

Factors affecting the Outcome of Treatment of Pulmonary Tuberculosis in Sub-Optimal Conditions:

An 18-month follow-up of 224 Patients

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SUMMARY

Two hundred and twenty-four unselected patients having pulmonary tuberculosis with positive sputum who started treatment at Chinambora hospital were followed up for 18 months.

The rate of "primary" isoniazid resistance was 8 per cent.

One hundred and thirty-two consecutive patients had the normal in-patient drug regimen; 26 of these were not seen at the end of the 18-month period. Of the other 106, one remained sputum-positive throughout the 18 months, 14 were known to have died and one had relapsed, making a total of 16 (15 per cent.) patients with an "unsatisfactory" outcome.

Among the whole group of 224 patients the factors significantly associated with an unsatisfactory result were age over 50, male sex, absconding from hospital, and default from treatment of four months or more. Previous treatment was relatively unimportant, as was initial isoniazid resistance. The death of 10 patients in the first month showed that late coming to hospital was a further cause of failures in treatment.

The results indicate that the chief needs are to improve the understanding of the patient and of the public of what the treatment of tuberculosis involves, to increase the patient's confidence in the staff and to reduce the period of in-patient treatment being given at that time.

BACKGROUND TO THE STUDY

Trials have shown that cheap modern drugs used under ideal conditions can produce a high proportion of successes in the treatment of pulmonary tuberculosis (East African/British Medical Research Councils, 1963; Tuberculosis Chemotherapy Centre, Madras, 1966). These

studies, however, are usually done on selected patients, and there is reason also to think that the results obtained in routine practice are much inferior to those of such studies, which usually have special treatment and follow-up arrangements. Kent (1968) was confident that the treatment success-rates achieved in Kenya and in other areas with sub-optimal services were less than 50 per cent with regimens which under trial conditions achieved 80 per cent. An editorial in *Tubercle* (1968) emphasises the basic difference between studies undertaken to evaluate drug regimens and those done to discover the results of routine treatment in practice, of which latter there is an unfortunate dearth. *Tubercle* also lists follow-up studies made in various places. In "developed" areas the numbers lost to follow-up varied from 5 per cent. to 28 per cent. and the minimum success rate from 80 per cent. to 85 per cent.; in India 57 per cent. to 63 per cent. were lost, and the minimum success rate was 21 per cent. to 27 per cent.

The investigation reported here was undertaken in 1964 to find out what degree of success is achieved under field conditions in the particular circumstances of Rhodesia and, in addition, to pinpoint as far as possible the factors that lead to failure.

MATERIAL

Two hundred and forty consecutive sputum-positive patients started a course of treatment for tuberculosis at Cinambora hospital between September, 1964, and July, 1966, inclusive. Sixteen patients lived in regions other than Mashonaland and were excluded at the start as they could not have been followed up as out-patients. This study is of the remaining 224.

Of these 224 patients, the first 92 were admitted during the period of a drug trial (Briggs *et al.*, 1968) in which 60 patients who gave no history of previous treatment and whose general condition was reasonably good were given, while in hospital, the following two-drug regimens: isoniazid 300 mg. daily with thiacetazone 150 mg. daily (17 patients); streptomycin 1 gm. daily with PAS 15 gm. daily (18 patients); and streptomycin 1 gm. daily with thiacetazone 150 mg. daily (21 patients). The other four patients in the trial had addresses outside Mashonaland. The 132 patients treated subsequent to the trial period had the normal hospital treatment described below.

The Mashonaland region, within whose tuberculosis programme these patients were managed, contains about one-third of the 4,000,000 population of Rhodesia. One other unit of the same size as Cinambora, and a number of smaller district units, treat tuberculosis patients in the

region. Cinambora, however, serves as the regional tuberculosis hospital; it is out in the country and its own direct catchment area is extremely small. Patients who leave it go to all parts of the region for out-patient treatment. As regards the quality of the intake, patients are referred routinely upon diagnosis from the various district centres and are not selected. Those already under treatment for some weeks or months who were referred to Cinambora as requiring special attention were not included in the series. The other units refer patients to the regional out-patient service in the same way as does Cinambora.

The patients were kept in hospital initially for about six months if progress was satisfactory. The normal treatment used at the hospital during this time was with streptomycin (1 gm. daily), isoniazid (300 mg. daily) and PAS (15 gm. daily). Each patient, while in hospital, had three sputum examinations each month and each had three-monthly radiological examinations. Any patient who, after a period of treatment, was considered on the evidence of persistently positive sputum smears and/or the results of sensitivity tests to have organisms resistant to the standard drugs was given a regimen consisting of three reserve drugs. Patients receiving these were kept in hospital throughout their treatment.

All those discharged to out-patient treatment had become sputum-negative, as demonstrated by at least two negative smear results. After

discharge, patients were treated at centres throughout Mashonaland, where tablets of isoniazid/thiacetazone (300 mg./150 mg.) were issued monthly.

Subsequent assessment of progress depended on three-monthly attendances at tuberculosis clinics held, usually at district hospitals, by the regional tuberculosis officer, or in a few instances by the local district medical officer. At these clinics a chest radiograph was taken; sputum examination was not done unless the patient had symptoms suggesting a relapse or there was radiological evidence of deterioration. All the patient's previous records and films were available at the reviews.

The routine described was adhered to in nearly every case, though there will have been occasional patients for whom variations were made.

DATA OBTAINED

(1) Initial

The initial information available on each patient included his sex, age as estimated by the qualified nursing staff, whether he had been treated previously (i.e., a relapsed patient or not) and sensitivity of his bacilli to isoniazid. The last investigation was done as time went on in three different laboratories, as shown in Table I.

The methods used for testing sensitivity to isoniazid were as follows:

Table I
INITIAL CULTURE AND SENSITIVITY RESULTS BY LABORATORIES

Laboratory:	W.H.O., Nairobi	Mpilo, Bulawayo	Brompton, London	All Laboratories
A. Culture—				
Contaminated	2	2	—	4
No result for non-technical reasons	8	—	—	8
Atypical bacillus	—	—	1	1
Negative	5	7	3	15
Positive	70	69	49	188
TOTAL	85	78	53	216
(Not sent for culture)				8
				224
B. Sensitivity to Isoniazid—				
No result	19	11	4	34
Sensitive	55	58	47	160
Resistant	11	9	2*	22
TOTAL	85	78	53	216
(Not sent for culture)				8
				224

* Patients whose specimens were sent to the Brompton laboratory had all denied having had previous treatment. This is the reason for the low incidence of isoniazid resistance among them.

WHO Laboratory, Nairobi: serial dilutions in Lowenstein-Jensen medium without potato starch, as described in connection with a study of drug resistance in Malawi (Shennan, 1964). Resistance was defined as growth on 1 ug./ml. or a higher concentration.

Mpilo Hospital Laboratory, Bulawayo: the same method as used in Nairobi.

Brompton Hospital Laboratory, London: serial dilutions in Lowenstein-Jensen medium as described by Briggs *et al.* (1968). Resistance was defined as growth on 0.2 ug./ml. or a higher concentration.

Table I shows that the proportions of successful cultures and of cultures showing isoniazid-resistance were comparable between the three laboratories.

(2) During Treatment

Information obtained during the period of 18 months was as follows:

- (a) The month in which sputum conversion to negative took place.
- (b) Whether the patient absconded from hospital at any time.
- (c) The time when he became an out-patient.
- (d) The number of months' default from in- and out-patient treatment and the mean stage at which this default took place.

(3) At 18 Months

The patients were divided into those whose outcome was "satisfactory" and those in whom it was "unsatisfactory." A "satisfactory" result meant that the patient was well and showed no sign of relapse when seen at 18 months (or in a few cases at 16 or 17 months, as that was the time of the last review within the 18-month period).

For the purpose of the correlations, nine patients who were not seen at 18 months, but who were making good progress and sputum-negative when last seen before 18 months and were "satisfactory," as defined, when reviewed after the 18-month point, were presumed to be "satisfactory" at 18 months. One patient who had been sputum-negative when last seen, and who did not attend a clinic at or after the 16-month stage, but was reported by another person to be alive and well at 20 months, was included in the "satisfactory" group.

An "unsatisfactory" result meant that either (a) the patient was known to have died (in the event, 29 of the 37 patients classed as "unsatisfactory" were in this group); or (b) the patient was known to have relapsed with positive sputum, but had not died (seven patients); or (c) as in the case of one patient, he was sputum-positive when seen both on the last occasion before the 18-month point and subsequent to 18 months, although he was not reviewed at the 18-month stage.

Special efforts were made to trace as many of the patients as possible after the 18-month period. However, they did not receive any specially intense treatment or supervision, so that their degree of success in treatment is representative of that for all Mashonaland patients admitted to Chinamora hospital.

RESULTS

(1) Initial Data

There were 148 males in the series, with a mean age of 39 years, and 76 females having a mean age of 32 years.

Twenty-eight (12 per cent.) of the 224 patients gave a history of treatment previously and had relapsed, while the other 196 were not known to have been treated before.

Two hundred and sixteen patients had sputum sent for culture and sensitivity to isoniazid (Table I). Of these, 34 failed to produce a sensitivity result; 22 of the remainder showed isoniazid resistance and the other 160 sensitivity, an overall resistance rate of 12 per cent. As shown in Table II, the rate of primary (*sic*) resistance to isoniazid was 8 per cent. This compares with 5 per cent. in Salisbury city itself as reported by Briggs in 1963 and with 8 per cent. for neighbouring Malawi in 1962 (Shennan, 1964). As 43 per cent. of previously treated patients showed isoniazid resistance, there was a high degree of correlation between the two factors.

(2) Data Obtained During Treatment

Stage of Sputum Conversion

In Table III will be seen the stage at which sputum conversion to negative took place in the

Table II
PREVIOUS TREATMENT AND ISONIAZID RESISTANCE

Sensitivity to isoniazid:	Not Sent or No Result	Sensitive	Resistant	All Tested	Percentage Resistant
Not previously treated	37	147	12	196	12/159 = 8%
Previously treated	5	13	10	28	10/23 = 43%
TOTAL	42	160	22	224	

224 patients. The commonest time was during the second month.

Abscending from Hospital

Twenty-nine in-patients absconded from hospital at some time. Table IV shows the numbers leaving in each month. Only nine absconded in the first two months, six of these in the first month.

Only three females out of 76 (4 per cent.) absconded compared with 26 males out of 148 (18 per cent.) ($P < 0.01$).

Table III

STAGE OF SPUTUM CONVERSION		
Converted in first month	31
" " second "	64
" " third "	40
" " fourth "	28
" " fifth "	10
" " sixth "	10
" " seventh "	3
" " eighth month or later	9
Converted, but stage not known	2
Not converted	27
		<u>224</u>

Table IV

STAGE OF ABSCONDING FROM HOSPITAL		
Absconded in first month	6
" " second "	3
" " third "	3
" " fourth "	3
" " fifth "	3
" " sixth "	3
" " seventh "	4
" " eighth month or later	4
Did not abscond	195
		<u>224</u>

Table V

PERIODS OF DEFAULT FROM TREATMENT		
Defaulted for one month	11
" " two months	21
" " three "	12
" " four "	14
" " five "	11
" " six "	12
" " seven "	5
" " eight months or more	32
Defaulted, period not known	8
Did not default	98
		<u>224</u>

Default from Out-Patient Treatment

Table V shows the numbers of patients defaulting for various lengths of time. No special period of default appeared to be favoured. The age-sex pattern was not striking, though there was somewhat more default among males and among patients aged 50 years and over. Pre-

viously treated patients showed no greater tendency to default than the others.

Table VI shows the amount of default of out-patients for the group whose sputum converted at one to three months and for the group converting at four to six months. Sixteen per cent of the one to three month converters defaulted for eight months or more, compared with 10 per cent. of the four to six month converters. This difference falls well short of significance at the 5 per cent. level, but these findings are of interest in relation to the outcome, discussed below.

(3) *Eighteen-Month Follow-Up*

(a) *Proportion of Successes at the End of 18 Months*

As has been explained, only the 132 patients who commenced treatment in the latter part of the study period between August, 1965 and July, 1966, received the normal in-patient regimen described above. In these 132 the outcome could be taken as representative of that for the normal turnover of patients at the hospital.

In initial factors they were similar to the total series of 224. Thus there were 82 males with an average age of 37 years and 50 females with an average age of 32 years. Sixteen (12 per cent.) had had treatment previously and relapsed and of 98 for whom isoniazid sensitivity test results were obtained, 15 (15 per cent.) had resistant organisms.

The outcome was as follows:

Total number of patients in the series: 132

Not followed as long as 18 months from the time of starting treatment 26 (20%)

Followed for 18 months: 106.

Satisfactory 90 (85%)

Unsatisfactory 16 (15%)

(b) *Details of "Not Followed," "Satisfactory" and "Unsatisfactory" Patients*

Not followed (26):

Absconded, sputum-positive, not seen again

Absconded, sputum-negative, not seen again

Lost as out-patient before 12 months in series

"Satisfactory" at 12 months, but defaulted before 18 months 10

Satisfactory (90):

Satisfactory when reviewed at 18 months

Last seen between sixteenth and seventeenth month inclusive, "satisfactory" then, and not defaulted during the last three months of the 18-month period 10

Sputum-negative and making normal progress when last seen before 18 months, and "satisfactory" when reviewed subsequent to 18 months 10

Unsatisfactory (16):

Died 1

Relapsed, still alive 1

Sputum-positive when last seen before 18 months, and again when reviewed after 18 months 14

Table VI

STAGE OF SPUTUM CONVERSION AND DEFAULT
in those discharged to out-patient treatment by the seventh month

Default, months:	0	1	2	3	4	5	6	7	Eight or More	Known Not	All Periods
Conversion stage—											
First to third month	41	6	11	9	8	4	4	2	16	4	105
Fourth to sixth month	14	1	2	2	1	4	2	—	3	1	30
All stages	55	7	13	11	9	8	6	2	19	5	135
(Not discharged to out-patient treatment by the seventh month)											89
											224

Table VII

AGE AND OUTCOME

Outcome:	Not Followed	Satisfactory	Unsatisfactory	All	Percentage Unsatisfactory
Age:					
0-19	7	25	—	32	0/25 = 0%
20-49	29	97	23	149	23/120 = 19%
50-69	6	23	14	43	14/37 = 38%
All ages	42	145	37	224	37/183 = 20%

Table VIII

SEX AND OUTCOME

Outcome:	Not Followed	Satisfactory	Unsatisfactory	All	Percentage Unsatisfactory
Males	32	86	30	148	30/116 = 26%
Females	10	59	7	76	7/66 = 11%
Both sexes	42	145	37	224	

One of the 14 deaths was known to be unrelated to tuberculosis; this was due to pelvic carcinoma in a female.

Ten of the deaths took place during the initial period of treatment in hospital and four after absconding from hospital.

(4) Influence of Certain Factors on the Outcome

All 224 patients were included in these analyses.

Age

In Table VII will be seen the effect of age, which was clearly correlated with a poor out-

come. None of those whose ages were estimated at less than 20 had an unsatisfactory result, compared with 19 per cent. of those aged 20 to 49 and 38 per cent. of those aged 50 and over.

Sex

Females were significantly favoured (Table VIII), having 11 per cent. of unsatisfactory results compared with 26 per cent. for males ($P < 0.02$). The better performance of females as regards absconding from hospital and default from out-patient treatment no doubt contributes to this difference.

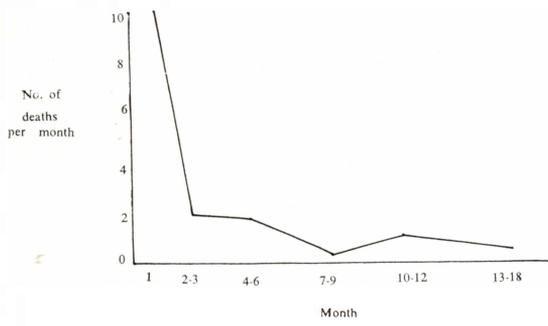


Fig. 1—Times of death.

Late Reporting for Treatment

Table IX shows the times of death for the 28 patients who died, and Fig. 1 indicates the numbers of deaths per month. Ten patients died during the first month of treatment.

Abscending from Hospital

The 10 patients who died during the first month are regarded as being ineligible to abscond from hospital and have been excluded from this

Table IX

TIMES OF DEATH

Died in first month	10
" " second	1
" " third	3
" " fourth to sixth month	5
" " seventh to ninth month	1
" " tenth to twelfth month	3
" " thirteenth to eighteenth month	3
Died, time not known	2
Not known to have died	196
	<u>224</u>

analysis. Table X shows the results. Though the high proportion (45 per cent.) of absconding patients who were not seen after 18 months decreases the significance of the figures, it will be seen that 69 per cent. of those who absconded and were followed successfully had an unsatisfactory result compared with only 10 per cent. for those who did not abscond.

Stage of Sputum Conversion

The degree of success in treatment following sputum conversion at different stages in the 28 patients who survived for six months or more after starting treatment, and whose stage of sputum conversion was known, is shown in Table XI. There was a well-defined difference between those converting by six months and those who converted later or never converted; 8 per cent. of 145 (33 not followed) compared with 44 per cent. of 16 (nine not followed). Rather surprisingly, those converting in the fourth, fifth and sixth months inclusive were also favoured in comparison with those whose conversion took place in the first three months. Ten per cent. of 101 among the latter had an unsatisfactory outcome as against 2 per cent. of 44 in the former group.

Default from Treatment

For this analysis, patients who were discharged to out-patient treatment by the seventh month were included. These were the ordinary run of patients who had done well up to that point. Most were made out-patients at the fifth, sixth or seventh month, though there was one who was discharged after three and one after four months.

A few patients absconded temporarily while in-patients, and these periods of default have been included.

There was a sharp division in the outcome between those who had up to three months of default and those who defaulted longer than that.

Table X

ABSCONDING AND OUTCOME in those surviving the first month of treatment

Outcome:	Not Followed	Satisfactory	Unsatisfactory	All	Percentage Unsatisfactory
Did not abscond	29	140	16	185	16/185 = 10%
Absconded	13	5	11	29	11/16 = 69%
TOTAL	42	145	27	214	
(Not eligible to abscond: died in first month)				10	
				<u>224</u>	

Table XI

STAGE OF SPUTUM CONVERSION AND OUTCOME
in patients surviving for six months or more

Outcome:	Not Followed	Satisfactory	Unsatisfactory	All	Percentage Unsatisfactory
Conversion stage—					
First month	9	19	3	31	3/22 = 14%
Second month	9	50	4	63	4/54 = 7%
Third month	11	22	3	36	3/25 = 12%
Fourth month	3	24	1	28	1/25 = 4%
Fifth month	1	9	—	10	0/9 = 0%
Sixth month	—	10	—	10	0/10 = 0%
After sixth month or not known to have converted	9	9	7	25	7/16 = 44%
Converted, but stage not known	—	2	—	2	
All stages	42	145	18	205	
(Died in first six months)				19	
				<u>224</u>	

Table XII

DEFAULT AND OUTCOME
in those discharged to out-patient treatment by the seventh month

Outcome:	Not Followed	Satisfactory	Unsatisfactory	All	Percentage Unsatisfactory
Default period—					
Less than four months	1	83	2	86	2/85 = 2%
Four months or more	23	18	3	44	3/21 = 14%
Not known	1	4	—	5	
All periods	25	105	5	135	
(Not discharged to out-patient treatment by the seventh month)				89	
				<u>224</u>	

Table XIII

AVERAGE STAGE OF DEFAULT AND OUTCOME

in those discharged to out-patient treatment by the seventh month who defaulted for four months or more

Outcome:	Not Followed	Satisfactory	Unsatisfactory	All	Percentage Unsatisfactory
Stage of default—					
Before 15 months	16	11	3	30	3/14 = 21%
Fifteen months or later	7	7	—	14	0/7 = 0%
All stages	23	18	3	44	
(Not defaulted for four months or more)				91	
(Not discharged to out-patient treatment by the seventh month)				89	
				<u>224</u>	

Table XIV
PREVIOUS TREATMENT AND OUTCOME

Outcome:	Not Followed	Satisfactory	Unsatisfactory	All	Percentage Unsatisfactory
Not treated before	39	127	30	196	30/157 = 19%
Treated before	3	18	7	28	7/25 = 28%
TOTAL	42	145	37	224	

Table XV
ISONIAZID RESISTANCE AND OUTCOME

Outcome:	Not Followed	Satisfactory	Unsatisfactory	All	Percentage Unsatisfactory
Sensitivity to isoniazid—					
Sensitive	31	105	24	160	24/129 = 19%
Resistant	6	13	3	22	3/16 = 19%
Not sent for culture or no result	5	27	10	42	
TOTAL	42	145	37	224	

Table XII shows the comparison between the two groups: the difference between 2 per cent. of 85 unsatisfactory for the low-default group and 14 per cent. of 21 for the high-default group is significant ($P \pm 0.02$).

The mean *stage* of default was found to have some bearing on the outcome in the 21 patients who defaulted for four months or more and who were successfully followed, as shown in Table XIII. Thus, in those whose mean default was before 15 months, three out of 14 had an unsatisfactory result, whereas all of the seven whose average default was at 15 months or later (i.e., who did not default until after they had had a year's treatment) were well at or after 18 months.

Previous Treatment (Relapse at this Admission)

Table XIV shows the comparison in the outcome between those who had had previous treatment and those who had had none. Previous treatment shows relatively little effect on the response.

Isoniazid Resistance

The results are shown in Table XV. As with previous treatment, isoniazid resistance did not affect the outcome. As was to be expected, it

was closely associated with previous treatment; this has been detailed under "Initial Data" above.

DISCUSSION

The Overall Results of Routine Treatment

We failed to find 26 (20 per cent.) of the 132 patients whose results after 18 months of normal routine handling are reported. It is difficult to say whether these would be in the main patients who remained well and so did not come back to hospital, or those who went home and died quietly, avoiding the health assistant who attempted to trace them. The minimum success rate in our series was 90 out of 132 or 68 per cent.

The failure rate of 15 per cent. in those traced is, of course, a relative matter. The longer the follow-up, the greater will be the failure rate. On the other hand, 18 months is a good follow-up period; a population of patients who have reached this stage without mishap is relatively stable, and as time goes on the liability to relapse decreases. Among a total of 82 patients in the whole series who were assessed as satisfactory at 18 months and who were in the study for not less than two years, 16 were not seen at or after two years, two had relapsed between 18 months and two years, and the remaining 64 were well. In these

few patients there was thus a 3 per cent. relapse rate between 18 months and two years.

Factors Affecting the Outcome

The significant factors which emerge as militating against a successful outcome are:

(1) *Late Reporting for Treatment.*—This is the only possible reason which can be assigned for the large number (10) of deaths that took place in the first month. It points to the need for one of the most difficult techniques in tuberculosis work—propaganda to the public at large, as opposed to the patient under treatment who is so much more accessible. Secondly, it indicates that corticosteroid drugs, if they can be given under adequate medical supervision, have a real place in the treatment of acutely-ill patients who have not had previous treatment.

(2) *Age and Sex.*—Patients of 50 and over were considerably worse off than those under 50, having 38 per cent. failures compared with 16 per cent. Only a small part of this was accounted for by a poorer attendance for treatment.

Females appeared to have a more suitable temperament for receiving a course of treatment for tuberculosis, as judged by their lower absconding rate and, to a lesser extent, their better attendance for out-patient treatment; and they enjoyed a much better outcome.

(3) *Absconding from Hospital.*—With 29 patients absconding at some time, 25 of these during the first seven months of treatment, this was undoubtedly a major cause of failure. Absconding represents a serious rift between the patient and the doctor and hospital—a clear breakdown of confidence; after the patient has absconded it is very difficult to bring him back under treatment. On the other hand, defaulters from out-patient treatment can readily be brought back and remain on good terms with the staff throughout. If the period of in-patient treatment had been limited to two months, only nine instead of 29 patients would have absconded.

(4) *Default from Treatment.*—The importance of regular treatment, accepted by all through experience, is well demonstrated here in figures: there was an unsatisfactory outcome in 14 per

cent. of those who defaulted for four months or more, but in only 2 per cent. of those with no default or with periods shorter than four months.

We would have expected *previous treatment* and *isoniazid resistance* (which are shown to be closely related) to exert an effect. However, their insignificance is satisfying in that it shows that it may not be too late for the wayward patient to mend his ways. It may be that the connection which is noted from time to time between these factors and success in treatment is largely due to the intrinsic tendency of the particular patient to default from treatment, which tendency produced the bacillary resistance in the first place. In this case proper handling and education of the patient after re-admission should do much to ensure a successful outcome.

CONCLUSIONS

The important correctable factors causing our patients to fail in their treatment were late reporting for treatment, absconding from hospital and default from out-patient treatment.

Other significant prognostic guides were the age of the patient and the stage at which the sputum converted.

Previous treatment (relapse on admission to the series) and isoniazid resistance at the start were of little or no importance.

The ideal patient is one who is aged under 50, who survives the first month of treatment, who does not abscond from hospital and who misses less than four months' out-patient treatment. Although in the group which had the normal regimens the outcome was unsatisfactory in 16 (15 per cent.) of 106 patients, for this class the figure was reduced to four (6 per cent.) of 69—with only two additional patients who were not traced.

The results indicate that the main effort required now is towards winning the confidence of the public and of the patients. The hospital period should be a time of education. Patients should be released much sooner to out-patient treatment than was done at the time and place of the study.