THE RESULTS OF TREATMENT OF PULMONARY TUBERCULOSIS AMONG AFRICANS

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Since the discovery of specific drugs, the past 15 years have witnessed the evolution of effective chemotherapy for pulmonary tuberculosis. It is now generally accepted that with drug treatment a high percentage of freshly diagnosed cases can be rendered bacteriologically quiescent and a proportion of chronic relapsing cases can be salvaged. These results have been achieved by the joint efforts of clinicians and laboratory workers. Unfortunately tuberculosis is rife among underprivileged populations in developing countries where the practising clinician may not have recourse to refined laboratory aids, and the question arises as to what results may be expected under such circumstances. The present study is an attempt to supply an answer to this problem.

On the Reef approximately 3,500 beds are available for Africans suffering from pulmonary tuberculosis; these are scattered among several hospitals whose annual turnover of patients is so great that specialized sputum investigations are quite beyond the resources of routine laboratories. At the time of this study facilities for sputum culture and tests for drug sensitivity of bacilli were not available and treatment was given according to current concepts. The methods and results presented here may serve as a guide to others who are obliged to treat tuberculosis under similar conditions.

MATERIAL AND METHODS

The hospital consists of a series of bungalow-type buildings. It provides wholesome food and is adequate for the treatment of routine cases but does not aspire to coping with problems requiring specialized medical or nursing attention.

Only simple procedures such as chest aspirations and blood transfusions are undertaken; patients requiring bronchoscopy, all types of surgery or specialized nursing are transferred to better-equipped hospitals. The trained White nursing staff supervises semi-trained African nurses. Three medical officers attend daily and each is responsible for about 80 patients.

The African patients treated at this hospital come mainly from Johannesburg, and are usually manual labourers. Although their home diet has a high calorie content it contains little animal fat and protein but a large proportion of carbohydrate and roughage in the form of maize and vegetables. Their biochemical background has been well documented[1] and differs in many respects from that of White subjects; the abnormalities relevant to this study are the high incidence of disordered serum proteins and fairly common evidence of liver dysfunction.

Sputa were examined by personnel trained at the SAIMR and smears were studied weekly and reported as positive or negative, but no attempt was made to assess the degree of intection. All patients admitted to the study had at least 4 consecutive positive weekly sputa.

One hundred consecutive patients admitted to hospital with positive sputum were included in this study. For administrative reasons males only were selected, but there are no grounds to believe that females fare any differently.

Four patients were aged 15 - 19 years, 4 were over 60 and the majority were between 30 and 50 years. For purposes of treatment patients were divided into 2 groups: 73 who had received no previous treatment were classified as 'fresh cases'. The remaining 27 patients had been treated previously; the majority had frequently relapsed or produced persistently positive sputa during the previous 2 - 8 years, but only 4 had relapsed for the first time. The clinical state was roughly assessed into 4 grades: moribund 2, very ill 47, ill 36 and fairly well 15 patients, i.e. about 75% were ill or very ill. As a group, previously treated patients were more gravely ill than fresh cases; 2 were moribund and died shortly after admission; only 1 patient with persistently positive sputum was in reasonably good physical condition.

The history of the duration of symptoms was usually inaccurate, as in some cases with a short history it was evident from X-rays that the disease was of long standing. Average weight on admission was 110 lb., and the average weight gain at discharge was 20 lb. (Fig. 1). The most common associated condition was generalized oedema and ascites (6 patients), which was not due to cardiac or renal disease. The condition is seen quite frequently among sick Africans[2] and may be related to their disordered serum protein pattern. One patient suffered from pellagra and 2 others from mental confusion which cleared on resolution of the lung disease. No patients in this series had overt evidence of tuberculosis infection outside the lungs.

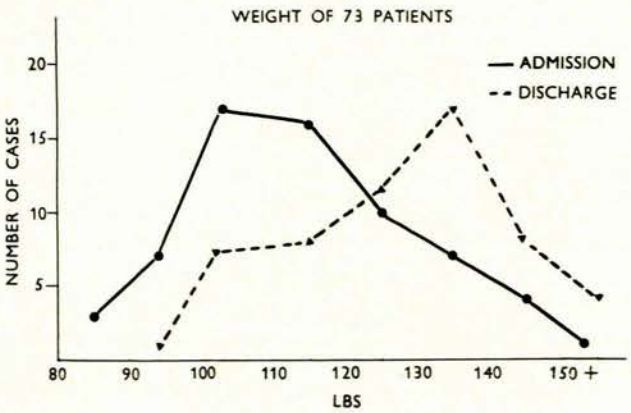

Fig. 1. Weight gain during hospitalization in 73 cases.

X-ray Findings

The majority of fresh cases had involvement of 1 - 3 lung zones; about one-third had more extensive infiltration and 4 patients had cavities with diameters in excess of 5 cm. (Fig. 2).

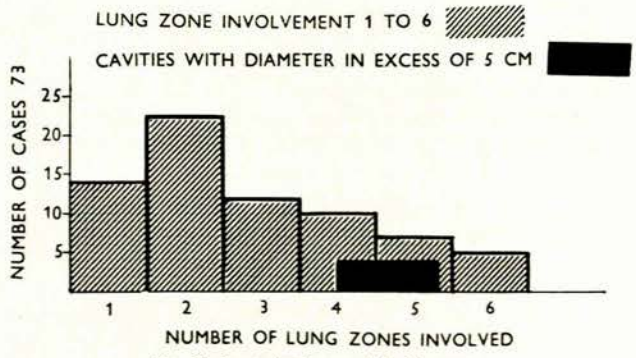

Fig. 2. Lung involvement in 73 cases.

Of the 27 previously treated patients, 9 had bilateral extensive cavitation (diameter greater than 5 cm.) and 8 had several small cavities; 8 had surprisingly unimpressive fibrotic lesions and 2 patients had lesions which resolved after treatment.

Treatment Regimens

Fresh cases received the following drugs: Isoniazid (INH) 500 mg. daily in divided doses; streptomycin sulphate, 1 G daily by intramuscular injection for 3 months; patients over 50 years of age received streptomycin sulphate only thrice weekly; sodium p-aminosalicylic acid (PAS), 15 G daily in divided doses. INH and PAS and pyridoxin (600 mg. daily) were given throughout the entire hospital stay. In some of the seriously ill patients prednisone, 30 mg. daily, was given for 2 - 3 weeks and then gradually reduced.

Previously Treated Cases

Four patients with first relapses were treated with standard drugs. The remainder received ethionamide, 250 mg. *t.d.s.* with pyrazinamide, 1 G *t.d.s.*, or cycloserine, 250 mg. *t.d.s.* The drugs were given for 3-monthly periods and permutated if the sputum remained positive. In 6 patients all 3 drugs were given. A close watch was kept for mental confusion and jaundice, and urines were tested weekly for bilirubin and urobilin.

In all cases the nursing staff personally supervised the taking of the medication. Progress was judged by sputum conversion, clinical appearance, weight, temperature and X-ray changes. No fresh patient was considered to have converted his sputum until he had produced 12 consecutive negative weekly smears, and previously treated patients were usually kept in hospital for at least 6 months after sputum conversion.

RESULTS

The majority of fresh cases started improving within a month and appeared well on discharge. In these patients sputa became negative after 1 - 4 months (Fig. 3). In 7 patients sputa remained positive for longer than 4 months.

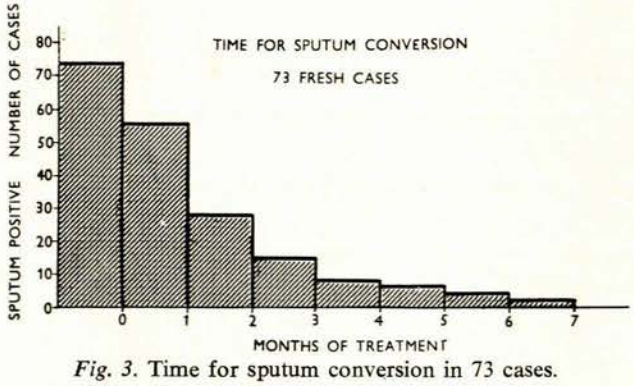

Fig. 3. Time for sputum conversion in 73 cases.

They were all very ill on admission and had bilateral disease but no large cavities. In all of them X-ray lesions resolved more or less completely and 5 finally appeared well when discharged. The remaining 2, however, despite negative sputa and X-ray evidence of resolution, were thin and sickly after a full year in hospital.

One patient who was not remarkably ill on admission nor had particularly extensive X-ray changes, produced persistently positive sputum for a year. Subsequently he failed to convert on secondary drugs. He was a man 35 years of age, reliable and cooperative. He denied having had previous treatment and had taken his tablets regularly. It is concluded therefore that he was infected with resistant organisms.

Summary of Results—Fresh Cases

Of 73 cases, 70 responded in a straightforward manner although 5 took longer than 4 months to convert their sputa. Two patients whose sputa became negative after 5 and 6 months and whose X-rays had resolved still appeared ill after a year in hospital, and one patient was a treatment failure.

TABLE I. RESULTS OF TREATMENT IN 73 'FRESH' CASES

Sputum converted to negative	*Time to convert*		*Failed to convert*
	1–4 months	*5–7 months*	
72 cases	65	7	1 case

Results in 27 Previously Treated Cases

Two patients died shortly after admission and a third died of Stevens-Johnson syndrome which appeared suddenly after months of treatment with secondary drugs. In 15 patients the sputum became negative in 1 - 7 months and remained so for the duration of their hospital stay.

TABLE II. RESULTS OF TREATMENT IN 27 CHRONIC POSITIVE CASES

Deaths in Hospital	*Sputum converted to negative*	*Time to convert*	*Failed to convert after at least 12 months*
3	15	1–7 months	9

Seven of this group looked well and had gained an average of 13 lb. (range 8 - 30 lb.) when discharged. Only 2 showed resolution of X-ray lesions. The remaining 8 patients gained less than 5 lb. in weight and looked ill when discharged.

In 9 patients sputa remained persistently positive after a year of chemotherapy and their X-rays were unchanged. Five gained 4 - 18 lb. in weight but with 1 exception they all appeared ill and most of them had persistent haemoptysis and severe dyspnoea.

DISCUSSION

At the time of this study we did not have laboratory facilities for routine sputum cultures and drug sensitivity tests. Moreover smears were examined merely to determine the presence or absence of bacilli with no attempt being made to grade the severity of the infection. Since the crucial point in treatment is to attain bacteriological quiescence, the question arises as to the validity of results based on smears. Several studies[3,4] indicate that smears are far less accurate than cultures; with persistently positive cultures smears are usually positive, but on the other hand as many as 25% of negative smears may prove positive on culture.

In the majority of fresh cases in this study the over-all clinical and radiological picture confirmed the sputum findings and indicated that bacteriological quiescence had in fact been achieved. However, there were 2 situations in which doubt existed about smear findings.

Among the fresh cases there was a group of slow converters in whom smears finally became negative after 5 or 6 months of treatment. Although some of these patients appeared well and their X-rays showed resolution, a few still looked ill and the problem was to decide whether these were still active cases despite negative smears. Clinical criteria were of no help since even known chronic positives may gain weight under hospital conditions. Radiological evidence was of doubtful value since X-ray resolution often lags behind sputum conversion. Similar doubts

applied to those 'chronic' relapsing patients whose sputa were converted but who showed little clinical or radiological improvement.

In both these groups it is quite possible that sputum cultures might have proved positive in a proportion of them; and for this reason the 'cures' claimed in these 2 categories may be somewhat optimistic.

The principles of chemotherapy have been more or less defined as a result of experiences of large scale trials in both Britain and the USA. It was soon found when INH was given alone that resistant organisms rapidly appeared in cultures.[5,6] In a tuberculous lesion there is an enormous actively multiplying bacillary population; INH acts best in such circumstances rapidly killing off the organisms but a proportion of resistant mutants appear; these are usually susceptible to either of the remaining 2 so-called first-line drugs, namely PAS and streptomycin. In practice therefore INH should never be used alone for the treatment of pulmonary tuberculosis and, moreover, bacterial resistance is delayed by adding PAS and/or streptomycin. It is accepted[7,8] that the following regimens are effective: (1) daily INH and streptomycin, (2) daily INH and PAS, (3) daily INH and PAS and streptomycin. INH with intermittent streptomycin is an ineffective combination. With all regimens the difficulty is to ensure that the patient takes the tablets which are unpalatable and can cause gastro-intestinal upsets. Moreover, since the addition of streptomycin increases the cost of treatment, efforts are continually being made to find cheaper and more acceptable regimens. One such study from East Africa[9] suggests that INH and 150 mg. of thiacetazone daily is an effective combination for adults, but as yet this regimen has not had official sanction. As regards the dosage of INH[10] it is now accepted that 4 - 7 mg./kg. in adults need not be exceeded as considerably higher doses are of questionable benefit and may produce crippling polyneuritis. Recently[11] it has been shown that a single daily dose of INH producing high blood peaks is more effective than divided doses.

The triple drug regimen (daily INH, PAS and streptomycin) is probably the most effective, but in patients over 50 years of age daily streptomycin is likely to produce ototoxicity. Although intermittent streptomycin with daily INH and PAS is acceptable treatment, it has been suggested that a smaller daily dose of streptomycin (0·75 G) may be given without loss of therapeutic efficiency and with a lower (7%) incidence of labyrinthine damage.[12] In many centres the triple regimen is used for the first 6 - 12 weeks, after which time streptomycin is omitted:[9,10] and it should also be abandoned at the patient's first complaint of giddiness attributable to labyrinthine disturbance. It is agreed that treatment with INH and PAS should be continued for about 18 months after the last positive sputum.

Without the help of sputum cultures and sensitivity tests the handling of fresh cases is based on the foregoing principles. As occurred in this series, there will be the occasional patient who has taken his drugs meticulously but has been infected with an organism resistant to one of the standard drugs. In Britain it is estimated that approximately 4·5% of all fresh cases have been infected with resistant organisms[13] and in South Africa the figure is approximately 6%;[3] a much smaller percentage of cases is resistant to 2 or all 3 major drugs.

The major difficulty in treating fresh cases is to know how to manage those patients who convert slowly. The simpler problem is the patient who is responding clinically but whose smears are still positive 5 - 7 months later. The decision to persist with standard drugs is easier since the bacilli found in smears may be scanty and decreasing in number, or they may be non-viable. Moreover, the occasional positive sputum report is due to observer error. The more difficult situation is the one where smears only become negative after 6 months of treatment and where the patient remains thin and ill. This slow progress may be due to the severity of the original infection, as in those fresh patients who have advanced cavitating disease, or to the fact that the organisms are resistant. The problem is to know whether to continue with the powerful standard drugs or change to secondary drugs which at best are poor substitutes. As a general principle, if smears are still positive after 6 months in these circumstances it is considered advisable that a change be made to secondary drugs.[14]

As regards the treatment of 'chronic' cases, some have had an adequate course of hospital treatment elsewhere and have relapsed because they have not continued taking INH and PAS after discharge. In these it is not unusual to find organisms which are still sensitive to standard drugs and these cases respond well to treatment. The majority however are persistently positive and their bacilli are resistant to many if not to all drugs. Basically the reason for this is inadequate original therapy. In many cases the patient is to blame either for not taking his drugs or for having absconded before his treatment has been completed.

Even with the aid of sensitivity tests, results in this group are indifferent.[15,16] Many patients have gross mechanical distortion with cavities which may harbour bacilli with varying sensitivities to both standard and secondary drugs. Without cultures and sensitivity tests, treatment is based on the assumption that bacilli are still sensitive to the secondary drugs. Currently the most effective combination is considered to be ethionamide, pyrazinamide and cycloserine; the best results are obtained by prolonged treatment with these drugs which however bring their own problems in the form of toxic and allergic reactions as in the 1 case in this series who died of Stevens-Johnson syndrome.

As regards our results, if all the slow converters are included as 'cures' then in this series there was only 1 solitary failure among 76 fresh cases. Crofton[7] claims that if drug resistance is avoided (and this implies the use of sensitivity tests) it should be possible to obtain negative sputum in 100% of cases. He quotes a series which included 40% far advanced and 40% of moderately advanced cases. On the other hand an MRC study[17] of fresh cases with chronic bilateral disease achieved only 91% conversion at the end of 1 year. In various other studies of fresh cases including cavitating ones, the failure rate after 17 months of treatment varied from 2 to 14%.[9,16] It seems clear that in fresh cases without extensive chronic cavitation, sputum conversion may be expected in the vast majority with standard treatment and without specialized laboratory studies.

As regards the group of previously treated patients, 4

were included who had been adequately treated months or years previously and who had relapsed for the first time. Two of these responded to standard drugs presumably because their bacilli were still sensitive. The majority of these patients however formed a pathetic group. They had usually spent years in and out of hospital because of persistently positive sputa or repeated relapses. About one-third had extensive destructive lesions, the rest had less impressive X-rays but none the less were grossly disabled by respiratory insufficiency. The death rate was considerable. In about 15 patients sputa were rendered negative and they were maintained in a quiescent state by prolonged hospitalization. The sputum findings do not however tell the story since a number with negative sputa still remained thin and in poor health. The remaining one-third of patients kept producing persistently positive sputa despite all forms of chemotherapy and were gradually consumed not only by their physical disease but by the ennui of hospital life and a growing despair about themselves and the fate of their families.

Other studies[14] have shown that there is no advantage to the patient with hospital as opposed to domiciliary treatment. Surprisingly this includes data from an underprivileged population. It may be that circumstances are different in South Africa, where the majority of males have to earn their living by heavy manual labour in a competitive market. Moreover attendance at outpatient clinics among Africans is poor and the standard of hygiene as regards sputum disposal primitive. One cannot escape the impression that patients benefit enormously from rest, food and the supervised chemotherapy in hospital, and therefore we tend to keep them in hospital as long as possible after sputum conversion.

SUMMARY AND CONCLUSIONS

This study reports the methods used and the results obtained in treating both fresh and chronic positive cases of pulmonary tuberculosis in Africans. Treatment was given without the aid of sputum cultures and drug sensitivity tests. Practical problems of management are discussed.

With reservations about the accuracy of our criteria of bacterial quiescence, it is concluded that a high 'cure' rate is possible in 'fresh' cases and that a proportion of chronic cases may be salvaged.

The requirements are comparatively few and consist of a trained person to study sputum smears, adherence to an orthodox regimen of treatment and scrupulous attention to the administration of drugs. To these must be added simple hospital accommodation, basic nursing and wholesome food.

This work would have been quite impossible without the help of the following: Drs. F. Galgut, B. Gayliss and J. A. Haggiyanes, Sisters D. Warter and H. C. Nel, Messrs. H. Letlaka and D. Gqibela, technicians trained by the SAIMR. I should like to thank Hospital and Nursing Suppliers (Pty) Ltd., for their cooperation.

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DIE ANTIBIOTIKUM-SENSITIWITEIT VAN GRAM-NEGATIEWE ORGANISMES BY DIE KARL BREMER-HOSPITAAL* 1960-1965

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Die doel van hierdie projek was om vas te stel of die antibiotikum-sensitiwiteit van sommige Gram-negatiewe organismes, wat in die roetine bakteriologie-laboratorium van die Karl Bremer-hospitaal teëgekom word, in die afgelope 5 jaar verander het.

Met dié doel voor oë is antibiogramresultate uit die laboratoriumverslae van 1960 met dié van 1964-1965 vergelyk. Gedurende hierdie tydperk het die antibiogrammetode, naamlik die papier-diffusiemetode, wat gebruik is, onveranderd gebly. Die konsentrasie van die antibiotika waarteen die sensitiwiteit van die organismes getoets is, was soos volg:

Streptomisien en chlooramfenikol	:	1,000 μg./ml.
Neomisien, novobiosien en tetrasiklien	:	2,500 μg./ml.
Eritromisien	:	300 μg./ml.
Kanamisien	:	1,500 μg./ml.

1 ml. antibiotikum-oplossing is gebruik om 50 papiertjies voor te berei.

*Voordrag gelewer op die 9e Akademiese Jaardag, Karl Bremer-hospitaal, Bellville, K.P.

Die Gram-negatiewe organismes waarvan die sensitiwiteit nagegaan is, was die volgende: *Proteus mirabilis, Proteus morgani, Escherichia coli, Klebsiella pneumoniae* en *Pseudomonas aeruginosa.*

Die resultate wat verkry is, word in Tabelle I - V aangegee. Die syfers toon die aantal stamme wat sensitief was vir die antibiotika persentasiegewys aan. Die gemiddelde fout, bereken volgens die formule: $m = \sqrt{\frac{z(100 - z)}{n}}$ waar m = gemiddelde fout, z = persentasie, en n = totale aantal, word in hakies langs elke syfer aangegee.

TABEL I. PROTEUS MIRABILIS (550 STAMME)

Antibiotikum	*% sensitief* 1960	*% sensitief* 1965	*% verandering*
Streptomisien	74 (±2·7)	88 (±1·6)	+14
Chlooramfenikol	79 (±2·6)	81 (±1·7)	+ 2
Tetrasiklien	13 (±2·1)	6 (±1·2)	− 7
Eritromisien	12 (±2·1)	4 (±1·1)	− 8
Neomisien	100 (±0·06)	95 (±1·2)	− 5
Novobiosien	45 (±3·2)	38 (±2·6)	− 7
Kanamisien	98 (±0·09)	90 (±1·4)	− 8