widely current misconception in medical circles in technically advanced countries that the United Nations specialized agencies have almost unlimited funds and that any developing country can obtain all the antituberculosis medicament it requires just for the asking. In fact, the total expenditure on every aspect of tuberculosis control in 1961 by U.N.I.C.E.F., W.H.O., and the U.N. Technical Assistance Fund was about $2,000,000 (International Union Against Tuberculosis, 1961).

Main Priority of Chemotherapy

Considering the available funds, the cost of current chemotherapy, and the consequent drug shortage, the need for a careful order of priorities is obvious. A rational main priority is to give *one year of chemotherapy to every newly diagnosed patient with active tuberculosis.* In implementing this priority, the regimen for the individual patient will largely depend on the available resources.

If the drug supplies are adequate, then there is no reason why the common policy of the technically advanced countries of beginning with several months of triple chemotherapy with the three standard drugs followed by a two-drug regimen for the rest of the year should not be followed (Table V). This is, for example, the standard practice in the Government chest-clinic service in Hong Kong. If, however, the budget

is smaller it may be possible to give only two-drug therapy, which is likely to be either isoniazid plus P.A.S. for the whole year or isoniazid plus streptomycin for an initial period followed by isoniazid plus P.A.S. With yet smaller budgets an initial period of two-drug therapy followed by isoniazid alone may be all that can be prescribed—a policy strongly

TABLE V.—*Main Priority of Chemotherapy: One Year of Chemotherapy for Every Patient With the Best Available Regimen*

Best Available Regimen	Maximal Effectiveness
Triple drug (isoniazid plus streptomycin, plus P.A.S.) → Double drug (isoniazid plus P.A.S.)	100%
Double drug (isoniazid plus P.A.S.)	90%
Double drug (isoniazid plus P.A.S.) → Single drug (isoniazid)	85–90%
Single drug (isoniazid)	70%

Factors influencing choice of regimen:
1. Stock of drugs.
2. Extent of disease on diagnosis.
3. Bacteriological response to treatment.
4. History of previous chemotherapy.

advocated by Canetti (1962). Finally, there will be clinicians who face a situation where, for all practical purposes, the only regimen available to them is isoniazid alone. In this difficult situation, where the practical choice may be to give no chemotherapy at all to the great majority of patients or prescribe isoniazid alone, the clinician can hardly be censured for giving isoniazid alone even though he is departing from the practice of countries with abundant drug supplies. A consideration of the extreme alternatives which face the clinician is relevant.

If a clinic in a developing country has a case-load of 2,000 new tuberculous patients a year, the two extreme choices for a clinician with a limited drug budget are: (*a*) to give best standard chemotherapy (triple-drug therapy for six months followed by isoniazid plus P.A.S. for six months) to about 100 patients in the expectation of attaining quiescent disease in practically every one but leaving 1,900 patients without any chemotherapy at all; or (*b*) with the same sum of money purchase drug to treat all 2,000 patients with isoniazid alone, with the aim of attaining quiescence of the disease in a maximum of some 70% (1,400) of the patients, leaving 600, the great majority of whom will be likely to have isoniazid-resistant infections.

When faced with the choice of leaving 1,900 patients untreated as possible sources of infection in the community or having 600 isoniazid-resistant treatment failures as a possible risk, it seems both unreasonable and unrealistic to expect a clinician not to use isoniazid alone. In contrast to the much-emphasized fear of a build-up of drug-resistance, the continued menace to the community which untreated patients with drug-sensitive organisms constitute is often overlooked. A considerable reduction in the number of infectious cases in the community resulting from the wide-scale use of chemotherapy might very well lead to major epidemiological benefits and more than offset the community risk of failure-cases excreting isoniazid-resistant bacilli. Further, new antituberculosis drugs might also radically reduce the risk of a build-up of drug resistance. In all events, it is much better to give a continuous course of *the best available* chemotherapy for a year to every new patient attending a clinic rather than to withhold chemotherapy from many and so drive the patients to take irregular and haphazard treatment from non-medical sources in the local bazaar, as happens so commonly at present.

There is little doubt that a major reason that so many patients present at chest clinics in developing countries with far-advanced disease and an unfavourable prognosis is the frequency with which they are sent away without any treatment. If it becomes known that a clinic gives treatment to every patient free of charge this can be depended upon to result in patients presenting with earlier lesions, and hence to improved prospects of cure. However, a clinician is only justified in using isoniazid alone with its resultant risks provided at the same time he is making every effort to increase the expenditure on drugs as much as possible by economizing rigidly on other aspects of the service and by forcefully impressing both on the authorities and on the patients the importance of adequate combined chemotherapy (see below).

The maximum use of the drug budget will be made if the physician calculates the expected number of new cases for the next year and then (if the budgetary is large enough) buys isoniazid for every new case for a year and with any residue purchases streptomycin and P.A.S. to give as a companion drug. There is clear evidence that 200 mg. of isoniazid daily is inadequate when used as primary treatment for patients weighing 100 lb. (45.4 kg.) or more, and that 400 mg. a day in *a single dose* is substantially better (Tuberculosis Chemotherapy Centre, 1960). In some communities peripheral neuritis will be a complication (Devadatta *et al.*, 1960) unless pyridoxine, probably in small dosage, is added (Devadatta *et al.*, 1960; Tuberculosis Chemotherapy Centre, 1936b). As a tuberculosis service expands, chemotherapeutic policy will move towards the best standards of the technically advanced countries.

When drug supplies are adequate for combined chemotherapy to be given to a proportion of cases, the patients should be classified into those likely to respond satisfactorily with isoniazid alone and those more obviously in need of combined chemotherapy.

(*a*) Of factors in the initial clinical condition, the more extensive cavitated cases and those whose sputum smear is heavily positive should, if possible, receive combined chemotherapy, isoniazid alone being given for limited lesions and for those only scantily positive or negative on smear.

(*b*) The bacteriological response to treatment can also be used as a guide, combinations being given while the sputum is positive on smear, and once the smear has become negative isoniazid alone.

(*c*) A history of previous chemotherapy will indicate a greater likelihood of initial drug resistance and hence the desirability of giving more intensive chemotherapy, the aim being to prescribe triple chemotherapy, especially if the disease is extensive.

If further experience shows that isoniazid plus thiacetazone is both effective and non-toxic in areas outside East Africa, this regimen would obviously be preferable to the much more expensive combinations of isoniazid with P.A.S. or with streptomycin and to the regimens of isoniazid alone, which are not so very much cheaper (Table IV). Similarly, other effective daily regimens and regimens of intermittent chemotherapy would be introduced within the general policy outlined above for obtaining the maximum therapeutic benefit from a limited drug budget.

Although a clinician should aim to give a year of chemotherapy to every patient, he may obtain evidence before then that there is no point in continuing. If at the end of six months of regular therapy the sputum is consistently positive for tubercle bacilli on direct smear examination, it can be predicted with confidence that bacteriological quiescence will not be achieved with the regimen. In addition, a study of the smear results over the period will show either no decline in the bacterial content of the sputum or else a fall in the number of bacilli in the sputum, or their disappearance, followed by an increase—the "fall and rise" phenomenon. A clinician with a limited drug supply should reassess every patient at six months to decide if a second six months of chemotherapy is indicated. (Clearly, negative sputum findings at six months are not an indication for stopping chemotherapy.)

The clinician with limited drug resources has two obligations directly connected with the aim of giving every patient

effective combined chemotherapy for a year—namely, (a) constantly to press the authorities to provide adequate supplies of drug for combined chemotherapy for all his patients, and (b) to educate the patient, his family, and the general public concerning the importance of adequate chemotherapy for tuberculosis.

Even the most poverty-stricken patients are sometimes prepared, when the position is fully explained to them, to purchase medicament, if only for a short period of time. The clinician should take full advantage of this willingness, since it might provide at least an initial course of a few weeks of combined chemotherapy. Patients should be warned not to accumulate debts in order to buy dietary supplements, and the much greater importance of purchasing antituberculous medicaments needs emphasis.

Subsidiary Targets of Chemotherapy

In addition to this main priority of giving one year of chemotherapy to every newly diagnosed patient there are three subsidiary targets of chemotherapy.

(1) To Have Adequate Reserve Regimens

It has already been pointed out that reserve regimens are expensive and they therefore have little place in therapy until a relatively advanced stage of development of a service has been achieved. Moreover, their efficient and economical use can best be supervised by both cultures and sensitivity tests undertaken by a skilled laboratory service, and this is unlikely to be available in the early stages of a programme.

(2) Second Year of Chemotherapy for Quiescent Cases

The relapse rate in a five-year period in the general run of patients with initially drug-sensitive organisms who have received a year of chemotherapy, whether combined or isoniazid alone, is likely to be in the order of 10% and at most 20%. Even if the relapse rate could be entirely prevented by a second year of chemotherapy it would be undesirable to give a second year of chemotherapy to 100 patients in order to prevent a maximum of 20 relapsing, unless every newly diagnosed patient with active disease could also be brought under effective chemotherapy.

When the stage of development is reached which makes it logical to give a second year of chemotherapy for patients with quiescent disease, there is evidence that for those patients without residual cavitation at one year it is adequate to give isoniazid alone for the second year. Thus, in a controlled comparison in Madras of a second year of chemotherapy with isoniazid alone (200 mg. a day for a patient weighing 100 lb. (45.4 kg.) or more) or a placebo, calcium gluconate (Velu *et al.*, 1960; 1961b), none of 103 patients who received isoniazid had a bacteriological relapse in the second year compared with 9% of 107 patients who received the placebo —a statistically highly significant difference ($P<0.005$). Since isoniazid alone prevented all relapses there would appear to be no justification for recommending that developing countries should follow the common practice of the technically advanced countries and give combined chemotherapy for a second year, which with isoniazid plus P.A.S. results in about a twentyfold increase in cost.

The position for patients with quiescent disease and residual cavitation at one year, the open-negative syndrome, is different. In the Madras series (Velu *et al.*, 1961b) 7% of 55 patients with residual cavitation who were prescribed isoniazid for the second year had a bacteriological relapse compared with 10% of 42 who received a placebo, which suggests that isoniazid alone in the 200-mg. dosage probably did not materially reduce the bacteriological relapse rate. Unless evidence becomes available that a larger dosage of isoniazid prevents relapse in the open-negative syndrome the aim must be to give combined chemotherapy for the second year, which has been shown to reduce the relapse rate substantially in patients with the open-negative syndrome (Medical Research Council, 1962).

(3) Chemoprophylaxis

The attack rate of tuberculosis in a two-year period in overcrowded close family contacts of infectious cases of tuberculosis, a high-risk group, has been measured in a study in Madras (Andrews *et al.*, 1960; Ramakrishnan *et al.*, 1961a). It was 6.4% for the whole period, being high in the early months of the patient's treatment and declining sharply subsequently, a pattern repeated in a later study (Ramakrishnan *et al.*, 1961b). Many, though not all, of these contact cases might have been prevented by chemoprophylaxis, although it is uncertain for how long such courses should be given. It seems likely, however, from the above attack rate that even in specially high-risk contact groups chemoprophylaxis for 100 subjects might prevent perhaps 10 cases of tuberculosis developing in a period of follow-up of several years. This is a small gain when balanced against the benefit from treating 100 cases of active tuberculosis, leading to the conclusion that chemoprophylaxis has little place in a programme until the service has reached an advanced stage.

It should be added that both a second year of chemotherapy for quiescent cases and chemoprophylaxis make demands not only on the financial but also on the organizational resources of what is all too commonly an already overstretched clinic service.

Bacteriological and Radiographic Assessment of Progress

In the technically advanced countries many authorities regard frequent cultures and sensitivity tests as essential if the progress of therapy is to be followed satisfactorily. It is common to find in developing countries that few laboratories can culture tubercle bacilli efficiently and that there is no laboratory at all capable of undertaking sensitivity tests, reliable by any reasonable standard, even to the common antituberculosis drugs. (There is still no general agreement concerning the way to perform or interpret drug-sensitivity tests, opinions differing widely from country to country and centre to centre (Canetti, 1957; Rist and Crofton, 1960).) Cultures and sensitivity tests require a well-equipped and well-staffed laboratory, a major expense in terms both of construction and of operation costs. It is difficult to estimate the cost of different laboratory procedures accurately, but under Indian conditions a culture of sputum costs approximately 10 times as much as a smear examination, and a sensitivity test to a single antituberculosis drug approximately 20 times as much (E. M. Mackay-Scollay, personal communication, 1962). It is therefore fortunate that much information can be obtained from smear examinations of the sputum and that it is often possible to predict from them what the results of cultures and sensitivity tests would be.

Smear Examinations

Provided decisions are not taken on the basis of a single observation, the bacteriological progress of treatment can be adequately supervised with an efficient service for examining sputum smears.

(*a*) If a patient who has sputum which is positive on smear examination made on diagnosis fails to respond satisfactorily to

chemotherapy, then either the sputum remains consistently positive on smear, or only occasional examinations are negative, or a "fall and rise" phenomenon occurs within the first few months.

(*b*) If a patient responds satisfactorily to chemotherapy the smears rapidly become negative, and if quiescence is achieved they remain so.

(*c*) If the disease relapses bacteriologically it is merely a matter of time before the sputum again becomes positive on smear.

(*d*) Smear-positive but culture-negative specimens may introduce a small element of error. It is, however, exceptional for a patient to produce such specimens frequently, and they are nearly always confined to scanty positive smears (Tuberculosis Chemotherapy Centre, 1959 ; Medical Research Council, 1962).

(*e*) Very occasionally the organisms are not tubercle bacilli at all. For example, leprosy bacilli must be borne in mind in endemic areas, but the diagnosis can usually be made clinically.

It is important that the smear service should be capable of processing large numbers of specimens reliably. A fluorescence microscopy service (Holst *et al.*, 1959) has the special advantages that it is relatively easy to check a sample of the smears, both positive and negative, at the end of every day's readings to ensure that the technician's standards are maintained, and that it is also more economical than a Ziehl-Neelsen service.

Cultures

Culture results during treatment usually add little to the findings on smear examination. They sometimes show that for a month or two a patient who has become bacteriologically negative on smear examination is still excreting tubercle bacilli. Also, a bacteriological relapse may be detected a month or two earlier by culture than by smear. It is, however, unusual for the sputum to remain consistently positive on culture but negative on smear.

Sensitivity Tests

Since reliable sensitivity tests are for all practical purposes not available, physicians in developing countries currently have no alternative but to depend on clinically available assessments. A careful history may reveal that a patient has had previous chemotherapy and with what drugs, indicating possible initial drug resistance. If, during treatment, a patient has sputum which is fairly consistently positive on smear at the end of six months of chemotherapy or later, it can be concluded that the disease is very unlikely to attain bacteriological quiescence on the regimen and that the patient has, in all probability, organisms resistant to the drug or drugs prescribed (Velu *et al.*, 1961a). If a patient has a bacteriological relapse while on chemotherapy, then, provided the prescribed medicament has in fact been taken, the organisms are in all probability resistant to the drugs in the regimen (Devadatta *et al.*, 1961 ; Velu *et al.*, 1961b ; Medical Research Council, 1962).

Radiography

Serial radiography to study the response to treatment has serious limitations. The interpretation of radiographic appearances, without a knowledge of the bacteriological status of the disease at the time, is very often unreliable. A radiographic series may show apparently unfavourable changes—for example, the enlargement of a cavity—and yet the disease becomes and remains bacteriologically quiescent. For patients under treatment radiographic examinations are required very infrequently, and little information is lost if a further radiograph is not taken for six or even 12 months, or not at all if resources are very limited, especially if the smears remain negative.

A sputum-smear service is both more informative and cheaper than radiography. At current prices in India a single sputum-smear examination in a fluorescence microscopy service costs approximately $0.02 (even when all positive slides are discarded). In contrast, in a clinic undertaking 25,000 examinations a year a full-plate (15 by 12 in.—38 by 30 cm.) radiograph costs approximately $0.90, and a 100-mm. radiograph approximately $0.25, figures which, incidentally, favour the abandonment of large-plate radiography in favour of 100-mm. radiography. Svoboda (1962) has calculated that in Czechoslovakia, using a 100-mm. apparatus instead of full-plate radiography, the saving on 8,600 exposures pays for the cost of the apparatus and its installation.

Diagnostic Use of Radiography and Bacteriology

It is a common experience in developing countries to find that a not inconsiderable proportion (sometimes as many as a quarter) of the patients being treated for tuberculosis do not, in fact, have the disease at all or else have healed lesions, wasting both medicaments and the full organizational resources of the tuberculosis service. From the patient's point of view, quite apart from the inconvenience of therapy and its possible toxicity, being labelled tuberculous may result in loss of job, of home, and of family reputation. To avoid diagnostic errors the radiographic resources, and when available cultures, can be used to greater benefit in the initial assessment of the patient than to follow the progress of therapy.

As laboratories become able to undertake sensitivity tests it is preferable to use them for surveys to measure the prevalence of drug resistance in the community (Fox, 1963, p. 130) rather than to study individual patients and their response to chemotherapy. When a stage is reached which makes it possible to use sensitivity tests in the individual patient, it is still most valuable to use them to investigate pretreatment specimens. The tests are more informative in patients with a history of previous chemotherapy than in patients without a history, since the former are much more likely to have drug-resistant strains, making the choice of a chemotherapeutic regimen of special importance. The next stage would be to use sensitivity tests on pretreatment specimens in patients with no history of previous chemotherapy, and last of all would come the use of sensitivity tests to follow the actual progress of treatment.

Sanatorium and Clinic Treatment

The current role of sanatorium treatment is a problem of major importance. As already indicated, many developing countries have very few sanatorium beds. Should these countries embark on programmes of sanatorium construction or should they concentrate their resources on ambulatory chemotherapy ? The decision must be made both on medical and economic grounds.

Medical Considerations

To determine the medical place of sanatorium treatment three questions must be considered : (1) Are the immediate results of sanatorium treatment superior to the results of treatment at home ? (2) Is the relapse rate in patients whose disease has become quiescent in a sanatorium lower than the relapse rate in similar patients at home ? (3) Does isolation in a sanatorium appreciably reduce the risk of contacts contracting the disease ?

All three issues have been investigated in studies in Madras. The findings, summarized elsewhere (Fox, 1962b), need only

brief reference here. There is, however, other information relevant to the first two questions in addition to the Madras findings.

Immediate Results of Sanatorium Treatment

There have been five controlled investigations providing information either on treatment in hospital or sanatorium compared with out-patient treatment, or on the role of bed-rest in comparison with ambulation in a sanatorium. In each of the five comparisons the two series of patients had the same antituberculosis chemotherapy.

Comparisons of Bed-rest and Out-patient Treatment

(*a*) Tyrrell (1956) compared bed-rest in a sanatorium with out-patient treatment in Glasgow, the out-patients being encouraged to remain up and about. Many of the patients had cavitated disease on admission and a positive sputum. At six months the results were closely similar; 10 of 45 in-patients and nine of 46 out-patients still had a positive sputum.

(*b*) In the study in Madras (Tuberculosis Chemotherapy Centre, 1959) a comparison was made of treatment at home with treatment in a sanatorium for a year with a standard combination of isoniazid plus P.A.S. All the patients had a positive sputum on admission and the great majority had far-advanced bilateral disease with cavitation. At 12 months bacteriological quiescence of the disease was achieved in 92% of 81 sanatorium and 86% of 82 home patients, according to a very strict criterion of quiescence. All the factors usually regarded as advantages of sanatorium treatment—namely, rest, good diet, good accommodation, nursing, and supervised administration of the medicament—did not lead to materially better results. Two unexpected disadvantages of sanatorium treatment were that the patients proved less co-operative than those at home, and sanatorium treatment was disruptive to family life.

(*c*) In a study in Scotland (Kay, 1937; Tuberculosis Society of Scotland, 1960) a comparison was made of a group of 49 patients with limited disease on bed-rest for a minimum period of three months, though not necessarily in hospital, with 54 leading a normal working life. All received at least six months of chemotherapy, and over half more than a year. The main assessment was three-monthly radiography, which showed similar results at every interval during the two-year period of observation. In the bed-rest series there were two bacteriological deteriorations compared with one in the group at work.

Comparisons of Bed-rest and Ambulation in Sanatorium

(*d*) Wier *et al.* (1957) compared rest and exercise in patients in a military hospital. They studied pleural effusion and minimal pulmonary tuberculosis in nearly 200 patients, and moderately or far advanced pulmonary tuberculosis in 203 patients. The response of all patients with pleural effusion and minimal disease was so good that a comparative evaluation was not possible. For the moderately or far advanced disease there was little to choose between the response of the 95 patients allocated bed-rest and the 108 patients on the exercise regimen in terms of general radiographic improvement, cavity closure, and sputum conversion at 120, 180, and 240 days. There was, if anything, an advantage to the exercise group in the two radiographic assessments. In both series every patient assessed at 240 days attained sputum conversion.

(*e*) Wynn-Williams and Shaw (1960) compared a group of 29 infectious patients on bed-rest for at least six months, or until cavity closure if this was earlier, with 33 patients on ambulation in hospital. By six months cavity closure occurred in 15 of the 29 patients on bed-rest and sputum conversion in 28 of them, compared with cavity closure in 20 of the 33 ambulatory patients and sputum conversion in all 33.

Summarizing, no study based on random allocation has demonstrated special benefits from sanatorium treatment when compared with treatment at home or from rest compared with ambulation.

Relapse

Information on relapse either in the second year or later has been obtained in two of the studies. (1) The study reported by the Tuberculosis Society of Scotland (1960) included a period when a considerable proportion of patients were receiving no further chemotherapy. There was no difference between the series in a two-year period of observation. (2) In the Madras study all the patients with quiescent disease at one year have been followed up to the end of the third year, half receiving isoniazid alone for at least the second year. Relapse occurred in 9% of 69 patients in the sanatorium series and 5% of 57 patients in the home series (Devadatta *et al.*, 1961). Neither study suggests that sanatorium treatment or rest reduces the risk of subsequent relapse.

Risk to Family Contacts

The risk to close family contacts resulting from the treatment of patients at home has been investigated in the home and sanatorium comparison in Madras (Andrews *et al.*, 1960; Ramakrishnan *et al.*, 1961a). The close family contacts of the sanatorium patients were exposed to two sources of infection—namely, the risk of the general environment in Madras and of contact with the index case before diagnosis. The home contacts were exposed, in addition, to continued contact with the patient during the year of domiciliary treatment. In order to detect new cases of tuberculosis the contacts were examined radiographically every three months in the first year and six-monthly thereafter. Tuberculin-test results, clinical data, and bacteriological findings were also available for an independent assessment. The attack rate in a two-year period was actually higher in the sanatorium contacts, 22 (8.0%) cases among 274 contacts, than in the home contacts, 12 (4.7%) cases among 256 contacts. Thus exposure to the index case during treatment was not an important source of risk. Considering the other two sources, there are good reasons, discussed by Andrews *et al.* (1960) and Ramakrishnan *et al.* (1961a), for believing that the major source of contact infection was exposure to the index case *before* diagnosis.

A study of all three questions posed above indicates that there is no adequate medical reason to prefer sanatorium treatment to treatment at home as a general policy even for patients with advanced disease in overcrowded poverty-stricken communities.

Economic Considerations

To compare the economics of tuberculosis therapy based on sanatoria or on chest clinics, two aspects must be considered—namely, the construction costs and the annual cost of treatment per patient. Although these vary, valid general comparisons are possible.

Construction Costs

In Kenya the cost of sanatorium construction per bed, according to Ministry of Works building standards, is about $2,800, whereas a chest clinic in Nairobi capable of carrying a case-load of 1,000 new cases of tuberculosis a year cost less

than 10 times that sum ($28,000) to build and equip (P. W. Kent, personal communication, 1962). In Hong Kong the cost of sanatorium construction per bed is about $1,750, whereas a clinic capable of handling 1,500 new cases of tuberculosis annually costs $43,000—only 25 times that sum (D. J. M. MacKenzie, personal communication, 1963). In India an average figure for sanatorium construction is about $2,500 per bed, whereas the cost of clinic construction according to a Central Government standard plan is $21,000—less than nine times that sum (P. V. Benjamin, personal communication, 1962).

Although a policy of much cheaper bed construction is possible, and has been instituted in some areas, this in itself implies a very considerable modification in attitude to sanatorium construction and facilities.

Cost of Therapy

In East Africa, sanatorium treatment costs approximately $820 a year per patient—about 15 times as much as ambulatory treatment ($55 per patient). In Hong Kong, sanatorium treatment (including modern thoracic surgery) costs $1,120 a year—about 20 times as much as clinic treatment ($60 a year). In India, sanatorium treatment costs in the region of $630 per patient a year—about 15 times as much as clinic treatment ($42 per patient).

Thus it is possible either to construct and equip a sanatorium ward with from 10 to 25 beds or to build a clinic which can handle an annual case-load of 1,000 to 1,500 newly diagnosed cases. Further, for the expenditure on one patient treated in sanatorium it is possible to treat 15 to 20 patients ambulatorily from a clinic. Even if a considerable increase in the number of clinic staff was made to permit intensive supervision of ambulatory chemotherapy, it would still be possible to treat 10 to 15 patients from a clinic with the expenditure on one patient in a sanatorium.

A Policy of Clinic Construction and Domiciliary Therapy

In summary, it seems clear from the medical and economic considerations that developing countries should pursue a policy which emphasizes clinic construction and domiciliary treatment rather than sanatorium treatment. However, each chest clinic conducting an ambulatory service needs a small number of hospital beds to which patients with tuberculous emergencies and complications or with other concomitant diseases can be admitted. Such cases need rarely remain in hospital for more than a few weeks (Tuberculosis Chemotherapy Centre, 1959).

There are some developing countries which in the past concentrated primarily on a sanatorium service and which are currently not able materially to increase their annual expenditure on tuberculosis. These countries might, in fact, expand their service by actually *shutting* sanatorium beds in order to free finances for the ambulatory treatment of a much larger number of patients. The time has come when, in the light of modern chemotherapy, every developing country must review its balance between sanatorium beds and facilities for ambulatory treatment.

Unfortunately some developing countries are still unduly sanatorium-orientated in their planning. Thus it was recommended (India, Ministry of Health, 1962, p. 250) that simultaneously with the expansion of the B.C.G. vaccination and clinic programme a main aim should be for a tuberculosis bed strength of not less than 100,000, representing an increase of 70,000 beds, and for 50,000 beds for isolation (it will be recalled that the total Government expenditure on health services in India is $0.46 per person per annum). From both the medical and the economic points of view this recommendation may be queried, since the cost of construction of 70,000 beds would provide many hundred clinics and the annual expenditure on 70,000 beds would pay for good standard clinic treatment for up to a million cases with active tuberculosis annually—that is, to two-thirds of the estimated total of 1,500,000 cases of open tuberculosis in the whole country.

The organization of clinics has been discussed elsewhere (Fox, 1963, pp. 119–134), but reference need be made here to the two keys to successful domiciliary treatment, which are: (*a*) the continuous provision of effective chemotherapy for an adequate period of time, and (*b*) ensuring that as much as possible of the prescribed medicament is actually taken by the patient. The available resources must be directed to see that these two aspects receive maximum attention. With this in view, clinics should be orientated to the supervision of the self-administration of medicaments by checks of the stocks of pills at surprise visits to the home and by testing urine specimens obtained at the same time for anti-tuberculosis medicament (Fox, 1962a). The value of such tests in supervising chemotherapy cannot be overstressed, since from the results it is possible to classify patients as "regular" or "irregular" takers of drugs, permitting greater concentration on supervising the irregular patients. As successful intermittent regimens become available (Tuberculosis Chemotherapy Centre, 1963a) entirely supervised administration of medicaments will be possible, necessitating a reorientation of clinic organization and staffing.

Conclusion

The developing countries have a wide spectrum of resources with, at one extreme, for all practical purposes no tuberculosis service, and at the other extreme a service which rivals those of many technically advanced countries. Although this lecture has mainly been centred around the countries at the lower end of the scale, clearly countries with greater resources can approach closer the policies of the technically advanced countries and might especially wish to do so in the management of drug-resistant cases. Even so, the general principles which I have set out still apply.

Finally, tuberculosis is usually one of a number of major health problems, and the expenditure on it must be related to a careful and realistic assessment of the overall health priorities of the community concerned.

Summary

Many developing countries are desperately short of funds for their health services and have major shortages of all cadres of medical, nursing, and technical staff.

Physicians treating tuberculosis in developing countries must be highly selective in their choice and application of facilities which exist in technically advanced countries.

The cost of antituberculosis medicaments is a very important consideration in developing countries.

The main priority of chemotherapy is to give every newly diagnosed case of active tuberculosis a year of uninterrupted chemotherapy with the best regimen which the budgetary permits.

The regimen will change as resources improve.

It is necessary to educate the authorities and general public concerning the importance of adequate chemotherapy for tuberculosis.

Subsidiary targets of chemotherapy are (*a*) to have drugs for reserve regimens; (*b*) to give a second year of chemotherapy for quiescent cases—namely, isoniazid alone if there

is no residual cavitation at one year and combined chemotherapy if there is; and (*c*) chemoprophylaxis of high-risk groups.

During treatment bacteriological examinations are more informative than radiography, and progress can adequately be assessed by smear examinations, which are very cheap. Initially, cultures should be reserved for diagnostic purposes and sensitivity tests for the measurement of the prevalence of drug resistance in the community.

A consideration of the results of controlled comparisons of sanatorium and clinic treatment, of rest in bed and ambulation in sanatorium, of the relapse rates in patients, and of the risk to contacts, as well as the economics of sanatorium and clinic construction and treatment, leads to the conclusion that developing countries should concentrate on ambulatory domiciliary chemotherapy.

Expenditure on tuberculosis must be related to the overall health priorities of the community.

Although the views expressed in this lecture are my own, they have crystallized as a result of a period of several years of work as a W.H.O. field-staff member and from many conversations with Indian, W.H.O., and M.R.C. colleagues.

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Studies on Eaton PPLO Pneumonia*

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American investigators, using the fluorescent antibody (F.A.) technique, have found that Eaton infection is common and occurs in all age-groups throughout the year. Thus Chanock *et al.* (1960) established it as the causative agent in 16% of the pneumonia and bronchitis observed in 110 infants and children. In a further one-year study of an adult military population (Chanock *et al.*, 1961a; Chanock, 1962) Eaton infection accounted for half of the 530 pneumonia cases which were studied, and it was estimated that this agent causes an average of 10% of acute illnesses of the lower respiratory tract. The university student material of Evans and Brobst (1961) had an Eaton infection incidence of 24%. Finally, in their study of adult subjects with primary atypical pneumonia Cook *et al.* (1960) established a rise in Eaton F.A. titre in 85% of 26 patients with cold and/or *Streptococcus MG* agglutinins and in 26% of 69 patients without cold agglutinins.

When Chanock *et al.* (1962a) showed that Eaton agent could be grown on Difco PPLO culture medium and identified it as a member of the PPLO group (pleuropneumonia-like organisms), it became possible to study Eaton infection by the complement-fixation (C.F.) technique. According to Chanock *et al.* (1962a) the Eaton C.F. antigen is a specific and moderately sensitive reagent for serodiagnosis of Eaton infection. It was estimated to be 80% as sensitive as the earlier F.A. technique (Chanock *et al.*, 1962b).

This paper is a report on the results of our studies of Eaton C.F. antibodies in patients with pneumonia who were treated at Aurora Hospital, Helsinki, from September 1962 to April 1963.

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