TUBERCULOSIS IN AN AFRICAN SETTING

The Therapeutic Problem

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THE therapeutic situation as regards the treatment of tuberculosis has been radically altered by the introduction of effective chemotherapeutic drugs.

In a little over a decade the prospect for the tuberculous has altered dramatically in the more economically advanced countries. In Europe, England and America the stature of tuberculosis as a public health problem is rapidly diminishing. While it is generally agreed that in these countries the epidemic wave of tuberculosis was already receding, it is certain that the advent of chemotherapy has accelerated this process.

In Africa and indeed many other countries with poor economic standards of life the position is far otherwise. While the problems of arthropod-transmitted disease have been exercising medicine in the tropics, pulmonary tuberculosis has been silently advancing in importance. It can be claimed today that tuberculosis is the major tropical illness.

The situation in Africa is obscured for the reason that the continent is vast, the peoples backward and the health services exiguous. In Southern Africa tuberculosis has for long presented a problem in the indigenous inhabitants. The disease was common, the progress rapid with a high mortality. The situation in tropical Africa is less well known.

In an attempt to answer this question the World Health Organization has attempted to survey the situation in Africa. To do this it has carried out a series of tuberculosis surveys in random populations, using the tuberculin test, sputum examination and radiology. The surveys were for the most part carried out in British territories. Unfortunately the population sample examined was in many cases too small to give an incidence figure with any precision. Thus in Uganda, with a population over 10 years of age of about four million, the number of cases of pulmonary tuberculosis with a positive sputum on microscopy was judged to be between 10,000 and 60,000 (WHO Uganda Survey, 1959). However, as only some 2,000 cases of tuberculosis were known to be under treatment the magnitude of the problem can be appreciated.

The African sample surveys covered a total population of 40 million Africans in all. Of the 30,000 cases tested with 5 TU of tuberculin (in a small proportion it was 1 TU), a reaction with induration of over 10 mm. or more occurred in 49%. In 34,500 people bacteriological examination showed tubercle bacilli on culture in 115 and acid-fast bacilli on microscopy in 128. These figures were based on population samples of 0.05 to 1%, and consequently the statistical accuracy of prediction varies within wide limits. The general conclusion, however, is that tuberculous infection is widespread and tuberculous disease by no means negligible (WHO/CCTA Seminar Nairobi, 1960).

At the conference quoted, French, Belgian and Portuguese delegates were all clear that tuberculosis was a serious problem in their African territories.

In certain areas of Africa conditions are much worse. Among the Agikuyu in the Kiambu district adjacent to Nairobi a high incidence of disease is present. A recent survey showed a case prevalence of pulmonary tuberculosis of 17.3 per thousand of which 5.1 were open cases (WHO/UNICEF, 1959). A high incidence of open and closed lesions in children was an additional finding.

In East Africa tuberculosis is certainly no new disease. Contact with Arabs and Asians on the coast must have introduced it to these regions long ago. In the region of the Great Lakes it was probably introduced by the Hamitic invaders from Abyssinia some three centuries ago. At present all over Africa the population is in transition from an agricultural or pastoral existence to a money economy. Towns and slums and a modern transport system dictate a new pattern of life favourable to the spread of the tubercle bacillus. We well may be witnessing an epidemic of tuberculosis on the upswing of the epidemic wave.

The therapeutic problem in tuberculosis is interlocked with the preventive aspect. The two cannot be separated in practice. However, it is proposed only to deal with the therapeutic problem alone, in as much as it is related to the African situation.

The type of disease seen is mostly the acute rapidly progressive disease as selected for the early Medical Research Council trials in England, but a comparatively rarely encountered form of disease in that country. Cavitation is early and extensive, and is of the tension variety with large thin-walled cavities. Bronchopneumonic spread is extensive and widespread. Several lung zones are affected by the time the patient presents. Constitutional symptoms are severe and the sputum copious and loaded with tubercle bacilli. The diagnosis is confirmed as readily with microscopy as with radiology. In fact, mass radiography is disappointing from the point of view of detecting the early cases.

Severe progressive primary and post-primary disease occurs in the adult, but is not as common as has been suggested. Prior to chemotherapy it could be said that cavitated pulmonary tuberculosis ran an acute and invariably fatal course in indigenous Africans. The number in which some form of collapse therapy was suitable was almost negligible in the author's experience. With the advent of chemotherapy it was apparent that the immediate response of pulmonary tuberculosis to these drugs was remarkably good. To define the usefulness and limitations of chemotherapy a series of controlled trials was begun in East Africa. An initial trial showed combinations of streptomycin or PAS with isoniazid were equally effective (Hutton, Lutalo, Fox and Williams, 1956). Compared with cases of similar disease in the U.K. the African cases responded as well if not better (Fox, Hutton, Sutherland and Williams, 1956). The initial trials covered only six months of continuous chemotherapy. A two-year follow-up showed that about a third of the cases had showed bacteriological or radiological deterioration at some time during the period. However, the remainder had reached quiescence, and only two of the original 56 cases had been lost to observation (Hutton, unpublished data).

The effectiveness of PAS in combination with isoniazid in treatment meant that there was the possibility of treating tuberculosis on a wide scale in Africa for the first time. Here was a treatment which could be given on an outpatient basis and could be given wherever there was medical staff available to supervise it. In countries with exiguous hospital services this was a considerable gain.

However, certain problems soon became apparent. The limitations of PAS in outpatient therapy have been noted (Stradling and Poole, 1958). The same trouble became apparent in East Africa. Home visiting of tuberculous cases in Kenya brought to light tins of unconsumed PAS in their huts (Kent, personal communication).

The second problem that concerned the widespread and prolonged use of chemotherapy was one of expense. Although streptomycin and isoniazid treatment costs about £11 per patient-year this usually involves in addition maintenance of the patient in hospital. PAS and isoniazid costs only about half this amount per patient-year, and can be given on an O.P. basis. However, in Uganda at one period a third of the total available expenditure on drugs was being used on anti-tuberculous drugs. With the particular aim of adapting chemotherapy to the African situation it was decided to conduct a series of controlled trials to answer the problems raised by chemotherapy. In recent years a series of co-operative investigations has been undertaken by hospitals in East Africa assisted by the Medical Research Council and co-ordinated by the Department of Medicine at Makerere College. Trials were undertaken to find a drug to substitute for PAS for use with isoniazid. Both diphenyl-sulphone and a substituted thiourea were considered promising, but neither were found to prevent the emergence of isoniazid-resistant strains (East African/British Medical Research Council, 1960b).

At the same time the question had been raised as to whether the use of isoniazid alone was justifiable in the treatment of tuberculosis. A World Health study group (WHO, 1957) suggested that, although combined chemotherapy was undoubtedly the combination of choice, there were important questions unanswered in the use of isoniazid alone. Many highly-resistant, catalase-negative organisms were shown to have attenuated virulence for guinea-pigs (Mitchison, 1954), and while it was not possible to show this for human beings the inference was that this might be so. It had been claimed that high-dosage isoniazid more readily led to catalase negativity in the resistant strains persisting (Russel and Dye, 1957). A controlled trial with patients in hospital for a year was undertaken in an endeavour to settle these points. Two regimes, a low-dosage isoniazid and a high-dosage isoniazid with pyridoxin were tested against the standard isoniazid-PAS regime. After a year it was shown that clinically and radiologically the PAS-isoniazid patients had done better than the high-dosage isoniazid patients and these, in turn, had done better than the low-dosage isoniazid group. Bacteriologically the differences were more striking. Compared with 87% of negative cultures in the controls, only 39% of the low-isoniazid group and 53% of the high-isoniazid group had negative cultures. A high degree of resistance to 50 µg. of isoniazid per ml. developed in the majority of resistant cultures. The difference between the high and the low dosage in respect of highly resistant cultures was

not apparent (East African/British Medical Research Council, 1960a).

The experience of Fox and his associates in India of two isoniazid regimes compared with isoniazid-PAS in a well-supervised outpatient trial was similar (Tuberculosis Chemotherapy Centre, Madras, 1960). That the highly-resistant, catalase-negative bacilli are not necessarily innocuous is suggested by the report of a case of human disease caused by infection with such a strain (Mitchison and Weiner, 1957). The emergence of drug resistance to isoniazid while not as immediately disastrous as the emergence of streptomycin resistance must be looked upon as a serious matter for the patient and the public.

While there remain certain unanswered problems about the use of isoniazid, it can be said that the use of isoniazid alone for the treatment of cavitated pulmonary tuberculosis is entirely unjustifiable.

The problem of drug resistance, particularly to isoniazid, is one that has emerged since the introduction of chemotherapy. In the cases of tuberculosis treated in the original trial starting in 1953, there were no initially drug-resistant organisms. By 1958 16% of new cases in East Africa showed a primary resistance to isoniazid and 12.9% to PAS (Pepys, Mitchison and Kinsley, 1960). This contrasts with the figures for Britain of 5.1% isoniazid resistance and 2.2% PAS resistance in new cases of pulmonary tuberculosis (Fox, Wiener, Mitchison, Gelhorn and Sutherland, 1957). In Ghana the state of affairs is similar to East Africa: 15.4% of new cases were resistant to isoniazid, PAS, or streptomycin. Of these, 9.1% showed isoniazid resistance (Bell and Brown, 1960). The causes of initial drug resistance are probably multiple. Antituberculous drugs can be obtained relatively easily in towns without prescription and self-medication is undoubtedly practised widely in parts of Africa. Practitioners often employ regimes where streptomycin is given irregularly or infrequently. Patients start therapy with private physicians and break off because of the financial burden of long-continued therapy. Patients on outpatient chemotherapy with PAS and isoniazid take the former drug irregularly or not at all. The extent to which there is transmission of resistant tubercle bacilli is difficult to assess as patients' denial of previous therapy cannot be relied upon. Often at a later stage in treatment a patient will confess to previous therapy whereas initially he denied this. The high incidence of PAS resistance is not so easily explained. The accuracy of assessment of PAS resistance is perhaps less easy. Resistance has undoubtedly increased. The possibility of some infections being bovine in origin might be a partial

explanation. Bovine strains of *Mycobacterium tuberculosis* may show a proportion naturally resistant to PAS (Wallace and Webber, 1956). Recently in Uganda it has been found that the proportion of cases of pulmonary tuberculosis due to the bovine bacillus is higher than at one time thought. However, this cannot be the whole explanation. In a study of cases of pulmonary tuberculosis developing drug resistance the presence of cavities over 4 cm. was one of the factors correlating with the development of resistance (Thomas, 1960).

While it is clear that well-supervised outpatient therapy with PAS-isoniazid gives good results (Tuberculosis Chemotherapy Centre, Madras, 1959) and under other than research conditions as shown in treating 2,000 cases in Tanganyika (Gordon, 1961) a cheap substitute for PAS is desirable.

Following a promising pilot trial with thiosemicarbazone in combination with isoniazid a controlled trial was undertaken with thiosemicarbazone in combination with isoniazid (East African/British Medical Research Council, 1960b). The regime employed was 150 mg. of thiosemicarbazone with 200 mg. of isoniazid daily in two divided doses. This combination was found to be of an equal order of effectiveness as a standard PAS-isoniazid regime given under hospital conditions. The main reason for abandoning the use of thiosemicarbazone originally was the occurrence of toxic reactions including agranulocytosis, and the introduction of streptomycin, PAS and isoniazid. Previous dosage had been above that employed here and no controlled assessment of the drug had been made. In the trial quoted, 10 of 51 cases receiving thiosemicarbazone and eight of 51 cases developed toxic reactions. Six of the 10 cases had skin rashes. In two a persistent leukopenia below a thousand polymorphs necessitated changing the regime. The two most serious drug reactions occurred in the PAS series. One death due to hepatic necrosis and one case of mental confusion with associated enlargement of the liver were attributed to PAS.

It was considered the toxicity of the drug at the dosage employed was one which would allow its use in therapy. The combination described has the advantage that a year's treatment costs less than £1. The two drugs can be easily combined in a single pill. Further studies on this combination appear promising. If the results previously obtained are supported, then an effective regime for the treatment of tuberculosis on a wide scale under African conditions will have been achieved.

While considering drug toxicity in respect of thiosemicarbazone it should be remembered that

the toxic potentialities of the three commonly-used antituberculous drugs are not negligible. Those of streptomycin are well known. PAS, considered relatively innocuous, has a relatively high incidence of drug rashes and gastro-intestinal disturbance, while serious hepatic damage is not too infrequent under African conditions.

In some tropical countries where nutrition is poor and there is a poor intake of the B group of vitamins toxic symptoms due to isoniazid are not uncommon. In Nigeria it has been observed that 20% of cases of tuberculosis on a daily regime of 300 mg. of isoniazid developed neurological disturbances (Money, 1959). These included encephalopathies, myelopathies of the spastic type, peripheral neuropathy and the painful-feet syndrome. Pellagra has been precipitated on occasion (Turner, 1960, personal communication). Fortunately, dried yeast appears to prevent and to cure in the early stages.

While it appears that we have got within measurable distance of a cheap, acceptable and effective chemotherapy which can be used on an outpatient basis on a large scale, certain problems remain.

Firstly there is the problem of persuading a patient to take a drug continuously and regularly for long periods of time even if the drug is effective. Attention has been called to the necessity of research in the motivation of regular drug-taking by patients (Fox, 1958). Where drugs can be given by another person, where doctor or nurse see the patient regularly, drug-taking will certainly be superior.

The problem of primary drug-resistance complicates the therapeutic attack very considerably. It is mandatory because of this that pretreatment cultures and sensitivity tests be carried out on all patients coming for treatment. Until the results are known the patient must be treated with a triple regime consisting of streptomycin, 1 g., with PAS, 20 g., and isoniazid, 300 mg., daily. This virtually imposes a hospital regime on all patients initially. A short period in hospital is a good thing for all cases of tuberculosis in that it enables the patient to be educated about his disease. However, this again raises the problem of beds for tuberculous cases in countries poorly equipped medically.

A further problem remains. Because patients have extensive cavitation and enormous bacillary populations and also because of default from therapy and failure to take a companion drug, a proportion will be left with organisms that are drug-resistant and disease still active.

In some cases quiescence and bacterial negativity may be obtained with pyrazinamide, 1.5 g. daily, combined with streptomycin (Valu,

Andrews, Angel, Devadala, Fox, Jacob, Nair and Krishnan, 1961). Unfortunately, a fairly high proportion developed streptomycin resistance.

Another combination which showed promise was ethionamide, 1 g. daily, combined with streptomycin (Hutton and Tonkin, 1960), but further controlled studies are necessary before this can be recommended without qualification.

Surgery is unlikely to be of value to more than a selected few of the treatment-failures. Chest surgeons are in any case rarities in tropical Africa.

It is inevitable that under present conditions a small percentage of cases will remain as treatment-failures. The extent to which they represent a menace to the community has not yet been measured and remains an important piece of investigation to be undertaken.

Whether the keeping of these patients on a high dose of isoniazid is capable of keeping their bacterial population for the most part highly-resistant, catalase-negative, and therefore relatively innocuous to themselves and their associates, is another problem urgently requiring elucidation.

In general, the use of isoniazid alone is best avoided. In cavitated disease it should never be used alone. However, there are situations where isoniazid alone may be permissible. In closed lesions and in particular the early primary and post-primary disease the bacterial population is comparatively very small compared with that in cavitated disease and the chances of breeding resistant mutants very low (Canetti, 1955). Clinically this has been borne out by Philips (1959) who found that in non-cavitated disease results with isoniazid alone equalled those of isoniazid-PAS. Unfortunately he does not say whether these patients were treated in hospital or not.

In monkeys isoniazid alone has been shown to be highly efficacious in primary prophylaxis against infection with virulent tuberculosis to which the monkeys were exposed. The controls suffered severe and progressive disease (Lambert, 1959).

It is, therefore, in the situation of primary prophylaxis where the patient is as yet uninfected and in secondary prophylaxis where the patient has been recently infected and there is a likelihood of him developing progressive disease that this therapy is indicated. Probably the only situation where primary prophylaxis should be used is in the protection of the infant of a mother with open tuberculosis. To remove an African child from its mother when it is on the breast virtually sentences it to death from gastro-enteritis and malnutrition. The child should be kept with the mother and be given 10 mg. of isoniazid per kg. of body weight. On this regime, which has been successfully used in very many cases, tuberculin conversion is prevented. It is necessary to raise the child's

immunity by the use of isoniazid-resistant BCG before prophylaxis is terminated, which in any case should not be done until well after the mother is sputum-negative. In children under the age of five showing unequivocal tuberculin conversion, secondary prophylaxis should be carried out. Similarly, in older children and adults showing recent conversion and constitutional signs attributable to progressive activity, secondary prophylaxis is required even with a normal radiograph. It should be remembered when considering the diagnosis of such cases that the ill-health is often attributed to 'malaria' on insufficient grounds.

At present effective therapy in Africa is beset with a number of problems. Cases presenting for treatment tend to be self-selecting. Their disease is, therefore, extensive because of delay in presenting themselves. They may well have had some chemotherapy which they have abandoned for various reasons. It is only when a system of case-finding can be adopted that the early case of tuberculosis will be discovered and treatment rendered less lengthy and more effective.

It should be stressed that the intelligent use of the tuberculin test and the microscopic examination of the sputum will probably do more to pick up the active and the infectious case of tuberculosis than the widespread use of X-rays. Mass radiography in these conditions is expensive and rela-

tively unrewarding. In the various surveys carried out by the World Health Organization the interpretation of abnormal pulmonary shadows has been difficult and uncertain.

In summary it may be said that the therapy of tuberculosis in Africa as it is today presents certain peculiar problems and difficulties. These are the consequence of poor economic circumstances and ignorance in a situation where the medical services are exiguous. Effective and cheap forms of chemotherapy suitable for domiciliary chemotherapy are now available. It should be stressed that these forms of therapy have been arrived at by the well-established practice of the controlled clinical trial. That this can be carried out under primitive conditions has been demonstrated. The problem of persuading patients to continue taking drugs regularly and for a long time requires further study. The serious incidence of drug resistance particularly to isoniazid has complicated the problem further. Until such time as therapy can be combined with a programme of case finding and prophylactic measures, including BCG vaccination, no real inroad will be made into the problem of tuberculosis in Africa. Adequate bacteriological facilities including facilities for the testing of organisms for sensitivity to the drugs used is essential in attempting to treat the disease.

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