

Towards the Rout of Tuberculosis in Rhodesia

BY

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PART II

THE WORK OF THE TUBERCULOSIS
SERVICE

TREATMENT: AS IN-PATIENT

No measures against tuberculosis, with the sole exception of BCG-vaccination, can succeed unless founded on a sound treatment organisation. This means that not only must the regimens be correct and prescribed for a long time, but machinery must be available for ensuring that patients persist with their treatment and for recording and checking lapses. Much field work is entailed for the staff of the MOH, who also have to keep a central register of all tuberculosis patients under treatment to ensure complete supervision.

Dr. E. Robinson laid a firm foundation for treatment by introducing sound drug regimens, having them accepted throughout the country, and having a unified form of case records printed for in- and out-patients.

Primary Treatment

Drug treatment of uncomplicated cases now consists of giving isoniazid, PAS and streptomycin in hospital for an initial period, which may be six months for an average case. After this, treatment is reduced to two drugs, either isoniazid-PAS or, recently, isoniazid-thiacetazone; these are given as out-patient if possible. Previously treated patients are given a very much longer period with all three drugs, since in these resistance to one of the drugs is much more likely to be present.

In newly-treated drug-sensitive pulmonary cases surgery is hardly ever necessary. The end-results of drug treatment are excellent. Often large sterilised thin-walled cavities are left, but these are very stable if a full 18-month course of treatment has been given (Fig. 2).

Drug Resistance

Rhodesia, like other countries, has had to meet the problem of drug resistance. The incidence here seems to be somewhat lower than in other African countries. For this we undoubtedly have to thank the careful control of tuberculosis treatment, which has included the insistence on in-patient treatment of all patients

not in a highly organised central domiciliary scheme.

Treatment of resistant cases, i.e., with secondary drugs and/or surgery, is reserved to five central tuberculosis hospitals—three government, one mission and one municipal. No patient on reserve drugs is allowed to be an out-patient. This system is effective in preventing the development of resistance to secondary drugs.

Laboratory Services

Until recently we were dependent on the WHO tuberculosis laboratory, Nairobi, for drug sensitivity tests, and only a small proportion of patients have had routine tests on admission. In most cases we have had to wait for the emergence of clinical resistance, which is defined as the presence of tubercle bacilli on sputum smear examination, without appreciable radiological improvement, after six months' continuous treatment with the three primary drugs. In such cases resistance is present to all the drugs and a complete switch has to be made to reserve drug treatment.

Now that our own laboratory has opened at Mpilo, however, it will be possible to develop a country-wide service for testing all new patients, with particular attention to those with

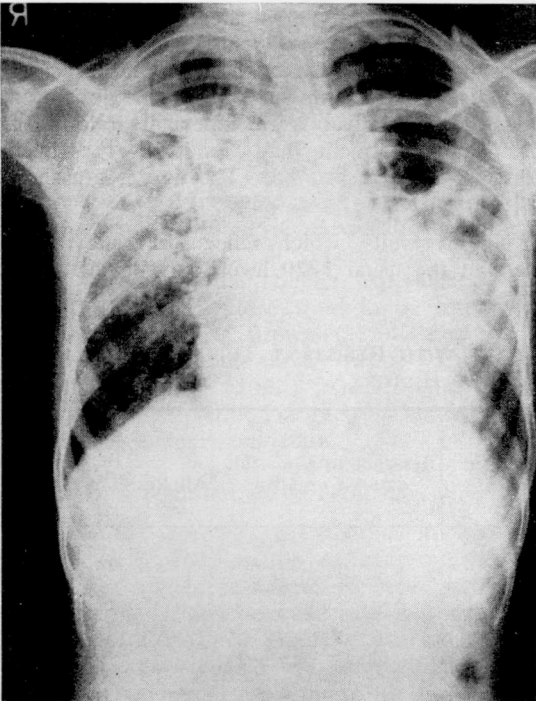


Fig. 1—Extensive lesions in both lungs. Appearance on admission to hospital.

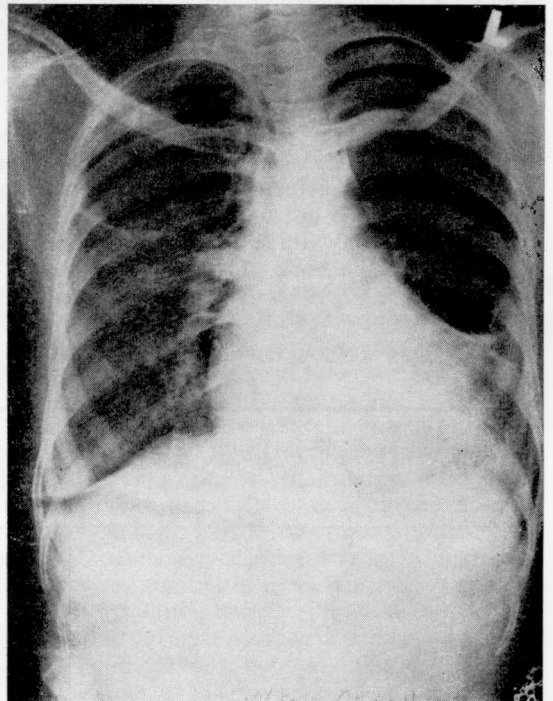


Fig. 2—After 18 months' treatment no further radiological changes over the previous six months.

a history of previous treatment. This means that instead of having to wait for the development of clinical resistance, the patients' *in vitro* sensitivities will be known two or three months after admission; treatment regimens can then be refined accordingly, in many cases by the combination of suitable primary and secondary drugs. At the same time it is hoped to move towards the transfer of all previously treated patients—that is, all those who are potentially resistant—to the major tuberculosis hospitals. Here they can be given interim drug regimens which seem suitable on the basis of their treatment history, pending the arrival of the sensitivity results.

Incurable Patients

We are now facing an increasing problem with the tragic cases who have become resistant to all drugs, including the five reserve drugs which have been introduced during the past four years. The majority of these have been patients who defaulted from treatment in some way or another, but a few have been the victims of our own ignorance at the time when we had not yet learned how to use the drugs. Some of this latter group date back to 1952, when they were treated with short courses or intermittent regimens, receiving two or three drugs for a month and then stopping for a month, and so on. The later practice of rotating two-drug regimens every three months was also unsatisfactory in cases already having unsuspected resistance to one drug. When the secondary drugs first came into use these patients were given them two at a time, or in a few cases even singly, a new one being added to the conflagration every time the last one failed—whereas now we know that only three-drug reserve regimens have a reasonable hope of success.

What to do with these patients is the pressing problem. They naturally object, sometimes violently, when they find that they are being detained in hospital without effective treatment. If they abscond the provincial MOH can have them brought back, but with persistent absconders and patients who will not accept hospital discipline we have very little legal power.

The question still awaits an answer. A possibility for investigation is the establishment of a settlement where such patients may have their families with them and farm a piece of land. This would have to be near a hospital so as to keep a close watch on contacts by frequent chest X-rays, and all contacts would have to have BCG before admission. Sheltered employment might be offered in a community agricultural or workshop scheme. A similar arrangement exists at Ngomohuru hospital for leprosy patients.

Apparent Relative Avirulence of Isoniazid-Resistant Tubercle Bacilli

There is some evidence that incurable patients with isoniazid-resistant organisms are less infectious than patients harbouring sensitive bacilli. These organisms have been shown to be less virulent to guinea-pigs. As far as man is concerned, it was found in 1963 in Nyasaland (as it then was), as an incidental finding in an investigation into the local incidence of drug resistance, that patients with isoniazid-resistant organisms having no history of previous treatment were relatively rare, especially if long-term isoniazid treatment had rendered the bacilli catalase-negative as well. The figures are shown in Table II.

These results, which reflect differences significant at the usual 1/20 level, may be interpreted

Table II

COMPARISON OF DIFFERENT CATEGORIES OF PATIENTS WITH RESISTANT TUBERCLE BACILLI
IN RELATION TO TREATMENT HISTORY

	Resistant Only to Drugs Other than Isoniazid	Resistant to Isoniazid: catalase-positive	Resistant to Isoniazid: catalase-negative	All Resistant Cases
Previously treated	6	14	19	39
Not previously treated	25	15	4	44
TOTAL	31	29	23	83
Percentage previously treated	19%	48%	83%	47%

to mean that isoniazid-resistant organisms, particularly if also catalase-negative, are less transmissible than other tubercle bacilli; or in other words, infection with these is less common than with ordinary bacilli. This may perhaps offer a grain of comfort in the difficult situation produced by incurable patients who may reach home in spite of everything we can do. It also rationalises the practice of giving isoniazid in large doses to these patients for want of anything better.

TREATMENT: AS OUT-PATIENT

The outstanding success of the drugs means that the individual patient is perfectly fit to return home and work after only a few months, or even weeks, of treatment, and it is therefore illogical to insist upon his or her remaining in hospital. It is obviously a great advantage to the patient if he can go home with his treatment. If he is kept in, his family is likely to suffer crippling financial disability; he frets and may abscond from hospital. All this, moreover, is done at considerable expense to the taxpayer. We therefore have to face the question: Is general domiciliary treatment workable in Rhodesia?

In the last few years the British Medical Research Council and the World Health Organisation have carried out a number of well-controlled investigations to determine whether out-patient treatment is satisfactory, even if given to the newly-diagnosed infectious case. Recently Wallace Fox (1964a), who directed most of this work, sparked off a controversy in the correspondence columns of the *British Medical Journal* by advocating that developing countries should adopt a universal domiciliary treatment system for all tuberculosis patients. In the ensuing verbal conflict experienced and even distinguished people were to be found on both sides; Bell and Brown (1964) and Heaf (1964) were conservative, while Lauckner (1964) and Menon (1964) joined Fox (1964b) in favour of the plan. The pros and cons therefore justify some examination.

Feasibility of Out-Patient Treatment

It is now accepted that success in treating tuberculosis depends on the use of two drugs to which the patient's organisms are sensitive. Hutton *et al.* (1956) demonstrated that isoniazid 200 mg. with PAS 20 G. daily was as good a combination as isoniazid with streptomycin; thus out-patient treatment was shown to be feasible at least.

As PAS is expensive, and as it is difficult and unpleasant for patients to take large quantities of it, there is a strong tendency for patients on the above regimen to neglect their drug treatment or to take isoniazid alone. The Medical Research Council of Great Britain (1960a) and the Tuberculosis Chemotherapy Centre, Madras (1960) tried isoniazid alone in various doses, but though the latter group found that isoniazid alone was more effective if taken in a single daily dose than if the dose was divided, it was clearly demonstrated in both trials that isoniazid/PAS is a superior regimen.

However, the Medical Research Council had more luck when (1960b) they compared isoniazid/thiacetazone with isoniazid/PAS. With the East African Medical Research Council (1963a) they later confirmed that isoniazid/thiacetazone is as effective a combination as isoniazid/PAS and no more toxic. This combination has the advantages of treatment by a single daily tablet, cheapness and the fact that one drug cannot be taken without the other.

The same workers (1963b) found that pre-treatment *in vitro* resistance to thiacetazone, like that to isoniazid, had an adverse effect on the outcome, whereas pre-treatment resistance to PAS did not appear to matter. It is therefore an advantage to have sensitivity test results for thiacetazone as well as for isoniazid in countries where these two drugs are used together as an out-patient regimen.

Isoniazid-thiacetazone was adopted as routine out-patient treatment in Rhodesia from mid-1964.

Second-Line Drug Regimens

With widespread and relatively ill-controlled out-patient treatment from the start, these regimens fail in a fairly high proportion of patients. Second-line regimens suitable for such cases necessarily include streptomycin. Velu *et al.* (1961) obtained 58 per cent. sputum conversions by giving streptomycin/pyrazinamide for one year as a second out-patient regimen to patients who had failed on isoniazid/PAS or isoniazid alone. With other co-workers, Velu (1964) demonstrated that streptomycin/pyrazinamide was somewhat more effective than streptomycin/PAS in initially sensitive cases. In cases where this second combination failed, Angel *et al.* (1963) obtained nine sputum conversions out of 14 patients after one year's treatment with cycloserine and ethionamide.

This combination was shown to be superior to cycloserine with thiacetazone.

Comparison of In-Patient and Out-Patient Regimens

The Tuberculosis Chemotherapy Centre, Madras (1959), demonstrated in a classical study that over a period of a year domiciliary isoniazid/PAS gave results as good as those from sanatorium patients given the same drug regimen. In mopping-up operations Velu *et al.* (1960) and Devadatta *et al.* (1961) found that in the second and third years there was no difference in the relapse rates between these two groups.

In support of this, Ramakrishnan *et al.* (1961c) showed that the diet has no effect on patients' progress.

Risk to Contacts of Infectious Out-Patients

Andrews *et al.* (1960) made the very interesting finding that there was little difference in the incidence of tuberculosis in contacts of patients under treatment in sanatorium or at home. Ramakrishnan *et al.* (1961a, 1961b) confirmed this for the second year and found that it was so even if isoniazid had been given alone in the first year. These findings cast a new light on the obvious objection to out-patient treatment of infectious patients—the danger of infection.

Out-Patient Treatment in Practice

Throughout Africa, even in urban practice, the results of out-patient treatment have been very poor, except in one or two places where an intensive control effort has been made over a relatively small area.

Lauckner (1956) recorded good results in the city of Ibadan, where he was giving twice-weekly streptomycin in addition to oral therapy; however, a later report on the same work by Owen *et al.* (1958) indicated many failures due to drug resistance, failure of patients to persist and misuse of drugs, including illegal trafficking.

In Ghana, Bell *et al.* (1961) lost sight of 91 (57 per cent.) of their 159 patients over a period of a year. In another series (1963) Bell and Brown lost 34 out of 112 (30 per cent.) in a year; and of the remainder, 23.5 per cent. were still sputum-positive at the end of the year, although all had had sensitive organisms at the start. Forty per cent. of those still positive were re-tested for sensitivity, and all had bacilli resistant to isoniazid.

In Senegal, Tete (1961) lost track of 879 (37 per cent.) of 2,355 urban patients in Dakar over 1½ to 2½ years.

Taute and Rabie (1959), in a rural area of the Transkei, South Africa, lost 20 per cent. of just under 8,000 patients in the first six months and nearly 50 per cent. failed to complete 18 months' treatment. The poor final results in those continuing—27 per cent. "satisfactory improvement" at 18 months—may have been partly due to the regimen prescribed, which was daily isoniazid in high doses with 2 G. of streptomycin in one weekly injection.

In Salisbury, Southern Rhodesia, Quantrill (1960) records that out-patient attendance was poor and that there was a relapse rate of 10 per cent. over a year.

The WHO Chemotherapy Centre, Nairobi (1963), concerned at the possibility that patients were not taking their drugs regularly, did an intensive investigation by means of pill counts and urine examinations, and found that less than 60 per cent. of patients, contacts and suspects took full doses of tablets in the first three months; later the figure fell even lower.

It is worth quoting verbatim the remarks of Roelsgaard *et al.* (1964), made after a detailed epidemiological study of "Tuberculosis in Tropical Africa." They say: "Even under optimal conditions, a disquietingly large proportion of cases undergoing chemotherapy . . . (at home) are irregular in intake of the prescribed drugs, or give up altogether after a brief period. The resulting inadequate treatment may well do more harm than good to the communities concerned by developing drug resistance and prolonging the life of a person with tuberculosis without eliminating the case as a source of infection.

"How this psychological barrier in self-administration of drugs is to be overcome is perhaps the biggest single question that has to be answered in the control of tuberculosis in developing areas. Before this answer has been found, chemotherapy must be used with caution and effective procedures for regular taking of drugs should be the primary objective in any public health programme involving treatment."

Controlled Out-Patient Treatment

In an area covering about one-eighth of Tanganyika, Gordon (1961) ran a successful out-patient scheme based on the co-operation of the community leaders. He gave his patients an initial period of two weeks to two months

in hospital and had a special staff to make weekly home visits. Later he was able to report a fall in the incidence of tuberculosis as a result of his campaign (Gordon, 1962).

Turner (1962) ran a similar scheme, also with good initial results, in the Nyeri district of Kenya; however, in 1963 he had to report 30 per cent. known failures after two years.

Robinson (1962b) opened the first out-patient treatment clinic in Southern Rhodesia in 1956, and ran a successful scheme in Bulawayo in close co-operation with the City Health Department. He also (1963) reported a defaulting rate in this scheme of 10 per cent. and a relapse rate of 5 per cent.

Conclusions from the Literature on Out-Patient Treatment

The Madras work has shown clearly that if it can be effectively applied, domiciliary chemotherapy is the best method to adopt.

The position regarding the application of such a scheme in the field is well summed up by Heaf (1964) in his letter on Fox's paper, where he makes the point that there is no universal formula that can be applied willy-nilly to all developing countries. There are great differences in wealth, in the influence of the doctor locally, in the nature of the patient and in his cultural conditioning to the taking of treatment on his own responsibility.

What can be said with confidence is that no successful scheme has yet been run in Africa without careful control, and that no successful scheme at all has been operated over more than a small fraction of a country.

Since Robinson's Mpilo clinic opened in 1956 a fair amount of out-patient treatment has been developed in Rhodesia, based chiefly on the main centres. This has always been done, and will continue to be done, in the closest co-operation with the public health authorities of the areas concerned.

Out-Patient Organisation in Rhodesia

By African standards Rhodesia is in a fortunate position in its relatively greater wealth and advancement of medical services. Where the majority of developing countries are trying to evolve tuberculosis out-patient treatment from no service at all, we are working downwards, as it were, from an in-patient service which could cope with all patients who presented themselves

for treatment. Where other countries, therefore, may be obliged to adopt haphazard and uncontrolled out-patient treatment due to their limited resources, we are able to convert the funds hitherto used for long-term in-patient treatment to provide adequate administrative, field and clerical staff to ensure an *effective* out-patient scheme that will result in a minimum of relapses and of drug-resistant cases.

Our aim is to keep the control of out-patients tight by having all domiciliary treatment managed by the provincial tuberculosis officer, though he may delegate the holding of clinics to other doctors by mutual agreement.

Tuberculosis clinics are held at certain centres on a fixed day each week or each month, depending on the load to be handled. Every patient discharged from a hospital for tuberculosis out-patient treatment is transferred directly to a tuberculosis clinic on the appropriate day. From then on his management is in the hands of the doctor running the clinic.

Clinics have to be "designated" in this manner to allow the provincial MOH to cover each clinic session with his own staff. In addition, every area in which out-patient treatment is permitted (which may be a zone of 15-20 miles round each recognised treatment centre) is covered by health assistant staff of the PMOH. In other words, out-patient arrangements can only be established when the PMOH gives the go-ahead.

The larger clinics work through outlying treatment centres, which may be government or mission hospitals, or even, in more scattered areas, local schools or similar assembly points where the health assistant meets the patients and hands them their drugs. Patients must attend their treatment centre once a month: from there they are conveyed once every three months to the clinic for review. Patients whose treatment centre is the clinic itself attend there monthly and see the doctor every time.

Every treatment centre keeps a tuberculosis out-patient book in a stereotyped form, and the local health assistant, by arrangement with the M.O., looks at this book at least once a month and visits any patient who has failed to come for treatment.

The PMOH staff who attend the clinic arrange for the recording of defaulters from review and for them to be brought in the next time.

Out-patient treatment is controlled by a central card-index in each PMOH's office. All the field personnel concerned in the work send in information of attenders and defaulters and of their success in bringing back the latter.

This scheme is less sociological and less intensive than that of Gordon in Tanganyika, referred to earlier. On the other hand, it combines the two vital qualities of *effectiveness* and *comprehensiveness*, and it is hoped that we shall be able to expand it until every patient living within monthly reach of a potential treatment centre can enjoy the benefits of out-patient treatment. A possible later development is the provision of bus fares to enable patients from almost any part of the country to reach a treatment centre once a month. In one or two areas voluntary bodies are doing this even now.

PREVENTIVE MEASURES

Mass Radiography

Salisbury, Bulawayo and Gwelo have their own mass radiography services, but the first government unit to serve the whole country started work in 1961. A second unit on two Land Rovers has been donated to the Ministry

by a group of voluntary societies, municipalities and industries in the Midlands and South-Eastern Provinces and started work recently.

It is clearly impossible to cover the whole country with mass radiography. We therefore have to choose the most susceptible groups and also have an eye to the areas where many people will come so that the units can work at maximum efficiency. At present, therefore, they are concentrating on mines, other industrial foci and towns. Many of these centres probably still act as foci of dissemination of infection to the rural areas.

The taking of the miniature X-ray is only the beginning of the investigation. Much work by the PMOHs is required to bring in suspects afterwards and have them examined, and considerable organisation is needed to synchronise the journeys with an investigation session. All this work, which in the United Kingdom falls within the province of the chest clinic service, has to be arranged from the scraps of time that people, both on the preventive and curative sides, have left over from their regular duties.

The results from mass radiography in Salisbury and Bulawayo have shown a dramatic fall,

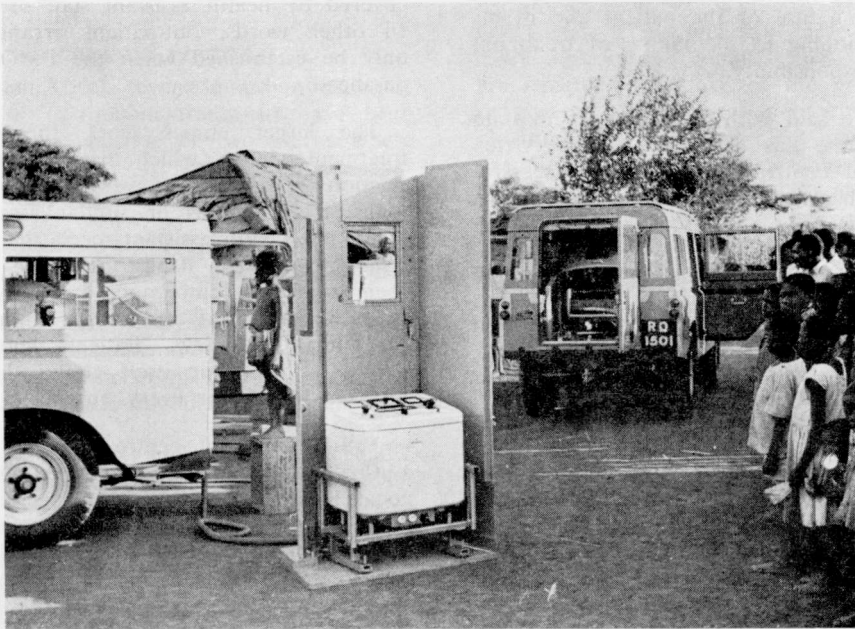


Fig. 3—Government Mobile Radiography Unit No. 2. Siemens machine with generator, mounted on two Land Rovers. (Photo by courtesy of Que Que Rotary Club, from their project "Prevention and Cure of Tuberculosis.")

from approximately six cases of active tuberculosis per thousand persons examined in 1958 to one to two per thousand in 1963. The government mobile unit No. 1 has revealed a rate of four to five per thousand in mining and smaller urban areas, two to three per thousand in rural areas and less than one per thousand in the peri-urban area around Salisbury.

Contact Tracing and Examination

The radiological examination of contacts of known cases of tuberculosis is the most fruitful method of case-finding. Unfortunately it is very cumbersome, because most contacts live in remote places and this makes transport a serious problem. Our contact examination service, in the areas for which the government health department is directly responsible, is thus very incomplete.

The yield of active tuberculosis cases from contact examination is between 40 and 50 per thousand, or ten times more than from mass radiography of the most productive areas.

BCG Vaccination

Vaccination remains the simplest and cheapest weapon against tuberculosis.

Table III

BCG VACCINATIONS DONE BY PROVINCIAL MEDICAL OFFICERS OF HEALTH, 1959-63

Year	Number of Vaccinations
1959	22,319
1960	79,326
1961	164,282
1962	121,205
1963	136,703
1964	199,731

Although the number of BCG vaccinations done annually has increased fairly rapidly (Table III), it is still desirable to push it up so that the coverage of the country's 4,000,000-odd population becomes nearly complete as soon as possible and to maintain it at that high level for a number of years.

The younger age groups receive most attention in the meantime, as more of them are tuberculin-negative and can benefit from vaccination; and also because the late teens and early twenties, when many start work and undergo a radical change in their mode of life, is the time when the greatest number of cases occur.

A massive BCG campaign should serve to prevent about 50 per cent. of cases of tuberculosis. This estimate is based on the assumptions that 10 per cent. of people would be missed by the campaign, that 30 per cent. of the population of all ages are already tuberculin-positive and so could not benefit, and that BCG protects 80 per cent. of negative reactors (Medical Research Council, 1956, 1959, 1963).

It is in fact true to say that a BCG drive is at present the only active country-wide measure directed at the drastic reduction of tuberculosis that comes into the realm of practical politics. Universal mass radiography would be prohibitively expensive, besides the immense organisation required for follow-up as well as subsequent treatment of cases found. Contact examination, while very productive of cases for the number of investigations undertaken, does not in itself provide a comprehensive scheme for the early reduction of tuberculosis incidence. Universal sputum examination is a method tried elsewhere, but, as mentioned later, it does not on the face of it appear to be a practical proposition.

BCG vaccination is practised in many different ways even in this small country. Of the four provincial health authorities, some do it by the multiple puncture method, others by injection; some do preliminary tuberculin testing, others consider this unnecessary; some do it together with smallpox vaccination, others fear that the dual demand on the immunological mechanisms may decrease the efficiency of both vaccines; some use freeze-dried vaccine, while



Fig. 4—Tuberculin testing prior to BCG vaccination, Chipinga district. (Photo: Mr. J. J. Fourie.)

others contend that this is less effective and prefer to accept the comparative inconvenience of fresh refrigerated vaccine.

The evidence in the literature on many of these points is somewhat slender.

The multiple-puncture method has been found to produce conversion rates a little lower than the intradermal (Griffith, 1959; Griffiths *et al.*, 1961; Bell, 1961; Bell, 1962), though greater pressure on the needles improves the conversion rate (Griffith *et al.*, 1963). In the newborn Griffiths (1960) found the multiple-puncture method with 20 needles and 2 mm. penetration considering the relative merits of the two methods it should be remembered that the multiple to be as good as the intradermal method. In multiple-puncture technique costs about four times as much as the intradermal using fresh liquid vaccine.

BCG-vaccination without preliminary tuberculin-testing has been increasingly practised in recent years without apparent ill effects. Cerf (1958) vaccinated 1,750 people intradermally in a pilot scheme in the (then) Belgian Congo with no harmful results, and a further 350,000 were done in a mass campaign without serious complications being reported. Fifty thousand children vaccinated in 1957 and re-examined in 1958 showed no gland abscesses. Gordon and Shelley (1959) gave freeze-dried vaccine intradermally to 1,750 people in East Africa and on follow-up found no lasting ill effects. In the Midlands and South-Eastern Provinces of Southern Rhodesia 137,000 people have been vaccinated intradermally with fresh liquid Danish vaccine in 1962-63. No special follow-up has been done, but no ill effects have been reported.



Fig. 5—BCG vaccination by multiple puncture, Salisbury city, 1964. No preliminary tuberculin test.

On this evidence we shall continue to develop vaccination without previous testing, while still hoping to see a well-controlled study, using known tuberculin-positive and tuberculin-negative subjects, emanate from Rhodesia itself.

Concurrent BCG and smallpox vaccination of the newborn was found by Moodie and Cheng (1962) to have no adverse effect on the vaccinia "take" rate or on the tuberculin conversion rate from BCG. No studies on adults appear to have been recorded.

Many papers have appeared on the relative merits of freeze-dried and fresh vaccines; in general the finding has been that fresh vaccine produces slightly better tuberculin conversion rates. The most valuable studies, perhaps, are those that deal with actual protection from tuberculosis. Gernez-Rieux *et al.* (1953) found as low a morbidity rate in a group who had been given freeze-dried vaccine as in one given fresh vaccine over a period of four years.

All this points to the need, stressed later, for organised local field research to guide us as to the best way to carry out this and other types of work.

SUMMARY

Drug therapy is the only important factor in the treatment of tuberculosis cases. The problem of drug resistance exists here and is met by the use of reserve drugs and surgery and by sensitivity testing; however, incurable totally-resistant patients are presenting an increasing problem. There is some evidence that the isoniazid-resistant bacilli excreted by these patients are less infectious than are sensitive organisms.

The literature on out-patient treatment is reviewed and the system adopted in Rhodesia is described. The amount of domiciliary treatment possible is limited by the problem of control. It is being extended gradually as the provincial medical officers of health find it possible to cover new areas with staff to do recording and follow-up work. A central card-index of tuberculosis out-patients is kept in each province. Patients not living in an "out-patient area" have to complete their treatment in hospital.

Case-finding by mass radiography and contact examination is carried out, but the numbers that these methods can deal with are limited. The most comprehensive preventive measure we have is BCG-vaccination and the amount of this done annually has been increasing steadily.

(To be continued)