ETHAMBUTOL IN THE RETREATMENT OF PULMONARY TUBERCULOSIS

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Ethambutol is the latest addition to the armamentorium in the fight against tuberculosis. It is a white, odourless, crystalline compound, heat stable and highly soluble in water. It is chemically unrelated to any of the previous anti-tuberculous drugs. There has been no reported cross-resistance with other anti-tuberculous drugs. After oral administration it is rapidly absorbed and peak serum concentration is reached after 2 to 4 hours. About 20% of the oral dose is excreted in the faeces, 10% is metabolised to inactive forms and the remaining 60-80% is excreted in the urine unaltered (Place VA. et al., 1966).

TABLE I

ETHAMBUTOL
1. Synthetic Compound.
2. Dextrorotatory isomer of 2, 2^1—(ethylenediimio) di-1-butanol dihydrochoride.
3. Unrelated to other anti-tuberculous drugs.
4. Orally administered.
5. 60-80% excreted unaltered in urine.
6. Peak Serum levels of 2-5 mcg/ml in 2-4 hours after administration.
7. Toxic effect—retrobulbar neuritis.
8. Toxic effect clears on drug withdrawal.
9. Effective against M. tuberculosis, M. bovis and some anonymous mycobacteria.
10. Dose 25 mg./Kg. for 60 days, then 15 mg./Kg.

The toxicity of Ethambutol is very low and the only serious toxic effect reported so far is retrobulbar neuritis. Two types of retrobulbar neuritis have been described—one involving the central optic fibres producing diminishing visual acuity, central scotoma and loss of ability to see green, and the other involving the periaxial fibres causing peripheral visual field defects without disturbances of visual acuity or colour vision. There has been no associated retinal changes (Tubercle, 1966). The ocular toxicity is dose dependent and usually clears on stopping the drug.

Ethambutol is active against M. Tuberculosis, M. bovis and some anonymous mycobacteria (Brit. Med. J. 1967; Davey M.E. 1966).

Using egg-yolk agar media, it has been demonstrated that most strains of M. tuberculosis are inhibited by an Ethambutol concentration of 1 mcg./ml.

The recommended dose of Ethambutol is 25 mg./Kg. for 60 days followed by 15 mg./Kg. thereafter.

PRESENT CLINICAL TRIAL

There have been encouraging reports regarding the use of Ethambutol in the retreatment of pulmonary tuberculosis (Bobrowitz, I.D. and Gokulanathan, 1965; Bobrowitz, 1966). As a result of this the present study was undertaken to determine its efficacy in a local population of tuberculous patients.

METHODS

All the patients in this study were retreatment cases of active pulmonary tuberculosis. Their sputa were persistantly positive for tubercle bacilli which were resistant to Streptomycin, P.A.S. and I.N.A.H. They had not had any new anti-tuberculous medication added to their regime during the previous six months. During those six months the pulmonary tuberculosis had shown roentgenographic worsening or had been unchanged.

The exclusions from the study were as follows:—Ethionomide and Pyrazinamide in the presence of significant hepatic dysfunction; cycloserine in patients with a history of convulsions or psychosis. Ethambutol was not given to patients with eye diseases that would prevent the evaluation of visual acuity.

The pretreatment investigations included chest roentgenograms, sputum concentrates and culture with sensitivity tests, haematological investigations (Hb, W.B.C., E.S.R., & P.C.V.), tests of renal function (Blood Urea, Blood Uric Acid & Urine for albumin, sugar and sedi-

ments), and S.G.O.T. Eye examination included visual acuity, colour discrimination, visual field and fundoscopy.

The treatment procedures included monthly chest roentgenograms, monthly sputum concentrates and cultures, monthly haematological investigations and monthly tests of renal function. If ethionamide or pyrazinamide were exhibited, then S.G.O.T. was determined every two weeks. Visual acuity and colour discrimination were checked every two weeks. Fundoscopy was only repeated if there were any changes in visual acuity or colour discrimination. Blood levels of Ethambutol were determined three hours after the morning dose at four weeks, eight weeks and six months.

Each patient received Ethambutol as a single oral dose in the morning. The dose of Ethambutol was 25 mg./Kg./day during the first sixty days and then 15 mg./Kg./day thereafter. Each continued to receive 300 mg. of I.N.A.H. as a single breakfast dose. In addition each patient received an oral anti-tuberculous drug which had not been given previously. The third drug that was used was either ethionamide 1 gm./day, pyrazinamide 1·5 gm./day or cycloserine 1 gm./day. The dosage of the third drug was reduced if there was intolerance.

CLINICAL MATERIAL

This report describes our experience in the use of Ethambutol in 34 patients. All had been infected with tubercle bacilli that were resistant to Streptomycin, P.A.S. and I.N.A.H. All were admitted to one ward for treatment and observation. All the patients were male. There were 32 Chinese, one Indian and one Pakistani and their ages varied from 32 years to 63 years. The age distribution is as shown in table II.

TABLE II

Age Groups in Years	Number
31 - 40	7
41 - 50	13
51 - 60	12
61 - 65	2

The disease was far advanced in 15 patients and moderately advanced in 19 patients. There were no patients with minimal disease.

TABLE III

Extent of P.T.B N.T.A . Classification	Number
Far Advanced P.T.B.	15
Moderately Advanced P.T.B.	19
Minimal P.T.B.	0

Most of the patients had been suffering from Pulmonary tuberculosis for more than 10 years. The longest duration being 22 years and the shortest 4 years. The average duration was 11 years.

TABLE IV

Duration of Pulmonary Tuberculosis in years	Number
0 - 5	3
6 - 10	11
11 - 15	15
16 - 20	4
21 - 25	1
Longest Duration	22
Shortest Duration	4
Average Duration	11

Most of the patients had other associated diseases as well. The commonest disorders were pulmonary fibrosis and emphysema which were found in 27 patients. This condition was severe enough to incapacitate most of them. The number of patients with other diseases is as shown in table V.

TABLE V

Associated Diseases	Number
Pulmonary Fibrosis and Emphysema	27
Cirrhosis of Liver	5
Non Specific Hepatitis	3
Diabetes Mellitus	2
Nephrolithiasis	3
Chronic Pyelonephritis	6
Chronic Nephritis	3
Ankylosing Spondilitis	1
Amyloidosis	1
Haemosiderosis	1

Many patients had two or more of the medical disorders mentioned above in addition to pulmonary tuberculosis.

All the patients were started on Ethambutol in June, 1966. In 8 patients it was combined with Cycloserine, in 12 patients with Pyrazinamide and in 14 patients with Ethionamide.

RESULTS

3 of the 34 patients dropped out of the trial after six weeks. One patient was taken off the trial because of noncooperation, one patient was transferred to a mental hospital for management of schizophrenia and one took his own discharge. The following analysis was done after 17 months of therapy.

TOXICITY

Ethambutol was well accepted and tolerated by all the patients. This was not so with the other secondary drugs. Ethionamide was the drug that was least tolerated by the patients. It was stopped in 2 patients because of toxic hepatitis; in 5 patients it was stopped because of intolerance and in 2 patients the dose was reduced because of intolerance.

Hyperuricaemia developed in 8 patients and in one patient gout was precipitated. The arthritic symptoms in this patient were controlled with colchicine and probenecid. Only one patient had his pyrazinamide stopped and this was because of raised S.G.O.T.

Cycloserine was stopped because of mental confusion and aggressive behaviour in 2 patients and because of convulsions in 2 patients.

Two patients developed ocular toxicity to Ethambutol. One patient started to have deterioration in colour vision and visual acuity 7 months after start of Ethambutol. There were no objective signs on fundoscopy. Toxicity in this patient is probably contributed to by the renal disease he had. He was detected to have chronic pyelonephritis and renal amyloidosis on renal biopsy. This patient has had pulmonary tuberculosis for 13 years and his sputum was converted when Ethambutol was stopped. His visual acuity and colour vision improved on stopping Ethambutol.

The other patient started to develop deterioration in colour vision and visual acuity 11 months after start of Ethambutol. His visual symptoms too improved on stopping Ethambutol.

SERUM LEVELS

The serum levels of Ethambutol were determined at 4 weeks, 8 weeks and 6 months. Most of the sera that were taken at 4 weeks and 8 weeks were spilt on air transit to the Lederle Laboratories in the U.S.A. and so were not available for analysis of serum levels. The available results revealed that most of the patients had serum levels in the therapeutic range of 2-5 mcg./ml.

BACTERIOLOGY

Sputum conversion was said to have occurred if three consecutive monthly cultures and concentrates were reported to be negative. 28 of the 31 remaining patients in the study had converted their sputum after 17 months of therapy. Sputum conversion occurred early in the 2nd and 3rd months of therapy.

TABLE VI

Drug	Toxicity	Intolerance	Number who had drug stopped
Ethionamide	Hepatic toxicity in 2. These 2 patients had raised S.G.O.T. and liver biopsy revealed toxic Hepatitis.	Anorexia nausea and vomitting in 7 patients	7
Pyrazinamide	Hyperuricaemia in 8 patients. Raised S.G.O.T. in 1 patient. Gout in 1 patient.	-	1
Cycloserine	Mental confusion and aggressive behaviour in 2 patients. Convulsions in 2 patients.	-	4
Ethambutol	Decreased visual acuity and inability to differentiate colours in 2 patients.	-	2

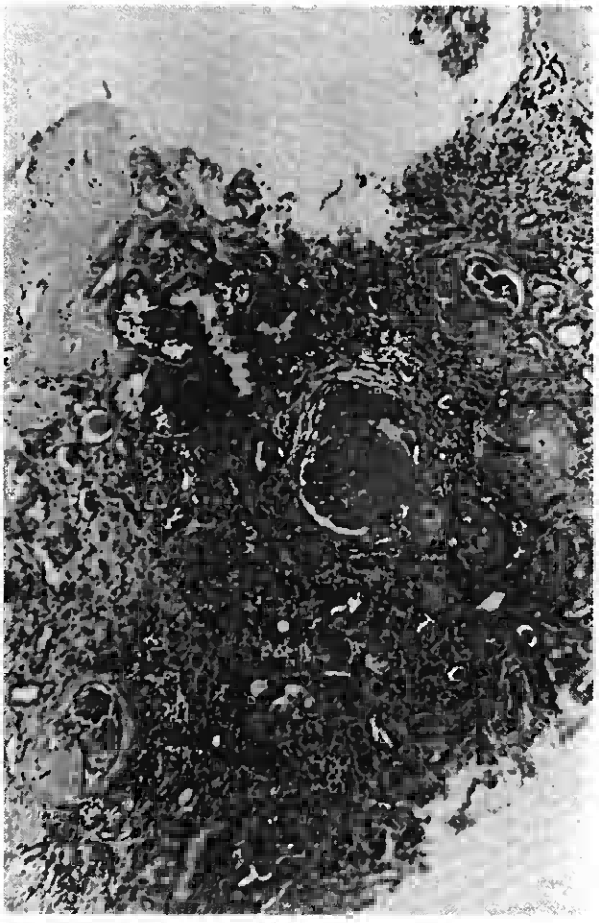

Fig. 1. Renal Biopsy of the 50 year old patient who developed ocular toxicity to Ethambutol showing renal amyloidosis.

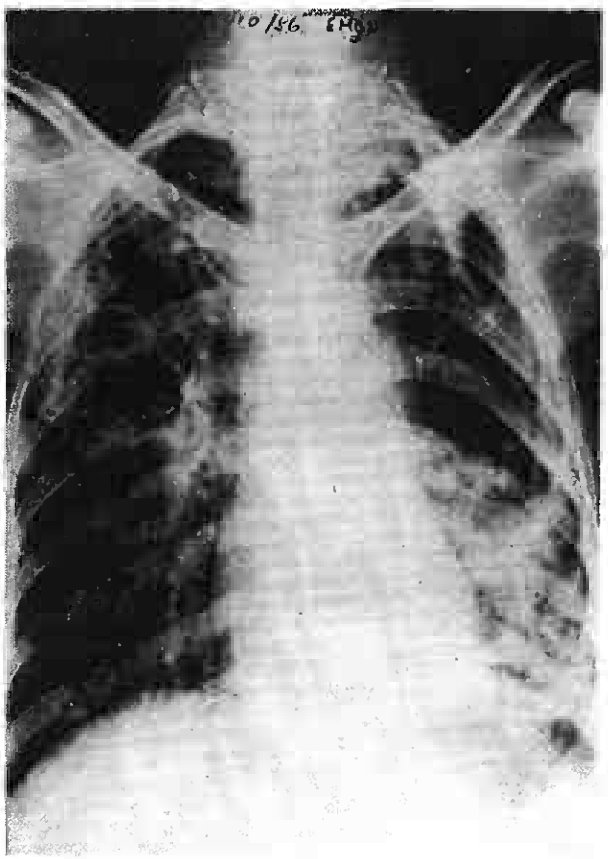

Fig. 2. Before treatment.

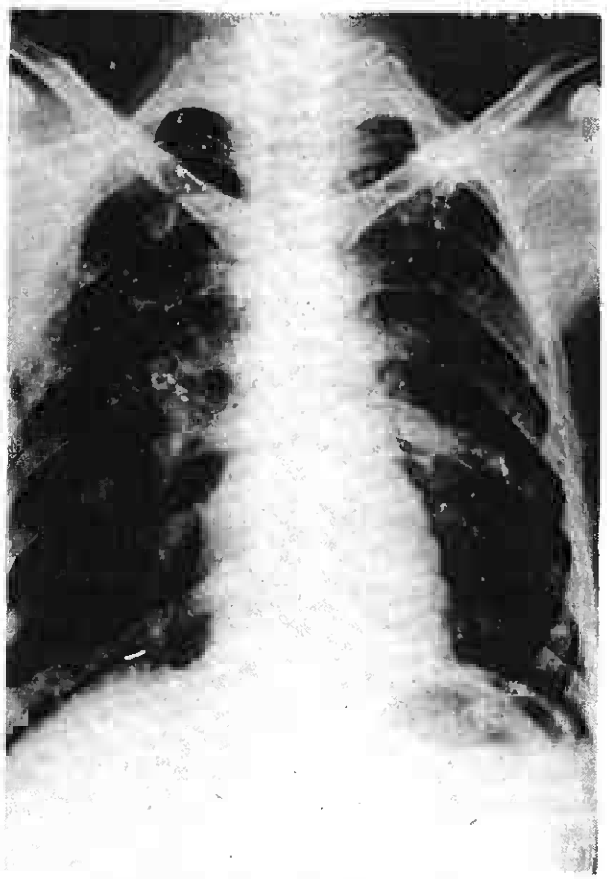

Fig. 3. After 9 months of treatment.

Radiographs of a 33 year old patient showing clearing of lesions after treatment. Sputum converted.

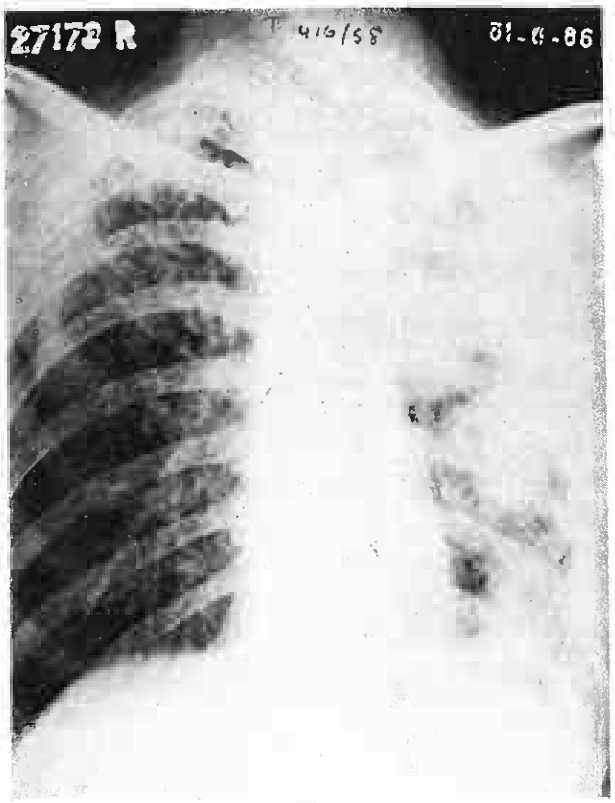

Fig. 4. Before treatment.

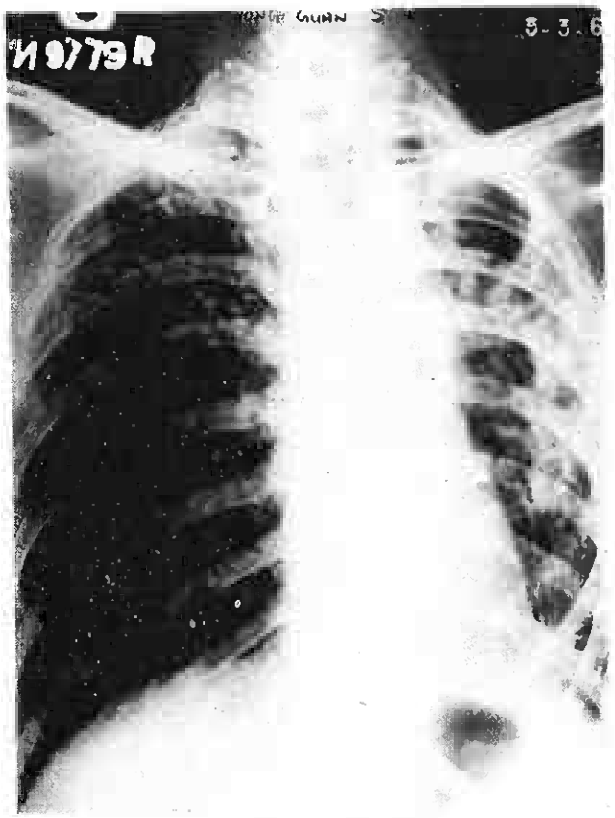

Fig. 5. After 9 months of treatment.

Radiographs of a 42 year old patient showing clearing of lesions after treatment. Sputum converted.

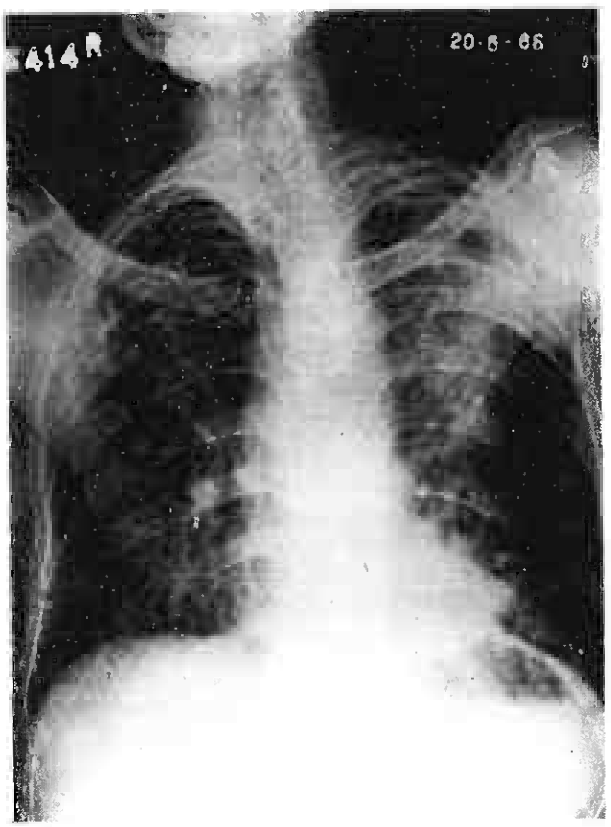

Fig. 6. Before treatment.

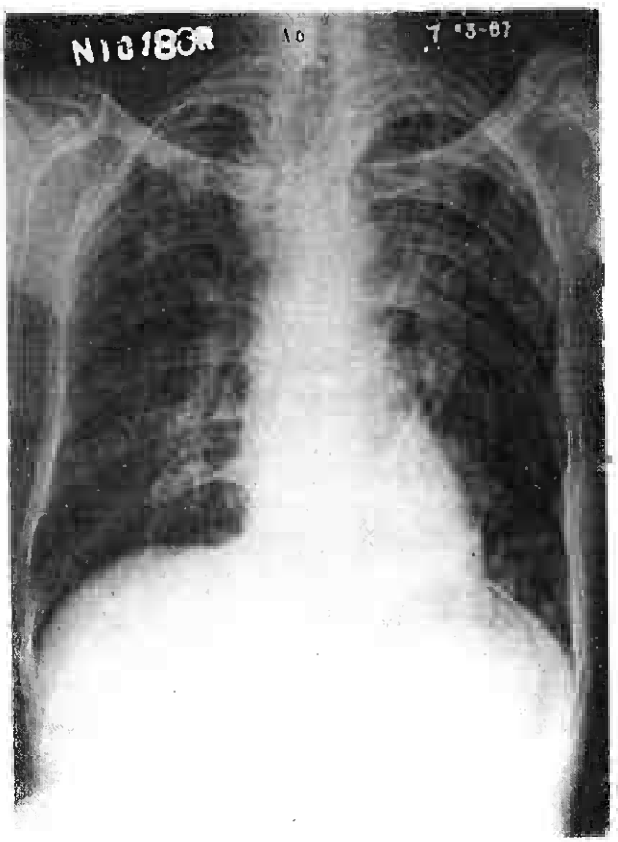

Fig. 7. After 9 months of treatment.

Radiographs of a patient with ankylosing spondylitis and pulmonary tuberculosis showing clearing of lesions. Sputum converted.

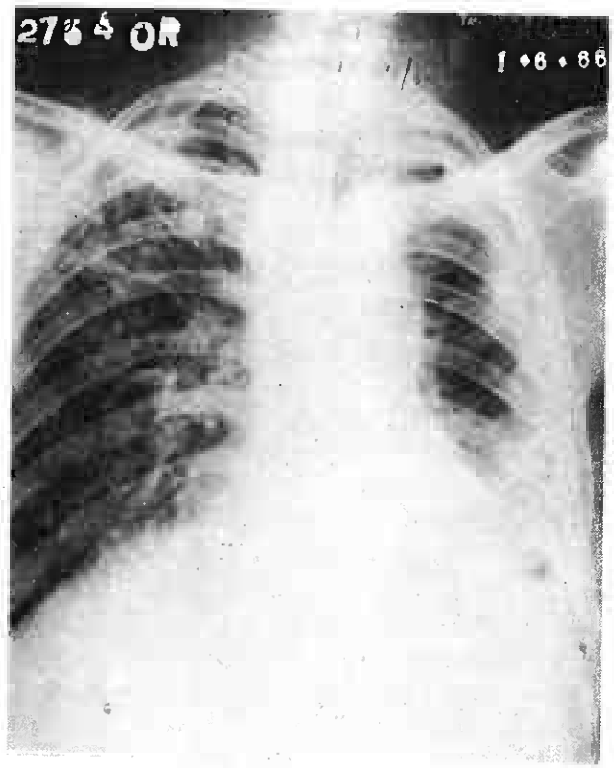

Fig. 8. Before treatment.

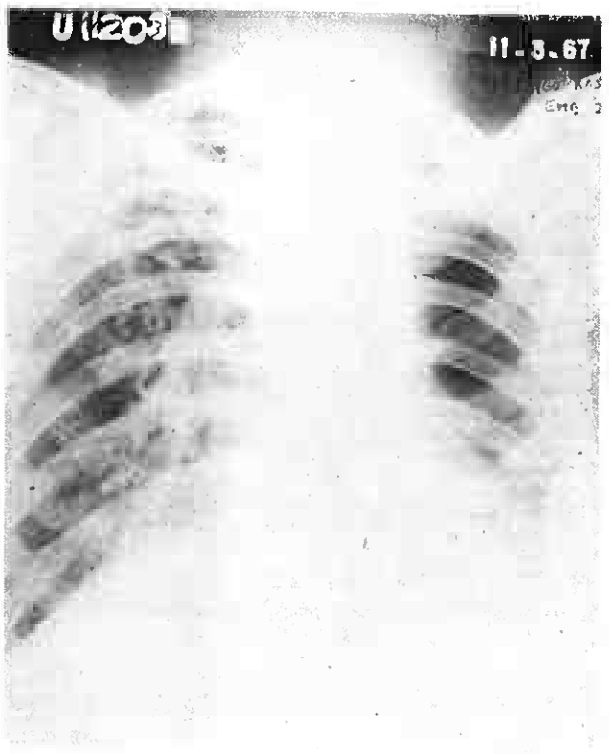

Fig. 9. After 9 months of treatment.

Radiographs of a 32 year old patient showing diminution in cavity size after treatment. Sputum converted.

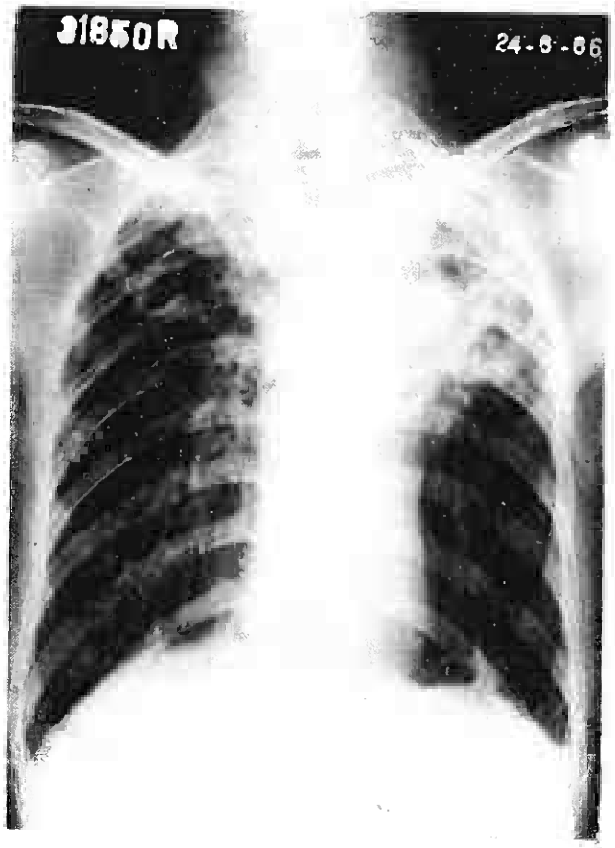

Fig .10. Before treatment.

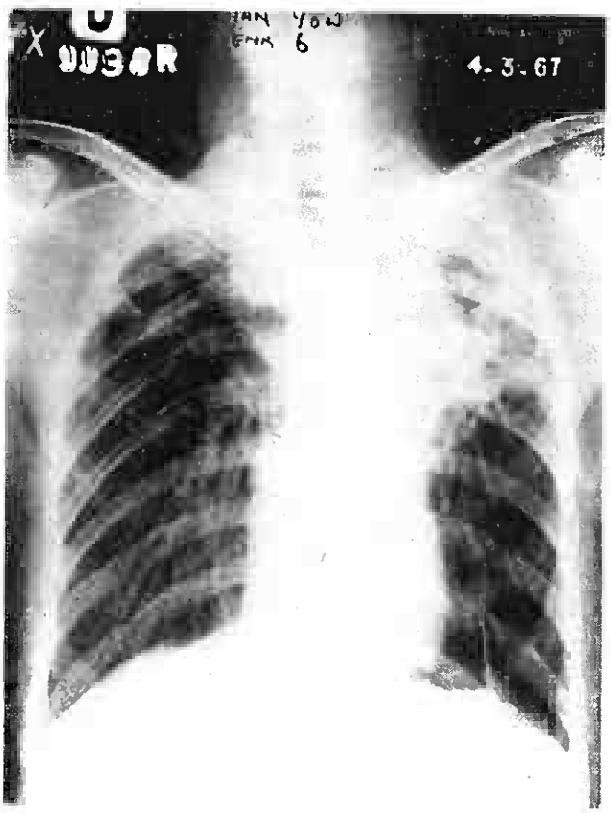

Fig. 11. After 9 months of treatment.

Radiographs of the 50 year old patient with pulmonary tuberculosis, renal amyloidosis and chronic pyelonephritis showing very little clearing of pulmonary lesions. This patient developed ocular toxicity to Ethambutol. Sputum converted.

TABLE VII

Sputum Status after 17 months	Number
Conversion	28 (90%)
Positive	3 (10%)

Three patients were taken off the trial as their sputum remained positive after 12 months of therapy.

RADIOLOGY

Most of the patients in this series had chronic fibroid pulmonary tuberculosis. Despite this there was from slight to marked radiological clearing of the lesions in 20 patients.

TABLE VIII

Radiological Status after 17 months	Number
Improvement	20 (65%)
No change	11 (35%)
Deterioration	0

Most of the patients showed clinical improvement and had put on weight. There were no deaths.

SUMMARY

Ethambutol in conjunction with one other oral secondary drug was used in the retreatment of pulmonary tuberculosis in 34 patients. 3 patients dropped out of the study because of the various reasons mentioned earlier. After 17 months of treatment sputum conversion and radiological clearing of the lesions was obtained in 20 (65%) patients. Sputum conversion alone was obtained in 28 (90%) patients. There was no clinical deterioration in any of the patients. Two patients developed toxic symptoms to Ethambutol. This improved on stopping the drug.

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