The CENTRAL AFRICAN JOURNAL OF MEDICINE

Vol. 1. No. 5 SEPTEMBER, 1955

CONTENTS

PUBLISHED BI-MONTHLY, ANNUAL SUBSCRIPTION £2 2s. 0d.

The Effect of Chemotherapy on Pulmonary Tuberculosis in the Central African

WHEN GIVEN FOR A PERIOD OF A YEAR OR LONGER.

BY

A. I. L. TURNBULL,

M.A. (Camb.), M.B., CH.B. (Edin.),

Medical Superintendent, Martin Sanatorium, Chinamora, S. Rhodesia.

The Editor of the *British Medical Journal* commented on the Seventh Report by the Tuberculosis Chemotherapy Trials Committee to the Medical Research Council as follows:[1] "It is unfortunate that clinical information is not available for periods of treatment longer than three months, since it is precisely in the period between three and six months that differences between different treatments may reveal themselves."

This statement has encouraged me to publish this paper, as the cases described received chemotherapy for a year or longer, and have been treated and followed up for at least 18 months and some for three years, the majority falling between the two extremes. The course of treatment (S.P.H.C.) adopted consisted of daily doses of streptomycin of 1 gramme, 12 grammes of paraminosalicylic acid (P.A.S.) and 300 mg. of isoniazid (I.N.H.) tablets for periods of five weeks excluding Sundays, with 28 days' rest from chemotherapy in between the courses. This regime gave by far the best results.

It was found that two other courses (S2.P.H. and S.P.C.) were unsatisfactory. For instance, streptomycin 1 gram. twice a week together with 12 gram. of P.A.S., and 200 mg. of isoniazid daily, for periods varying from four to six months, with no rests in between (S2.P.H.) produced the worst results, the failure to respond to treatment being six times as bad as with (S.P.H.C.). It was also found, despite what had been stated to the contrary in the seventh M.R.C. trials report,[2] that when patients had received daily streptomycin of 1 gram. and P.A.S. 12 gram. for three months or more before receiving the bi-weekly streptomycin (S2.P.H.) course, the results were equally bad.

The results with (S2.P.H.) were worse than those obtained before the advent of I.N.H., when the patients received streptomycin 1 gram. daily together with 12 gram. P.A.S. at monthly intervals (S.P.C.).

The African tubercular subject is usually so far advanced that it is impossible to arrest the disease in three months. This is because either the advance of the disease is so rapid or that they are unaware of the presence of the disease. We rarely see a case with a minimal lesion.

When the poor results with these two treatments (S2.P.H. and S.P.C.) were observed, it was decided to give S.P.H.C. in order that drug resistance may be avoided, since it had then been recognised that by combining streptomycin and P.A.S. resistance was delayed (M.R.C. trials[3]).

In my experience the problem of the treatment of pulmonary tuberculosis is a matter of degree. The worse the case, the longer the treatment required and the greater the danger of drug resistance. Furthermore, it was thought that the giving of three synergistic drugs together would delay resistance even longer. From the clinical results obtained over one year, this would appear to be the case.

METHODS AND PROCEDURE FOR CASES TREATED BY S.P.H.C.

It is difficult to keep Africans in bed without constantly watching them: most of them take a fair amount of exercise before they are officially described as convalescents. It is equally difficult to regulate the amount of exercise they take when they are convalescent. If at the end of a further three months their condition is the same, they are discharged, it being considered then fairly safe to assume that the disease is arrested. After discharge they are requested to report every three months. The majority of the patients complied with this request, although some waited for four or even five months before reporting. On the whole I have been able to keep a fairly good check on their progress.

A patient is allowed to be ambulant when his sputum has been negative for four consecutive months, the B.S.R. is within normal limits, and no signs of activity are detected physically or radiologically.

The patients were not specially selected. They were the first 50 patients to be admitted to the sanatorium from October, 1952, onwards, when

this treatment was introduced. Very old and very young subjects are not included.

CONDITION ON ADMISSION

Of the 50 subjects, 34 were males; the average age was 28.5 years, the youngest being 11 years and the oldest 45 years. Twenty-two had bilateral disease with cavitation, nine were unilateral with cavitation, and 19 without cavitation (13 being bilateral and 6 unilateral).

Forty (80 per cent.) were febrile. Forty-eight had positive sputa and there was no doubt, radiologically and clinically, that the remaining two cases had pulmonary tuberculosis.

The blood sedimentation rates (Westergren mm. in first hour) in the 50 subjects studied were:—

B.S.R.	*Number of Patients.*
10 mm. or less	1
11—20 mm.	3
21—50 mm.	21
51 mm. and over	25

RESULTS

The progress or otherwise of the cases during a 12 months period is given with regard to temperature, weight gain, radiological changes, sputum conversion and B.S.R. changes.

TEMPERATURE

A patient was considered afebrile if the temperature was below 99° F. every day for the last week of each three months of treatment. It was decided not to include a temporary rise in temperature of under three days' duration, which was obviously due to some intercurrent infection, such as malaria or tonsillitis. Forty (80 per cent.) were febrile for the first week or more after admission. At the end of three months six (15 per cent.) were febrile: 34 (75 per cent.) were afebrile, or 44 (80 per cent.) of the whole group of 50 were afebrile. At the end of six months none was febrile, four being afebrile at the end of four months and one at the end of five months. None was febrile at the end of 9 to 12 months.

WEIGHT GAINS

The results are given on Table I. It will be seen that only 48 out of the 50 patients are shown in the first three months, as two were too ill to be weighed for some time after admission. The average gain was 13.4 lbs., and is similar to those of the streptomycin and I.N.H. trials of the Medical Research Council [3] for three months' continuous treatment.

The difference in weight between the end of three months and the end of six months is given in the second line. The gain in weight was maintained in 44 patients. Three were stationary and the same number lost weight, but no patient lost more than 2 lbs. The average gain in weight was 7.6 lbs. Eight of the patients were convalescent before the end of six months.

At the end of nine months there were only 47 results available, as three of the patients had been discharged. The average gain in weight was slight, being 3 lbs., 37 having gained weight. Two were unchanged and eight had lost weight. None had lost more than 4 lbs., and the average loss of the eight patients was 2.3 lbs. But 20 of the 47 were convalescent and had no signs of activity, either clinically or radiologically.

At the end of twelve months only 36 results were available, more patients having been discharged. Twenty (55 per cent.) gained weight. There was no change in six, while ten lost weight. The greatest loss was 5 lbs., and the average loss of the 10 who lost weight was 2.3 lbs. The average gain in weight was small, being only 2 lbs.

Table I.—Weight Changes at the End of Each Period of Three Months.

At the end of	Total Weighed. No.	Improvement 21 lbs. or more. Per cent.	Improvement 14-20 lbs. Per cent.	Improvement 7-13 lbs. Per cent.	Less than 7 lbs. Per cent.	No change. Per cent.	Deterioration. Less than 7 lbs. Per cent.	Average Gain in weight per patient. in lbs. (b)
3 months	48 (a)	17	35	19	29	Nil	Nil	13.4 lbs.
6 months	50	10	6	32	40	6	6	7.6 lbs.
9 months	47	Nil	Nil	17	62	4	17	3 lbs.
12 months	36	Nil	3	8	44	17	28	2 lbs.

(a) Two were too ill to be weighed on admission.
(b) The average gain in weight includes No Change and Losses in Weight.

It should be noted that the average gains mentioned above, and in the last column of Table I, is the average of all patients, including the losses. Twenty out of the 36 patients whose weights were available at the end of 12 months were convalescent. The average gain at the end of the first six months was 21 lbs., so a further gain of 5 lbs. in the last six months may be regarded as satisfactory.

CHANGES IN RADIOGRAPHICAL APPEARANCES AT THE END OF EACH PERIOD OF THREE MONTHS

Table II shows the above. One plus indicates slight improvement, 2 plus moderate improvement, and 3 plus great improvement.

Deterioration is indicated in the same manner. The degree of improvement is given in each three months compared with the X-ray at the end of the previous three months. Examples to illustrate this classification will be shown.

The last column of this table gives the number and percentage of X-rays of the original 50 which were clear at the end of each three months. This figure was 26 (52 per cent.) at the end of 12 months. Many of the remaining 24 (48 per cent.) showed no signs of activity. But as it is very hard to give a definite opinion from X-rays alone whether or not activity exists, no figures of non-activity are given.

Forty-six out of 50 (92 per cent.) improved in the first three months; 41 improved in the second three months; 32 out of 45 (71 per cent.) improved in the third three months; and 17 out of 34 improved during the last three months. The other 17 showed no change, but 10 of these were already clear at the end of nine months.

The degree of improvement decreased rapidly at the end of each three months, but it must be remembered that more and more X-ray films were becoming clear, and there was far less opportunity for the bigger degrees of improvement. There was no deterioration during the last six months. In other words, radiological improvement was maintained during the whole 12 months, and although only 17 out of 34 showed improvement at the end of the last three months, 10 of the 17 which showed no improvement were already clear, so that 27 out of 34 (79 per cent.) either showed improvement or were clear.

BLOOD SEDIMENTATION RATES

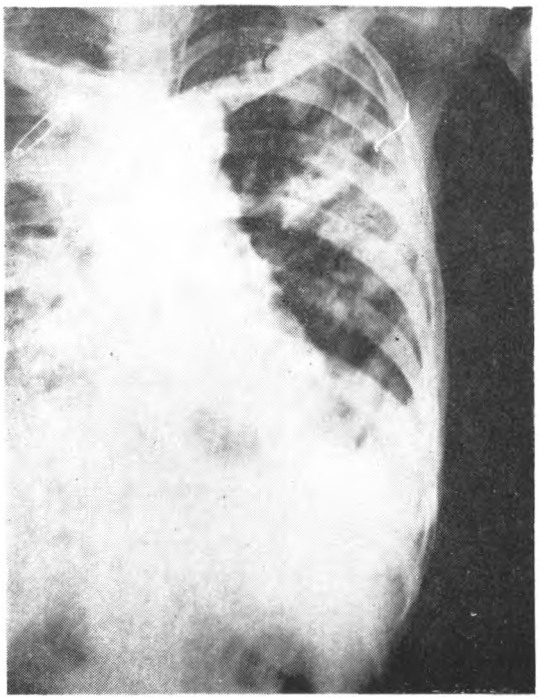
Table III gives the blood sedimentation rate at the beginning of each three months, and the percentage of cases in each group whose B.S.R. was below 10 at the end of each three months. One case had an initial B.S.R. below 10 on admission. It will be seen that 16 out of 46 cases (35 per cent.), whose initial B.S.R. was 21 or more, were 0-10 at the end of three months. This does not compare very favourably with the 45 per cent. obtained with streptomycin and I.N.H. in the Medical Research Council Trials,[3] but it must be remembered that 50 per cent. of our cases had an initial B.S.R. of 51 or more, compared with the 27 per cent. of the Medical Research Council Trials.

The reduction of the B.S.R. from over 10 or more to less than 10 continued steadily during each three months, although the results at the end of the ninth month were not quite as good as at the end of the third, sixth and twelfth months. The improvement can be perhaps appreciated better by studying the last column in Table III, which gives the total number with a B.S.R. of over 10 or above normal at the end of each three months. The results were 30 at the end of three months, 15 at the end of six months, 10 at the end of nine months, and only 6 at the end of 12 months. The remaining 44 had either a B.S.R. below 10 or had been discharged, the disease being arrested.

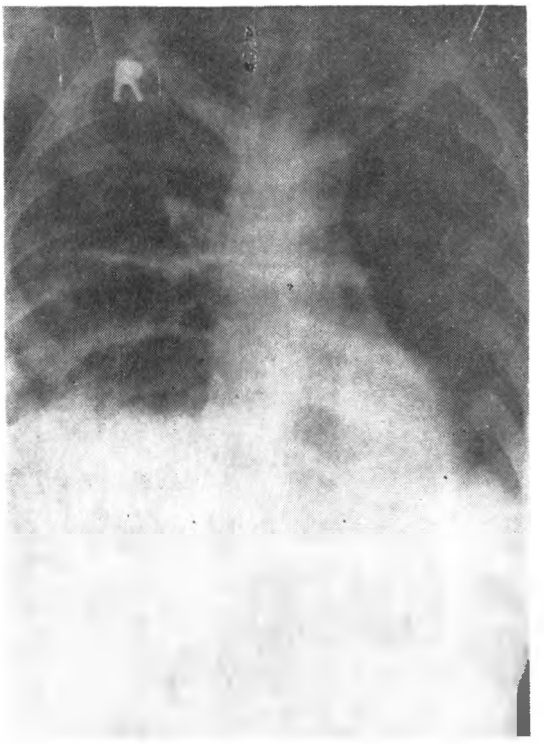
Table II.—Changes in Relative Radiographic Appearance at the End of Each Period of Three Months.

At the end of	Total X-rayed. No.	Improvement. 3 Plus. Per cent.	2 Plus. Per cent.	1 Plus. Per cent.	No Change. Per cent.	Deterioration. 1 Minus. Per cent.	2 Minus. Per cent.	3 Minus. Per cent.	Total Clear. Per cent.
3 months	50	34	50	8	4	Nil	4	Nil	Nil
6 months	50	6	22	54 (a)	12	6	Nil	Nil	14
9 months	45	Nil	11	60 (b)	29 (c)	Nil	Nil	Nil	40
12 months	34	Nil	Nil	50 (d)	50 (e)	Nil	Nil	Nil	52

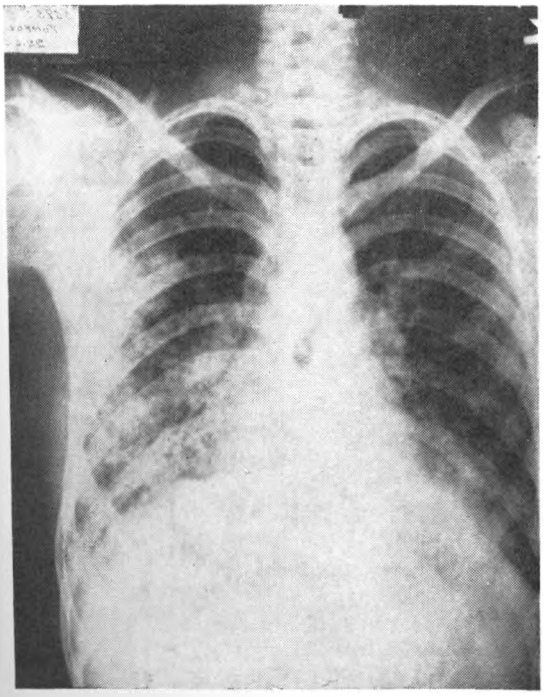
(a) 26 per cent. of this number were clear; (b) 48 per cent. of this number were clear; (c) 31 per cent. of this number were clear at the end of six months; (d) 35 per cent. of this number were clear; (e) 59 per cent. of this number were clear at the end of nine months.



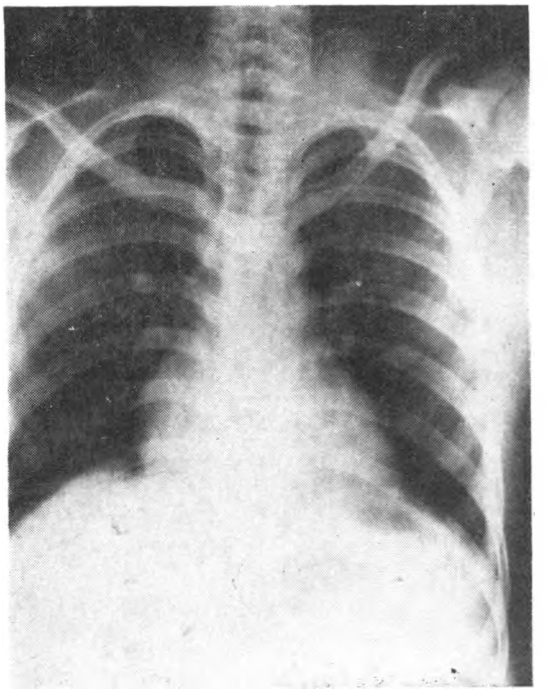
Ester's first X-ray. Extensive infiltration both lungs, especially the right.



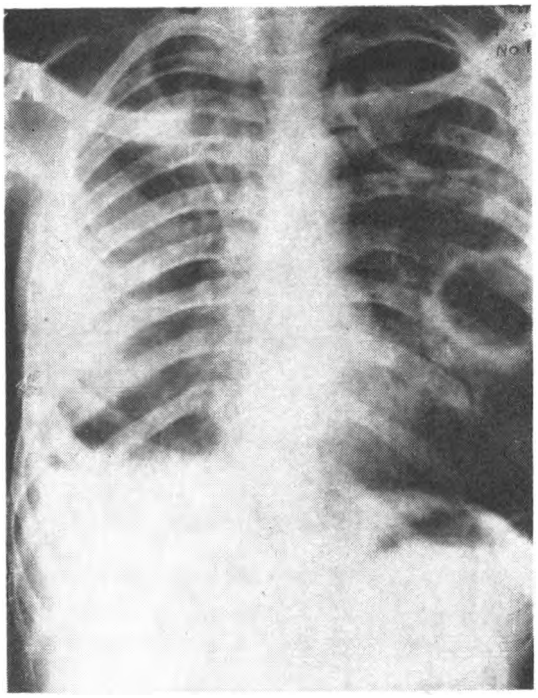
Ester's second X-ray four months later. Improvement + 3 (Treatment SPHC).



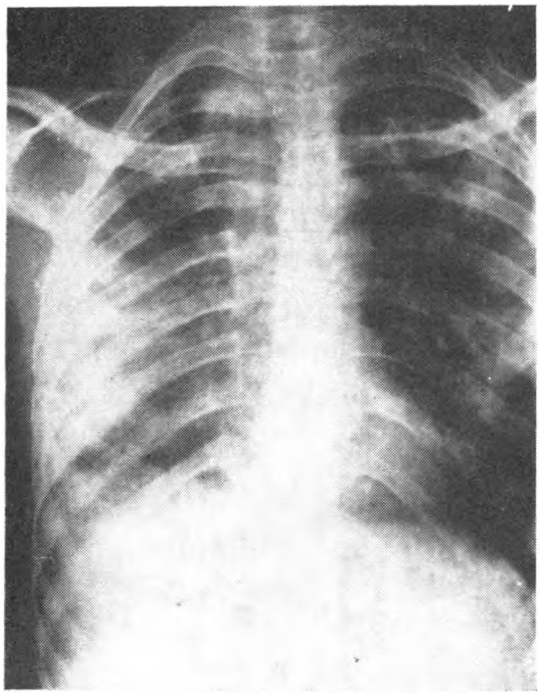
Tunyoxide's first X-ray on admission. Infiltrative disease is present, mostly in the right lung and left base.



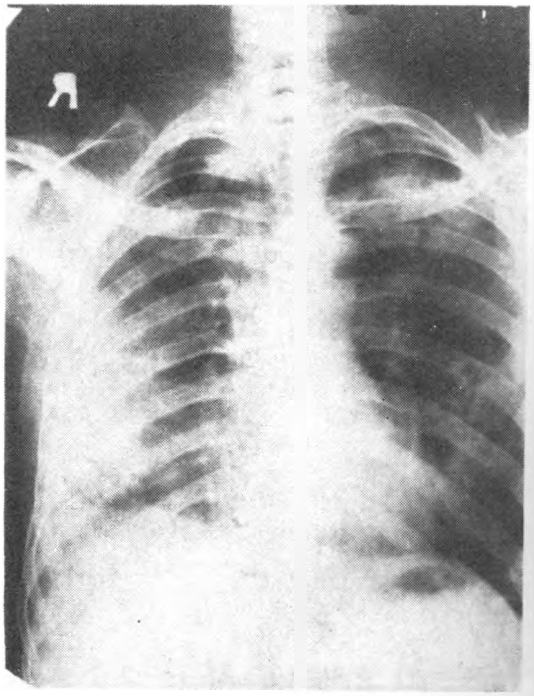
Tunyoxide's second X-ray after three months in hospital. Improvement + 2 (Treatment SPHC).



Takariwa's first X-ray on admission. Note the two large cavities in the left lung.



Takariwa's second X-ray after three months in hospital. Improvement + 3.



Takariwa's third X-ray after six months (Treatment SPHC).

Table III.—Cases with a Raised B.S.R. at the Commencement of each Course of Three Months, Giving the Percentage Whose B.S.R. was Below 10 at the End of Each Three Months.

Each period of 3 months.	11—20. Total No. at commencement of each three months.	11—20. Percentage normal at end of each three months.	21—50. Total No. at commencement of each three months.	21—50. Percentage normal at end of each three months.	51 or More. Total No. at commencement of each three months.	51 or More. Per centage normal at end of each three months.	All Cases with an Initial B.S.R. of 21 or More. Total No. at commencement of each three months.	All Cases with an Initial B.S.R. of 21 or More. Per centage normal at end of each three months.	Total No. remaining with B.S.R. Over 10.
3 months	3	100	21	48	25	24	46	35	30
6 months	15	73	9	44	6	17	15	33	15 (a)
9 months	8	63	5	40	2	Nil	7	29	10
12 months	7	43	3	33	Nil	Nil	3	33	6

(a) One case whose B.S.R. was less than 10 at the end of three months had relapsed.
(b) Two cases whose B.S.R. was less than 10 at the end of six months had relapsed.

SPUTUM CONVERSION

The results described are those of direct examination only, as we have no facilities for culturing the organism. They are single examinations made at monthly intervals.

Two of the 50 were negative on admission, although clinically and radiologically they definitely had quite extensive pulmonary tuberculosis, one having miliary tuberculosis. They both responded to treatment and the disease was arrested. They are not included in the Table IV or in this discussion on sputum conversion.

The total positive at the end of three months was 33 (69 per cent.), but 39 (81 per cent.) were positive and nine (19 per cent.) were scanty positive on admission. At the end of nine months it was reduced to seven (16 per cent.), and at the end of twelve months only five (10 per cent.) were positive.

The last column of Table IV probably gives a clearer picture of the success in converting positive sputa to negative. In this column the total number of patients who were negative is given, and at the end of nine months this includes three that were discharged. And at the end of a year 15 were discharged. But before being discharged as being arrested, these cases had had negative sputa for seven consecutive months, and so it was fairly safe to assume that they were still negative.

Forty-three of the 48 patients (90 per cent.) had negative sputa at the end of a year. Since then another patient has been discharged with the disease arrested, thus bringing the total of cured patients to 92 per cent. Five (10 per cent.) had positive sputa; of these, one became negative four months later, and has since had negative sputa for seven months and been discharged.

Forty-six (92 per cent.) of the cases described have now been discharged, the disease having been arrested. One died. Three (6 per cent.) still have positive sputa. The shortest

Table IV.—Sputum Conversion at the End of Each Period of Three Months.

At the end of	Total patients examined.	Percentage positive.	Percentage scanty but positive.	Percentage of total positive including scanty.	Total per cent. negative or discharged after seven negative sputa.
3 months	48	17	52	69	31
6 months	48	4	23	27	73
9 months	45	2	13	16	85
12 months	33	3	12	15	90

time for a patient to become convalescent was five months, and the longest 16 months, the average being 8.5 months. The shortest time for a patient to be discharged, the disease having become arrested, was seven months, and the longest 24 months. The average time was 12.6 months.

SUMMARY

Fifty cases of pulmonary tuberculosis, treated with daily amounts of streptomycin, P.A.S. and I.N.H. given together, for courses of five weeks, excluding Sundays, with 28 days' rest between courses (S.P.H.C.), have been described. Treatment continued for periods varying from one to two years.

Forty-six (92 per cent.) subjects have been discharged, and the disease appears to be arrested. Three (6 per cent.) continued to have positive sputa and one (2 per cent.) has died. The response to treatment at the end of every three months for a year is given.

From the weight gained, the radiological improvement, the effect on the blood sedimentation rate and sputum conversion, it would appear that S.P.H.C. continues to act upon the disease for at least a year.

The danger to Africans of giving bi-weekly streptomycin together with daily P.A.S. and I.N.H. continuously for periods varying from three to six months (S2.P.H.) is stressed. Even when, as in 27 of the 47 cases, they had previously received daily streptomycin and P.A.S. (S.P.C.) in the same manner as (S.P.H.C.) for periods varying from three to six months before receiving bi-weekly streptomycin (S2.P.H.), 50 per cent. still had positive sputa or had died. These patients later had the same course of (S.P.H.C.). So the difference in results cannot be put down to any difference in institutional treatment.

Acknowledgment

My thanks are due to Dr. R. M. Morris, O.B.E., Secretary of the Ministry of Health of the Federation of Rhodesia and Nyasaland, for permission to publish this paper. My thanks are due to Sister Mary Joseph, O.P., and the other Dominican Sisters who took the X-rays, and to Mr. Gumbo Kanongoni who performed the blood sedimentation rate estimations and examined the sputa.

REFERENCES

1. Editorial. *Brit. Med. J.*, 19 Feb., 1955.
2. Seventh Report to the Medical Research Council by Tuberculosis Chemotherapy Committee. Quoted *Brit. Med. J.* (1955). Feb., 435.
3. Second Report to the Medical Research Council by Tuberculosis Chemotherapy Trials Committee. Quoted *Brit. Med. J.* (1953). March, 521.