A Concurrent Comparison of Intermittent (Twice-Weekly) Isoniazid plus Streptomycin and Daily Isoniazid plus PAS in the Domiciliary Treatment of Pulmonary Tuberculosis

TUBERCULOSIS CHEMOTHERAPY CENTRE, MADRAS [1]

Previous reports from the Tuberculosis Chemotherapy Centre, Madras, have established that ambulatory treatment of pulmonary tuberculosis with the combination of isoniazid and PAS, administered daily, yields satisfactory results. However, in the usage of any unsupervised regimen, reliance must be placed on the co-operation of patients in self-administering their drugs. Irregularities in drug-taking, which are not uncommon, may lead to unfavourable therapeutic results; this might be avoided by supervised administration of the drugs. Daily supervision is clearly impracticable in developing countries but regimens in which the drug is administered intermittently-say, twice a week or less frequently-are, if effective, more likely to gain general application.

This paper presents the results of a controlled study of a fully supervised intermittent regimen of isoniazid (12.5-16.1 mg/kg body-weight, orally) plus streptomycin (injected in a uniform dose of I g), given together twice weekly, compared with a standard, unsupervised, daily, oral regimen of isoniazid (3.7-63 mg/kg body-weight) plus sodium PAS (0.2-0.3 g/kg body-weight), given in two doses. The intermittent regimen was at least as effective as the standard oral regimen, and although the incidence of temporary giddiness in patients receiving this regimen was rather high, this did not appear to have any long-term importance nor did it appear unduly to affect the co-operation of the patients. These encouraging findings suggest a possible change in the orientation of drug-administration for tuberculosis in developing countries.

[1]The Centre is under the joint auspices of the Indian Council of Medical Research (ICMR), the Madras State Government, the World Health Organization (WHO) and the Medical Research Council of Great Britain (MRC). The members of the scientific staff of the Centre with major responsibility for the work reported here are: Dr Hugh Stott (WHO), Senior Medical Officer; Dr J. J. Y. Dawson (WHO), Dr C. V. Ramakrishnan (ICMR) and Dr S. Velu (Madras Government), Medical Officers; Dr S. Devadatta (ICMR), Assistant Medical Officer; Dr S. R. Kamat (ICMR), Senior Research Officer; Dr J. B. Selkon (WHO), succeeded by Dr E. M. Mackay-Scollay (WHO) in January 1962, and Dr S. P. Tripathy (ICMR), Bacteriologists; Mr C. Narayanan Nair (ICMR), Assistant Bacteriologist; Mr D. V. Krishnamurthy (ICMR), Biochemist; Mr C. V. Jacob (ICMR) and Miss S. Joseph (ICMR), Laboratory Research Assistants; Mr K. L. Thomas (WHO), succeeded by Mr P. M. Hinchliffe (WHO), Laboratory Technician; Mr K. Ramachandran (ICMR) and Mr P. R. Somasundaram (ICMR), Statisticians; and Mr B. Janardhanam (ICMR) and Mr N. Nataraja (ICMR), Senior Assistant Statisticians.

The research of the Centre is guided by a Project Committee consisting of three ICMR representatives (Dr P. V. Benjamin, Convenor, succeeded in July 1962 by Dr N. L. Bordia, Dr J. Frimodt-Møller and Dr K. S. Sanjivi), the Director of the ICMR (Dr C. G. Pandit), the Director of Medical Services, Madras State (Dr V. R. Thayumanaswamy, succeeded in November 1961 by Dr A. B. Marikar), a WHO representative (appointed for each meeting), an MRC representative (appointed for each meeting) and the Senior Medical Officer of the Centre (Dr Hugh Stott). The joint secretaries are Mr D. Chakravarti, and Mr B. S. Verma succeeded by Mr V. S. Talwar in April 1962. The MRC (acting through its Tuberculosis Research Unit) is responsible for advising WHO on the research in accordance with plans prepared by the Project Committee. Close contact is maintained between this Centre, Dr P. D'Arcy Hart (MRC Tuberculosis Research Unit), Dr Wallace Fox (MRC Tuberculosis Research Unit), Dr Ian Sutherland (MRC Statistical Research Unit) and Dr D. A. Mitchison (MRC Group for Research on Drug Sensitivity in Tuberculosis).

The great majority of the patients in the present study were referred to the Centre from the Government Tuberculosis Institute, Madras (Director: Dr M. A. Hamid) and the Corporation Tuberculosis Clinic, Pulianthope (Medical Officer in Charge: Dr V. S. Selvapathy).

I. INTRODUCTION

The domiciliary chemotherapy of tuberculosis conducted from outpatient clinics is widely practised in developing countries. Under such conditions reliance is placed on the co-operation of the patients in self-administering their drugs orally, a practice which is known to have serious limitations (see review by Fox, 1962). Although fully supervised daily chemotherapy has been conducted by some (Stradling, 1957 ; Stradling & Poole, 1958 ; Velu et al., 1961b ; Angel et al.; 1963 ; M. P. Flynn, personal communication, 1963), this is clearly impracticable as a general policy for developing countries. If, instead, fully supervised chemotherapy could be given *intermittently,* for example, twice a week or even less frequently, it would become more generally applicable.

Previous studies at the Centre suggested a rational basis for intermittent chemotherapy. In a comparison of three regimens of isoniazid alone with a standard regimen of isoniazid plus PAS (Tuberculosis Chemotherapy Centre, 1960) it was found that a moderate daily dosage of isoniazid (approximately 9 mg/kg body-weight) was more effective when given in one dose than when given in two doses. There was evidence that this was because a high peak concentration of isoniazid in the serum played a more important role in the response to treatment than the maintenance of a continuous inhibitory level of the drug (Gangadharam et al., 1961b). It was therefore decided to study a regimen which included a high dose of isoniazid in which the interval between the doses was extended. It seemed unlikely that the efficacy would be seriously diminished by a limited degree of intermittency, in view of the observation that patients who showed irregularity (on the evidence of urine tests for drug) in taking isoniazid in a single large daily dose (approximately 14 mg/kg) responded to treatment as well as those who were completely regular (Tuberculosis Chemotherapy Centre, 1963a, 1963b).

There is experimental evidence that isoniazid given once weekly in the guinea-pig (Palmer et al., 1956) or the mouse (Bloch, 1961) and streptomycin given every five days in the guinea-pig (Corper & Cohn, 1947) are effective in suppressing the development of tuberculosis. Further, Grumbach et al. (1952) have shown that an intermittent regimen of a combination of streptomycin plus isoniazid given to mice every three days is as effective in controlling tuberculous infection as a continuous daily regimen of the combination given in one-third of the intermittent dosage.

In view of the findings in this Centre and the above experimental evidence it was decided to test the effectiveness of a combination of the two most potent standard antituberculosis drugs, namely isoniazid and streptomycin, given under supervision twice weekly, the minimum interval considered to offer substantial practical advantages over regimens prescribed daily. Isoniazid was to be given in a high dosage of approximately 14 mg/kg body-weight and streptomycin in a uniform dose of 1 g, which, in view of the light weight of the patients in Madras, is a higher dosage than is customary elsewhere.

The detailed results of a controlled comparison for a year of this supervised intermittent regimen with the standard, unsupervised, daily regimen of isoniazid plus PAS is presented in this report. The bacteriological results at six and nine months have already been reported in a preliminary communication (Tuberculosis Chemotherapy Centre, 1963c).

II. PLAN AND CONDUCT OF THE STUDY

The patients were drawn from the same area in Madras City as in previous investigations (Tuberculosis Chemotherapy Centre, 1960, 1963a, 1963b). As before, nearly all came from the poorest sections of the population and the great majority were referred to the Centre from tuberculosis clinics where they had attended with symptoms. They were admitted on the same criteria as in the earlier investigations. In particular they had bacteriologically confirmed pulmonary tuberculosis, were aged 12 years or more, were judged to be co-operative (that is, were prepared to have one year of domiciliary chemotherapy and to attend for subsequent follow-up) and had either received no antituberculosis chemotherapy or had received it for not more than two weeks.

PRETREATMENT INVESTIGATIONS

The pretreatment investigations included:

(1) A full clinical examination, including the assessment of the general clinical condition, weight (lb), and examination of the urine for albumin and sugar.

(2) A full-plate postero-anterior chest radiograph and a standard series of tomographic cuts.

(3) The examination by direct smear and culture of a minimum of four sputum specimens; two were produced overnight in the home (collection specimens) and two were expectorated under supervision at the Centre (supervised spot specimens).

(4) Tests of sensitivity to isoniazid, streptomycin and PAS on two cultures.

(5) The determination of the rate of inactivation of isoniazid.

CHEMOTHERAPEUTIC REGIMENS

The two chemotherapeutic regimens studied were an intermittent supervised regimen of isoniazid plus streptomycin given together twice weekly (SHTW), and a standard, unsupervised, daily regimen of isoniazid plus PAS (PH). It was decided to use a high dosage of isoniazid in the intermittent regimen in order to achieve high peak serum levels. The dosage selected was known to have only a small risk of acute toxicity even when given daily (Tuberculosis Chemotherapy Centre, 1963a, 1963b).

The dosages of isoniazid and PAS were graded according to the patient's weight (Table 1). If, at a monthly examination, the patient had gained weight and moved into a higher weight category, the dosages were increased. The dosages were not reduced for loss in weight. The streptomycin was given in a uniform dosage of 1 g to all patients irrespective of weight. The details of the dosages for patients weighing 100 lb (45.5 kg) were as follows:

SHTW. Streptomycin sulfate by intramuscular injection in a dose equivalent to 1 g of streptomycin base plus isoniazid in a single oral dose of 650 mg (as three tablets containing 200 mg each and one tablet containing 50 mg of isoniazid) ; both drugs were given together twice weekly, at intervals of three and four days alternately.

PH. Isoniazid 200 mg daily plus PAS (sodium salt) 10 g daily ; the two drugs were given together in eight cachets (four in the morning and four in the evening), each cachet containing 25 mg of isoniazid and 1.25 g of PAS (sodium salt).

For patients in the SHTW series, the mean daily dosage of streptomycin at the start of treatment was 27.0 mg/kg body-weight (range 18.2-53.7 mg/kg) and the mean initial dosage of isoniazid was 13.9 mg/kg (range 12.5-16.1 mg/kg). For patients in the PH series, the mean daily dosage of isoniazid at the start of chemotherapy was 4.4 mg/kg body-weight (range 3.7-6.3 mg/kg) and that of PAS 0.22 g/kg (range 0.18-0.32 g/kg).

Both chemotherapeutic regimens were prescribed for a period of 12 months in the first instance.

ALLOCATION OF CHEMOTHERAPY

On the basis of the postero-anterior radiograph and the tomographic series, each patient was classified into one of the following three categories by the Centre's medical staff :

(1) patients with no definite cavitation ;

(2) patients with cavitation, the diameter of the largest cavity not exceeding 3 cm ; and

(3) patients with cavitation, the diameter of the largest cavity exceeding 3 cm.

The allocation of treatment was done by the statistics department from three separate series of sealed envelopes (one for each of the above three groups), based on random sampling numbers. Nobody had prior knowledge of the chemotherapy which any individual patient would receive.

The first allocation was made on 21 June 1961 and the last on 10 January 1962, by which date 165 patients had been allocated to treatment, 83 to the SHTW series and 82 to the PH series.

GENERAL MANAGEMENT

All patients were treated on a domiciliary basis. The SHTW patients were asked to attend the Centre twice weekly to receive a dose of isoniazid (under the direct supervision of the clinic staff) followed by an injection of streptomycin. The PH patients were instructed to attend the Centre once a week for a supply of cachets which were to be taken at home. If any patient failed to attend on the appointed day, a home visit was paid by the health visitor the next day as a reminder; the management of patients who failed to attend

despite the reminder was decided by the Centre's medical staff.

In other respects the management of the patients followed the same lines as in previous investigations at the Centre (Tuberculosis Chemotherapy Centre, 1960, 1963a, 1963b). In brief, two visits were usually paid by the health visitors to all patients every month at approximately fortnightly intervals ; at one visit (an unannounced one in the middle of the month) the stock of cachets was counted and a specimen of urine was collected from the PH patients, but no routine procedure was undertaken in the case of the SHTW patients. The other visit (at the end of each month) was to deliver a sputum specimen bottle.

Patients who were initially too ill to attend the Centre had their chemotherapy administered at home (SHTW series) or had a stock of cachets delivered to them at home once a week (PH series). As soon as they had improved sufficiently, usually after one or two months, they were changed to the ordinary routine of clinic and home visits. The large majority of patients were ambulant much of the time.

ASSESSMENTS OF PROGRESS

Assessments made at monthly intervals after the start of chemotherapy included (a) the weight. (b) a postero-anterior chest radiograph, (c) the examination of two collection and one supervised spot specimen of sputum by smear and culture. and (d) tests of sensitivity to the allocated drugs on one positive culture.

URINE TESTING FOR ISONIAZID OR PAS

In order to check the self-administration of medicine in the PH patients, a urine specimen was obtained at each weekly visit to the Centre and at the unannounced visit to the home each month and tested for PAS by the ferric chloride test (Simpson, 1956). In the early stages of the study, a single specimen of urine was collected from each of about a third of the SHTW patients approximately 24 hours after the supervised administration of their drugs. This was tested by the combined naphthoquinone-mercuric chloride test (Gangadharam et al., 1958).

III. BACTERIOLOGICAL AND ASSAY PROCEDURES

EXAMINATION OF SPUTUM SPECIMENS, AND SENSITIVITY TESTS

The methods used for examining sputum specimens and for performing tests of sensitivity to isoniazid, streptomycin and PAS are similar to those described elsewhere (Tuberculosis Chemotherapy Centre, 1959). In brief, sputum smears were examined by fluorescence microscopy and were graded as 3-plus, 2-plus, 1-plus or negative. Sputum specimens, after treatment with 4% NaOH for 20 minutes, were cultured on Löwenstein-Jensen medium which did not contain potato starch (Jensen, 1955). The cultures were examined weekly for between eight and nine weeks and reported as negative if no growth was present by that time. Sensitivity tests were set up on Löwenstein-Jensen medium slopes containing the concentrations of drug set out below as well as on a drug-free slope as a control. The standard sensitive strain, H37Rv, was also set up with each batch of tests. Sensitivity tests for PAS were set up using a 1: 10 dilution of the standard suspension as recommended by Selkon et al. (1960). The tests were read after four weeks' incubation at 37°C. The drug concentrations used were as follows:

	Drug concentration in mg/ml	
Drug	*Test strain*	*H37Rv*
Isoniazid	0.2, 1, 5, 50	0.025, 0.05, 0.1, 0.2, 1
Streptomycin	4, 8, 16, 32, 64	1, 2, 4, 8
Sodium PAS dihydrate	0.5, 1, 2, 4, 8, 16	0.125, 0.25, 0.5, 1, 2

DEFINITIONS OF BACTERIAL DRUG RESISTANCE

In the following definitions of resistance,. " growth " has been defined as 20 colonies or more :

Isoniazid

Pretreatment tests. Resistance was defined as:

(a) growth on 1 µg/ml on one culture irrespective of the result on the other culture;

(b) growth on 0.2 µg/ml but not on 1 µg/ml followed by growth on 0.2 µg/ml in a repeat test on the same culture, irrespective of the result on the other culture ; or

(c) growth on 0.2 µg/ml but not on 1 µg/ml on both cultures, irrespective of the results of repeat tests.

Tests during treatment. Resistance was defined as growth on 0.2 µg/ml or a higher concentration.

Streptomycin

Pretreatment tests. Resistance was defined as:

(a) a resistance ratio (RR) of 8 or more on one culture irrespective of the result on the other culture ;

(b) an RR of 4 followed by an RR of 4 or more in a repeat test on the same culture, irrespective of the result on the other culture; or

(c) an RR of 4 on both cultures, irrespective of the results of repeat tests.

Tests during treatment. Resistance was defined as an RR of 8 or more, or an RR of 4 followed by an RR of 4 or more in a repeat test on the same culture.

PAS

Pretreatment tests. Resistance was defined as:

(a) an RR of 8 or more on both cultures ;

(b) an RR of 8 or more on one culture, and an RR of 4 on the second culture followed by an RR of 4 or more in a repeat test on the same culture ; or

(c) an RR of 4 followed by an RR of 4 or more in a repeat test, on both cultures.

Tests during treatment. Resistance was defined as an RR of 8 or more, or an RR of 4 followed by an RR of 4 or more in a repeat test on the same culture.

SERUM ISONIAZID ASSAYS

The rate of inactivation of isoniazid was determined for each patient before treatment following the method described by Gangadharam et al. (1961a). The results will be reported elsewhere.

TABLE 1
DOSAGE OF DRUGS IN RELATION TO BODY-WEIGHT

Regimen	Body-weight (lb)	Actual amount of drug given			Dosage in relation to body-weight			Number of patients (on admission)
		Isoniazid (mg)	strepto-mycin (g)	PAS (sodium salt) (g)	Isoniazid (mg/kg)	strepto-mycin (mg/kg)	PAS (sodium salt) (g/kg)	
SHTW (Twice weekly)	40-49	300	1.0	—	18.7–13.4	55.8-44.6	-	2
	50-59	350	1.0	—	15.6–13.0	44.4-37.2	-	1
	60-69	400	1.0	—	14.8–12.7	37.0-31.7	-	11
	70-79	450	1.0	—	14.2–12.5	31.6-27.8	-	13
	80-89	550	1.0	—	15.2–13.5	27.7-24.6	-	26
	90-99	600	1.0	—	14.7-13.3	24.8-22.2	-	13
	100-109	650	1.0	—	14.4–13.1	22.1-20.1	-	9
	110-119	700	1.0	—	14.1–12.9	20.1-18.5	-	3
	120-129	800	1.0	—	14.7–13.6	18.4-17.0	-	
PH (Twice daily)	50-59	150	-	7.50	8.7-5.6	-	0.33-0.28	3
	60-69	150	-	7.50	5.8-4.8	-	0.28-0.24	6
	70-79	150	-	7.50	4.7-4.2	-	0.24-0.21	19
	80-89	175	-	8.75	4.8-4.3	-	0.24-0.22	14
	90-99	175	-	8.75	4.3-3.9	-	0.21-0.19	16
	100-109	200	-	10.00	4.4-4.0	-	0.22-0.20	10
	110-119	200	-	10.00	4.0-3.7	-	0.20-0.18	2
	120-129	200	-	10.00	3.7-3.4	-	0.18-0.17	1

IV. THE PATIENTS ADMITTED TO TREATMENT

In all, 165 patients were admitted to treatment, 83 to the SHTW and 82 to the PH series.. Of these, 15 (four SHTW, 11 PH) were subsequently found to have been excreting organisms resistant to isoniazid and/or streptomycin on admission ; they have been excluded from the main analysis and are considered. on page 264 et seq. There remain 150 patients (79 SHTW, 71 PH) in the main analysis who, on admission to the study, *(a)* had organisms sensitive to isoniazid and streptomycin, *(b)* had had, so far as is known, no previous chemotherapy, or, in eight patients (three SHTW, five PH) up to two weeks' chemotherapy and *(c)* had followed the prescribed regimen for 12 months apart from the variations mentioned on page 260 et seq., unless chemotherapy was terminated owing to death, tuberculous deterioration, major toxicity or uncooperativeness.

Only two of the 150 patients yielded organisms resistant to PAS on admission. Since both patients were in the SHTW series, they have not been excluded from the main analysis.

PRETREATMENT COMPARISON BETWEEN THE TWO SERIES

Of the 79 SHTW patients 59 % were males as compared with 69 % of the 71 PH patients. About half the patients were between the ages of 15 and 34, namely, 49 % of the SHTW and 56 % of the PH series. The distributions of the general condition of the patients on admission were very similar ; thus 13 % of the SHTW patients and 17 % of the PH patients were in good condition, 71 % and 65 %, respectively, in fair condition and 16 % and 18 %, respectively, in poor or very poor condition. The two series had broadly similar weight distributions (Table 1).

The extent of cavitation, the total extent of the radiographic lesion and the number of lung zones involved in disease were assessed, as described previously (Tuberculosis Chemotherapy Centre, 1960). from a single full-plate radiograph by an independent assessor (Dr J. Frimodt-Møller), who was unaware of the treatment series of any patient. Cavitation was present in 95 % of the SHTW and 94 % of the PH patients ; it was extensive or moderate in 62 % and 58 % respectively (Table 2). Gross or extensive disease was present in 28 % of the SHTW patients as compared with 31 % of the PH patients, and four or more lung zones were involved in 48 % and 52 %, respectively.

TABLE 2

RADIOGRAPHIC AND BACTERIOLOGICAL CONDITION ON ADMISSION TO TREATMENT

Condition on admission to treatment	SHTW patients		PH patients	
	No.	%	No.	%
Extent of cavitation :				
Nil	4	5	4	6
Slight	26	33	26	37
Moderate	30	38	30	42
Extensive	19	24	11	15
Total extent of disease :				
Trivial or slight	6	8	1	1
Limited	16	20	22	31
Moderate	35	44	26	37
Extensive or gross	22	28	22	31
Number of lung zones involved in disease :				
1, 2 or 3	41	52	34	48
4, 5 or 6	38	48	37	52
Bacterial content of sputum : [a]				
Direct smear negative	8	10	7	10
Direct smear positive:				
1-plus (scanty)	18	23	13	18
2-plus (moderate)	41	52	44	62
3-plus (heavy)	12	15	7	10
Total patients	79	loo	71	100

[a] First or only collection specimen.

Considering the bacterial content of the first or only collection specimen of sputum, 67 % of the SHTW patients had a 3-plus or 2-plus smear as compared with 72 % of the PH patients ; only 10 % of patients in each series had a negative smear.

To summarize, the two series of patients were similar on admission to treatment.

V. COMPARISON OF THE RESPONSE TO TREATMENT IN THE TWO TREATMENT SERIES

CLINICAL

Deaths

Three patients died of pulmonary tuberculosis, one (SHTW) within 24 hours of admission, one (PH) in the first week, and one (SHTW) in the sixth month. The last patient yielded negative cultures at three and four months, had a radiographic deterioration, presumed to be tuberculous, in the fifth month, and died in a seriously malnourished state with very extensive disease ; no culture results were available at five months. One other patient (PH), all of whose cultures were negative from the first month onwards, died suddenly from a non-tuberculous cause (believed to be pulmonary embolism) in the eighth month. Permission for autopsy was refused for all four patients.

Premature termination of the originally prescribed chemotherapy owing to radiographic deterioration

If a patient was considered by the Centre's medical staff to have a definite radiographic extension of the disease which had not been present at one month, a course of penicillin was given for a minimum of 10 days. If the lesion persisted or showed a further spread the complete radiographic series was shown to an independent assessor, Dr K. S. Sanjivi, who was unaware of the treatment the patient was receiving. He decided whether or not the extension was sufficiently serious to warrant termination of the prescribed chemotherapy. Two patients (one SHTW, one PH) had their prescribed chemotherapy terminated in the twelfth month for this reason. No patient had treatment terminated for serious clinical deterioration.

Premature termination of the originally prescribed chemotherapy owing to toxicity

As in a previous study (Tuberculosis Chemotherapy Centre, 1960) patients whose prescribed chemotherapy was stopped for more than six weeks on account of toxicity were classified as having had their chemotherapy terminated for toxicity; this applied to three patients (all PH), treatment being terminated in the first, fifth and ninth month, respectively. However, a decrease in the dosage of streptomycin because of toxicity (page 261) or the addition of pyridoxine for the treatment of isoniazid toxicity (page 262) to the chemotherapeutic regimen was not regarded as a termination of chemotherapy due to toxicity.

Premature termination of chemotherapy owing to uncooperativeness

Eight patients (seven SHTW, one PH) became uncooperative and stopped treatment, two in the third, one in the seventh, three (including the PH patient) in the eighth, one in the ninth and one in the tenth month.

TABLE 3

CHANGES IN RADIOGRAPHIC APPEARANCES IN THE 12-MONTH PERIOD [a]

Period	Treatment series	Total patients [b]		Improvement								No change		Termination of prescribed chemotherapy during the period owing to deterioration		Tuberculous death	
				Exceptional		Considerable		Moderate		Slight							
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
0-6 months	SHTW	77	100	0	0	35	45	32	42	8	10	0	0	0	0	2	3
	PH	69	99	0	0	29	42	34	49	4	6	1	1	0	0	1	1
0-12 months	SHTW	72	100	3	4	41	57	22	31	2	3	1	1	1	1	2	3
	PH	66	102	2	3	37	56	23	35	1	2	1	2	1	2	1	2

[a] Two separate assessments on standard radiographs.

[b] Excluding patients who, during the set period, died of a non-tuberculous condition or had their prescribed chemotherapy terminated on account of toxicity or non-cooperation.

Presentation of the results for the patients who died, whose chemotherapy was prematurely terminated or who became uncooperative

Patients who died of tuberculosis or whose prescribed chemotherapy was terminated owing to deterioration of their disease usually remain in the totals for the whole year. The patient who died of a non-tuberculous cause has been included up to the time of death and those whose originally prescribed chemotherapy was terminated for reasons of toxicity or uncooperativeness have been included up to the time of termination of treatment.

Weight changes

During the 12-month period, 84 % of 68 SHTW patients and 91 % of 66 PH patients assessed gained weight ; the average change in weight was a gain of 8.9 lb (4.0 kg) and 8.1 lb (3.7 kg), respectively.

Radiographic changes

The radiographic changes were evaluated by an independent assessor, Dr J. Frimodt-Møller, who was unaware of the treatment which any patient had received. The changes were assessed for the first six months and then for the year ; the findings are presented in Table 3.

During the first six months, 87 % of 77 SHTW patients as compared with 91 % of 69 PH patients showed moderate or greater improvement. The proportions of patients who died of tuberculosis were 3 % and 1 %, respectively. Over the full 12 months 92 % of 72 SHTW patients and 94 % of 66 PH patients showed moderate or greater improvement, and 4 % and 3 %, respectively, died of tuberculosis or had their chemotherapy terminated on account of deterioration. Thus, the radiographic progress of the two treatment series was similar.

Changes in cavitation

Table 4 presents the changes in cavitation for the 12-month period as assessed by the independent assessor. Cavitation disappeared in 24 % of 70 SHTW patients as compared with 21 % of 63 PH patients, and became less in 69 % and 68 %, respectively. The progress of the two series was also similar when patients with extensive, moderate or slight initial cavitation were considered separately.

Five patients (two SHTW, three PH) had no cavitation on admission ; in one (PH) of them it appeared at 12 months.

TABLE 4

CHANGES IN CAVITATION IN THE 12-MONTH PERIOD IN PATIENTS WITH CAVITATION ON ADMISSION TO TREATMENT [a]

Extent of cavitation on admission to treatment	Treatment series	Total patients [b]		Disappearance of cavitation		Cavities smaller or fewer		No change		Cavities larger or more numerous		Termination of prescribed chemotherapy owing to deterioration		Tuberculous death	
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Extensive	SHTW	18	101	1	(6) [c]	16	(89)	0	(0)	0	(0)	0	(0)	1	(6)
	PH	9	100	1	(11)	7	(78)	0	(0)	1	(11)	0	(0)	0	(0)
Moderate	SHTW	26	100	4	15	19	73	0	0	1	4	1	4	1	4
	PH	29	99	4	14	21	72	2	7	0	0	1	3	1	3
Slight	SHTW	26	100	12	46	13	50	1	4	0	0	0	0	0	0
	PH	25	100	8	32	15	60	2	8	0	0	0	0	0	0
Total patients with cavitation	SHTW	70	99	17	24	48	69	1	1	1	3	1	1	2	3
	PH	63	101	13	21	43	68	4	6	1	2	1	2	1	2

[a] Assessment on standard radiographs on admission to treatment and at 12 months.
[b] Excluding patients who had their prescribed chemotherapy terminated on account of toxicity or non-cooperation.
[c] The parentheses indicate percentages based on fewer than 25 observations.

BACTERIOLOGICAL

Smear and culture results

The smear and culture results of the first (or only) collection specimen of sputum at each month are shown in Table 5. At three months, the culture was negative in 82 % of 76 SHTW and 72 % of 69 PH patients ; at six months the proportions were 89 % and 88 %, at nine months 93 % and 89 %, and at 12 months 94 % and 89 %, respectively.

Multiple specimens were examined for each patient monthly, the average number of test results per month ranging from 2.6 to 2.9 for patients in both series. The percentage of patients each month with at least one positive culture is shown for the two series in the figure overleaf. In both series, there was a rapid decline in the proportion of patients with at least one positive

TABLE 5

PRESENCE OF TUBERCLE BACILLI IN SINGLE COLLECTION SPECIMENS OF SPUTUM

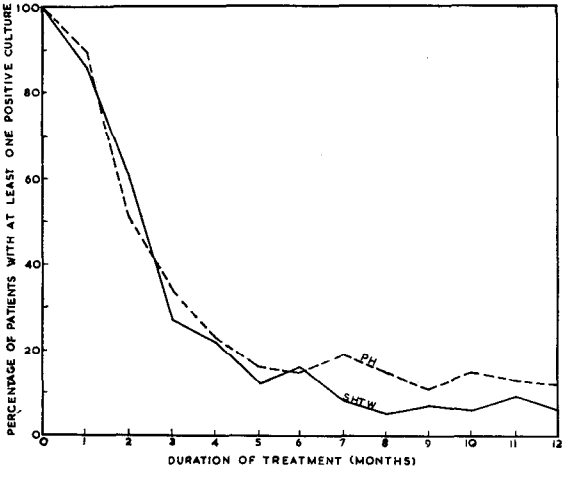
Months after start of chemotherapy	Treatment series	Total patients [a]	Termination of prescribed chemotherapy on account of deterioration, or tuberculous death	Culture positive		Culture negative [b]	
				Smear positive	Smear negative	No.	%
0	SHTW	79	0	71	7	1	1
	PH	71	0	63	6	2	3
1	SHTW	78	1	35	23	19	24
	PH	70		24	30	15	21
2	SHTW	75		15	21	38	51
	PH	69	1	13	16	39	57
3	SHTW	76	1	5	8	62	82
	PH	69	1	4	14	50	72
4	SHTW	72	1	3	9	59	82
	PH	68		5	5	57	84
5	SHTW	74	1	2	4	67	91
	PH	64	1	6	2	55	86
6	SHTW	75	2	3	3	67	89
	PH	67		3	4	59	88
9	SHTW	72	2	2	1	67	93
	PH	65		2	4	58	89
12	SHTW	72	3	1	0	68	94
	PH	66	2	3	2	59	89

[a] Patients who died of a non-tuberculous condition or had their prescribed chemotherapy terminated on account of toxicity: or non-cooperation are excluded thereafter.

[b] Even if the smear was positive.

culture, and, in the second six months, this proportion was usually slightly smaller in the SHTW series.

PERCENTAGE OF PATIENTS EACH MONTH WITH AT LEAST ONE POSITIVE CULTURE FROM MULTIPLE BACTERIOLOGICAL SPECIMENS



Sensitivity tests

Isoniazid. The results of isoniazid sensitivity tests are set out in Table 6. (These were not available for 10 (2.6 %) of 383 cultures.) At three months, a resistant culture was obtained from three (4 %) of 76 SHTW patients and from two (3 %) of 69 PH patients. The corresponding proportions at six and 12 months were 5 % and 10 %, and 1 % and 6 %, respectively. Considering the proportions of positive cultures that were resistant, three of 20 cultures at three months were resistant in the SHTW series as compared with two of 20 in the PH series ; at six months the proportions were four of nine and seven of eight cultures, respectively. In the second six months of treatment, 12 (80 %) of 1.5 cultures in the SHTW series and 41 (84 %) of 49 cultures in the PH series were resistant.

Streptomycin. At one month, two (3 %) of 78 SHTW patients yielded a streptomycin-resistant culture ; this proportion remained practically the same for the rest of the year. In the second six months of treatment, 11 of 15 positive cultures tested were resistant, all with resistance ratios of more than eight.

Emergence of resistance in the SHTW patients. Resistance to isoniazid or streptomycin (or both) emerged during treatment in 10 of the 78 SHTW patients. Sputum conversion (that is, three consecutive months of culture negativity) occurred after the emergence of resistance in five patients ; in four of these, only a single culture was resistant (two to isoniazid, one to streptomycin and one to both) and the fifth patient had two cultures resistant to isoniazid. A further three patients each yielded an isolated positive culture which was resistant (two to isoniazid and one to both isoniazid and streptomycin) after sputum conversion. All these eight patients were regarded as having had a favourable response to treatment at 12 months (see page 258 et seq). Of the remaining two patients, both of whom were classified as having had an unfavourable response to treatment, one had isoniazid-resistant cultures at each month from two to 12 months, the cultures at three, five, seven and subsequent months being streptomycin-resistant also. The other patient had isoniazid-resistant cultures at each month from two to 11 months when treatment was terminated owing to radiographic deterioration. The cultures in this patient were streptomycin-resistant at one, three, and five to 11 months. In both patients the majority of the cultures were fairly highly resistant to isoniazid (growth on 5 µg/ml) and to streptomycin (RR of more than 8).

Of the remaining 68 patients, who never yielded a resistant culture during treatment, none remained consistently bacteriologically positive with isoniazid-sensitive and/or streptomycin-sensitive organisms throughout the 12 months.

Emergence of resistance in the PH patients. Resistance to isoniazid emerged during treatment in 14 of 69 PH patients. In three, sputum conversion occurred after the emergence of a single isoniazid-resistant culture. A further four patients produced one or more resistant cultures after sputum conversion. One of these produced an isoniazid-resistant culture at 11 months but an isoniazid-sensitive culture at 12 months, and has been classified as having had an unfavourable response to treatment. Of the other three, one produced resistant cultures at five and eight months, another at seven, eight, nine and 10 months and the third at 10, 11 and 12 months ; according to definition, only the last patient has been regarded as having had an unfavourable

TABLE 6

RESULTS OF ISONIAZID-SENSITIVITY TESTS IN THE 12-MONTH PERIOD[a]

Months after start of chemotherapy	Treatment series	Total patients[b] (A)	Patients culture positive with sensitivity test results								
			Total results available (B)	Sensitive	Resistant				Total resistant		
				No growth on 0.2 μg/ml	Growth on 0.2 but not on 1 μg/ml	Growth on 1 but not on 5 μg/ml	Growth on 5 but not on 50 μg/ml	Growth on 50 μg/ml	No.	% of (A)	% of (B)
1	SHTW	78	67	67	0	0	0	0	0	0	0
	PH	69	60	56	4	0	0	0	4	6	7
2	SHTW	76	45	41	1	2	1	0	4	5	9
	PH	69	35	34	0	1	0	0	1	1	3
3	SHTW	76	20	17	1	0	1	1	3	4	(15)[c]
	PH	69	20	18	1	1	0	0	2	3	(10)
4	SHTW	73	14	12	0	0	1	1	2	3	(14)
	PH	69	14	8	1	3	2	0	6	9	(43)
5	SHTW	74	8	4	1	1	1	1	4	5	(50)
	PH	68	9	1	0	5	1[d]	2	8	12	(89)
6	SHTW	75	9	5	0	0	1	3	4	5	(44)
	PH	67	6	1	0	4	2[d]	1	7	10	(88)
7	SHTW	74	3	1	0	0	1	1	2	3	(67)
	PH	68	12	4	0	4	3	1	8	12	(67)
8	SHTW	72	2	0	0	0	1	1	2	3	(100)
	PH	65	9	1	0	4	2	2	8	12	(89)
9	SHTW	70	3	1	0	0	1	1	2	3	(67)
	PH	64	6	0	0	1	3	2	6	9	(100)
10	SHTW	67	2	0	0	0	1	1	2	3	(100)
	PH	65	9	1	0	3	2	3	6	12	(89)
11	SHTW	68	4	1	1	0	0	2	3	4	(75)
	PH	62	7	0	0	1	2	4	7	11	(100)
12	SHTW	69[e]	1	0	0	0	0	1	1	1	(100)
	PH	64[e]	6	2	0	0	3	1	4	6	(67)

[a] All patients had strains sensitive to isoniazid before treatment.

[b] All patients who died are excluded after their death and patients who had their prescribed chemotherapy terminated on account of toxicity or non-cooperation are excluded thereafter.

[c] The parentheses indicate percentages based on fewer than 25 observations.

[d] No test result on 50 μg/ml for one (or only) patient.

[e] Excluding 1 patient who deteriorated and had his prescribed chemotherapy terminated. (The culture at 11 months yielded growth on 50 μg/ml.)

response to treatment. A further seven patients had bacteriologically active disease throughout with resistant cultures first emerging at one, three, four, four, four, four and five months, respectively. (All the cultures isolated during treatment from four of these patients were sensitive to PAS.)

Of the remaining 55 patients, who never yielded an isoniazid-resistant culture during treatment, only one was persistently bacteriologically positive with isoniazid-sensitive organisms throughout the year ; this patient was irregular in taking his drugs, had treatment changed to twice-weekly streptomycin plus isoniazid in the ninth month on account of toxicity to PAS, continued to excrete isoniazid-sensitive organisms for the rest of the year, and has been regarded in this section as having had an unfavourable response to treatment.

Resistance to PAS emerged during treatment in 13 patients. Eight of these yielded a PAS-resistant culture on one occasion only and sputum conversion occurred thereafter in five ; the other three (including the one who persistently produced isoniazid-sensitive cultures) produced the resistant culture at seven, 10 and 12 months, respectively, and had an unfavourable response. A further four patients yielded two resistant cultures each; in three, this was followed by five or more months of culture negativity and the fourth, who produced resistant cultures at six and nine months, had bacteriologically active disease at 12 months. Finally, one patient produced resistant cultures at seven, nine and 10 months and had active disease throughout. (Of the five patients with PAS-resistant strains who had an unfavourable response to treatment, isoniazid resistance preceded PAS resistance in four; the fifth was isoniazid-sensitive throughout.)

In summary, isoniazid resistance emerged in nine of the 78 SHTW patients and in 14 of the 69 PH patients. However, in only three SHTW and 10 PH patients were two or more resistant cultures produced ; two of the former and eight of the latter had an unfavourable response to treatment. Resistance to streptomycin was observed in five SHTW patients ; two of these yielded resistant cultures on more than one occasion and both had an unfavourable response. PAS resistance emerged in 13 PH patients and was associated with an unfavourable response in five.

Both patients in the SHTW series who remained consistently bacteriologically positive yielded organisms with fairly high degrees of resistance to isoniazid and streptomycin. Isoniazid resistance emerged in seven of eight patients who remained consistently bacteriologically positive in the PH series, and PAS resistance in four.

RESPONSE TO TREATMENT DURING THE 12 MONTHS

Table 7 presents a classification of all the patients at 12 months, based primarily on the bacteriological response to treatment. In all, 92 % of 72 SHTW patients as compared with 80 % of 66 PH patients had bacteriologically quiescent disease and 3 % and 5 %, respectively, had disease of bacteriologically doubtful status, which is also regarded as a favourable response to treatment (Velu et al., 1960, 1961a). The proportions of patients with an unfavourable response to treatment, defined as death from tuberculosis, bacteriologically relapsed disease or bacteriologically active disease at 12 months including termination of prescribed chemotherapy owing to deterioration, were 6% for the SHTW and 15 % for the PH series ; this difference is not statistically significant ($P > 0.1$).

Twelve patients (seven SHTW, five PH) are not included in the above totals, eight (seven SHTW, one PH) because they became uncooperative and stopped treatment, three (all PH) because they had their prescribed chemotherapy terminated on account of toxicity and one (PH) because he died from a non-tuberculous cause.

Four of the seven uncooperative SHTW patients stopped treatment in the third, eighth, ninth and tenth months (after one, six, three and four consecutive months, respectively, of culture negativity). Nevertheless, one had cultures examined at 10, 11 and 12 months, a second at 11 and 12 months, and the other two at 12 months. All the cultures were negative and consequently the four patients were regarded as having had a favourable response. Two patients had an unfavourable response. One of these stopped treatment in the seventh month after six consecutive months of smear and culture negativity and produced two positive cultures (isoniazid-resistant, streptomycin-sensitive) at 12 months. The other, who had stopped treatment in the third month after one month of culture negativity, was examined at seven months when he produced one positive culture (sensitive to both isoniazid and streptomycin) ; he subsequently died of pulmonary tuberculosis in the

TABLE 7

CLASSIFICATION OF ALL PATIENTS AT THE END OF 12 MONTHS ACCORDING TO THEIR RESPONSE TO TREATMENT

Classification at the end of 12 months		Treatment series			
		SHTW		PH	
		No.	%	No.	%
Patients with bacteriologically quiescent disease :	First month of persisting culture negativity				
that is, patients whose cultures were all negative for at least the last three monthly examinations-i.e., at 10, 11 and 12 months	1	9		6	
	2	16		19	
	3	17		7	
	4	7		9	
	5	6		6	
	6	1		1	
	7	7		1	
	8	2		3	
	9	0		1	
	10	1		0	
	Total	66	*92*	53	*80*
Patients with disease of bacteriologically doubtful status : that is, patients whose cultures were all negative at three or more consecutive monthly examinations but who produced a single positive culture at one of the lastthree monthly examinations-i.e., at 10, 11 or 12 months		2	*3*	3	*5*
Total patients with favourable response		68	*94*	56	*85*
Patients with bacteriologically relapsed disease : that is, patients whose cultures were all negative at three or more consecutive monthly examinations, but who produced two or more positive cultures in the last three monthly examinations-i.e., at 10, 11 and 12 months		0	*0*	3	*5*
Patients with bacteriologically active disease :					
that is, *(a)* patients whose cultures were never all negative at three consecutive monthly examinations, or		1	*1*	5	*8*
(b) patients who deteriorated and had their prescribed chemotherapy terminated		1	*1*	1	*2*
Tuberculous deaths		2	*3*	1	*2*
Total patients with unfavourable response		4	*6*	10	*15*
Total		72	*100*	66	*100*
Patients who became uncooperative and stopped treatment		7	–	1	–
Patients who had their prescribed chemotherapy terminated on account of toxicity		0	–	3	–
Non-tuberculous death		0	–	1	–
All patients		79	–	71	-

eleventh month. The seventh patient stopped treatment in the eighth month after five consecutive months of culture negativity ; she refused to attend the Centre subsequently for examination and it was therefore not possible to assess the status of her disease at 12 months. The uncooperative PH patient, who had been persistently sputum positive with isoniazid-resistant organisms, stopped treatment in the eighth month ; at 10 and 11 months, he produced isoniazid-resistant strains and has been regarded as having had an unfavourable response. If the seven uncooperative patients (six SHTW, one PH) whose response could be assessed are taken into consideration in assessing the therapeutic efficacy of the two regimens, the proportions with favourable response become 92 % of 78 SHTW patients and 84 % of 67 PH patients ($P \simeq 0.2$).

Three patients (all PH) had their originally prescribed chemotherapy terminated on account of toxicity, one in the first month, one (culture negative at four months) in the fifth month and one, who had been persistently sputum positive on smear and culture with isoniazid-sensitive strains, in the ninth month. One patient (PH), who had consistently negative cultures from the first to the seventh month, died from a non-tuberculous cause in the eighth month.

VI. RESPONSE TO TREATMENT RELATED TO VARIOUS FACTORS ON ADMISSION TO TREATMENT

Table 8 relates factors in the pretreatment condition to the frequency of unfavourable response to treatment (defined on page 258). Of 44 SHTW patients with extensive or moderate cavitation 9 % had an unfavourable response as compared with none of 28 with slight or no cavitation ; the corresponding proportions for PH patients were 24 % of 38 and 4 % of 28. Of 21 SHTW patients who had gross or extensive disease, 10 % showed an unfavourable response as compared with 4 % of 51 with less extensive disease ; the corresponding proportions for PH patients were 40 % of 20 and 4 % of 46. Of 36 SHTW patients with four or more lung zones involved in disease, 6 % had an unfavourable response as compared with 6 % of 36 with fewer zones involved ; the corresponding figures for the PH patients were 29 % of 34 and none of 32. With regard to the bacterial content of the sputum, 6 % of 48 SHTW patients with 3-plus or 2-plus smears showed an unfavourable response as compared with 4% of 24 with 1-plus or negative smears, and among PH patients 15 % of 47 as compared with 16 % of 19, respectively.

In summary, there was some evidence from both series that an unfavourable response to treatment occurred more frequently in patients with larger radiographic lesions than in patients with relatively small lesions. However, the differences were significant only in the PH series in respect of the total extent of disease and the number of lung zones involved in disease ($P \simeq 0.001$).

VII. TOXICITY AND OTHER COMPLICATIONS

DRUG TOXICITY

Of the 150 patients in the main analysis, two (one SHTW, one PH) who died within a week of starting treatment have been excluded from the analysis of drug toxicity as they were observed for so short a period. There remain 78 SHTW and 70 PH patients.

Streptomycin

Complaints of giddiness were used to assess the incidence of possible streptomycin oto-toxicity. Only spontaneous complaints were recorded ; in order to prevent the patients and nursing staff from becoming unduly conscious about the occurrence of symptoms and signs of toxicity, it was the policy not to interrogate the patients to elicit symptoms. In the present study, giddiness occurred usually half an hour to two hours after the injection and was normally short lasting, rarely persisting overnight.

Spontaneous complaints of giddiness were recorded at some time during the year for 27 (35 %) of 78 SHTW patients–for 17 on one occasion, and for 10 on more than one occasion (namely, twice in five, three times in three, four

TABLE 8
RESPONSE TO TREATMENT RELATED TO VARIOUS FACTORS ON ADMISSION TO TREATMENT [a]

Condition on admission to treatment	SHTW series		PH series	
	Total patients	Unfavourable response [b]	Total patients	Unfavourable response [b]
Extent of cavitation :				
Extensive	18	1	9	3
Moderate	26	3	29	6
Slight	26	0	25	1
Nil	2	0	3	0
Total *extent of disease :*				
Gross or extensive	21	2	20	8
Moderate or limited	46	2	45	2
Slight or trivial	5	0	*1*	0
Number of long zones :				
6, 5 or 4	36	2	34	10
3, 2 or 1	36	2	32	0
Bacterial content of sputum : [c]				
3-plus	10	1	5	0
2-plus	38	2	42	7
1-plus	17	1	13	3
Negative	7	0	6	0
Total patients	72	4	66	10

[a] Excluding patients who died of a non-tuberculous condition or had their prescribed chemotherapy terminated on account of toxicity or non-cooperation.
[b] For definition, see text (page 258).
[c] Direct smear grade on first or only collection specimen.

times in one and five times in one). Of the 10 patients who complained more than once, five had their dosage of streptomycin reduced to approximately 15 mg/kg body-weight, three of them for the rest of the year and two for only two and four weeks, respectively ; giddiness was complained of subsequently by three on only one occasion and by one on two occasions. Of the 17 patients who complained on a single occasion, five did so in the first three months, one in the second three months and 11 in the last six months. Of the 10 patients who complained on more than one occasion, the numbers who complained for the first time in the corresponding periods were four, four and two, respectively.

It is uncertain how often the complaints of giddiness were due to streptomycin toxicity as giddiness was also noted in eight (11 %) of the 70 PH patients even though it was less likely to have been recorded in them because it is not a recognized toxic manifestation of therapy with PAS plus isoniazid.

Hypersensitivity reactions to streptomycin were not encountered.

Isoniazid

Two (3 %) of the 78 SHTW patients and none of the 70 PH patients developed toxic reactions attributed to isoniazid. One patient had convulsions a few hours after the administration of

chemotherapy on two occasions (in the first and sixth weeks) ; they did not recur after pyridoxine, in a dosage of 6 mg twice weekly, was added to the patient's chemotherapy. The other patient developed peripheral neuropathy in the second month ; pyridoxine in a dosage of 6 mg twice weekly was added to the patient's chemotherapy with subsequent improvement. In both, the SHTW regimen was continued.

PAS

Three (4 %) of the 70 patients developed cutaneous hypersensitivity reactions to PAS, one in the first and two in the second month of treatment. Treatment had to be terminated in these patients in the first, fifth and ninth month, respectively, as the reactions could not be controlled in spite of attempts at desensitization under cover of corticosteroids.

As in earlier studies (Tuberculosis Chemotherapy Centre, 1959, 1960), gastrointestinal side-effects were unimportant and did not make it necessary to reduce the dosage of the drug in any patient.

In summary, giddiness was a common complaint and occurred in 35 % of the patients in the SHTW series and 11 % of the patients in the PH series ; however, a reduction of streptomycin dosage became necessary only in five SHTW patients. Isoniazid toxicity occurred in two SHTW patients and was treated successfully with a small dosage of pyridoxine. PAS hypersensitivity led to termination of chemotherapy in three PH patients.

UNCOOPERATIVE PATIENTS

Seven SHTW patients became uncooperative and stopped treatment, two in the third, one in the seventh, two in the eighth, one in the ninth and one in the tenth month. One, who had severe asthma, stopped because he was disappointed that his treatment was not controlling his asthmatic attacks; a second, who was an alcoholic, spent a term in prison and refused to attend the Centre after his release. Four others (including one alcoholic) complained of giddiness (on four, two, one and one occasions), the dosage of streptomycin being reduced in one. In these four patients streptomycin toxicity may have played a part in the patient's stopping treatment. The seventh patient stopped treatment for no apparent reason. One PH patient, who was an alcoholic, became uncooperative and stopped treatment in the eighth month.

HOSPITAL AND SANATORIUM ADMISSIONS

Two patients were admitted to sanatorium on account of pulmonary tuberculosis. One (SHTW) died of tuberculosis (in the sixth month) the day after admission and the other (PH) was an in-patient for 43 weeks for a pyopneumothorax with a bronchopleural fistula. In-patient treatment for non-tuberculous conditions was given to four SHTW patients for three, five, five and 27 weeks, and five PH patients for one, two, two, five and eight weeks.

VIII. REGULARITY OF ADMINISTRATION OF CHEMOTHERAPY

MISSED OR LATE ATTENDANCES IN THE SHTW SERIES

As stated earlier (page 249), it was a rule that patients should attend the Centre for their treatment. However, chemotherapy was given in the home on 148 occasions to 13 patients who were too ill to attend the Centre. To discourage the rest of the patients from defaulting deliberately in order to obtain treatment at home, chemotherapy was very seldom given to them in the home-namely, to three patients on a total of four occasions.

During the year each patient was scheduled to attend on 104 occasions for the supervised administration of chemotherapy. Attendances which were early by one or more days did not cause any extra work for the Centre's staff but attendances late by one or more days or missed altogether entailed one, two or three additional home visits.

An analysis was undertaken to study the regularity with which the patients attended the Centre for treatment. In brief, 6335 (87.0 %) of the 7279 scheduled attendances were made on the appointed day or earlier, on 4.7 % of occasions the patients attended one to three days late, and 8.3 % of the attendances were missed altogether. The detailed findings are presented in Table 9.

TABLE 9

REGULARITY OF ADMINISTRATION OF CHEMOTHERAPY IN SHTW PATIENTS AS ASSESSED BY MISSED OR LATE ATTENDANCES FOR TREATMENT

Percentage of attendances missed [a]	Patients [b]		Of these, number of patients who attended late
	No.	%	
0	7	*10*	**2**
1-4	25	*35*	**18**
5-9	19	*27*	**17**
10-14	6	*8*	**6**
15-24	9	*13*	**9**
25 or more	5	*7*	**5**
Total	71	*100*	57

[a] Excluding periods in hospital or sanatorium. For patients who died of tuberculosis or had their chemotherapy terminated on account of deterioration, the percentage is based on attendances up to (but not including the month of death or termination.

[b] Excluding one patient who died within 24 hours of admission and seven patients who had their prescribed chemotherapy terminated on account of non-cooperation.

It will be seen that seven (10 %) patients received all the prescribed chemotherapy during the year, 44 (62 %) patients failed to receive chemotherapy on 1-9 % of occasions, 15 (21 %) on 10-24 % of occasions and five (7 %) on 25 % or more of occasions.

Patients who were frequently non-attenders also frequently attended late by one day or more; thus, of seven patients who never missed an attendance, only two attended late on one or more occasions during the year, as compared with 18 of 25 who missed 1-4 % of attendances, 17 of 19 who missed 5-9 % and all of 20 who missed 10 % or more.

An analysis (not tabulated here) was undertaken to study whether there were any differences in the regularity of attendance during the course of the year. In the first three months of treatment, 46 % of 71 patients attended on the appointed day or earlier on all occasions, as compared with 23 % of 69 in the second three months, 28 % of 69 in the third, and 22 % of 68 in the last three months of the year of treatment. The proportions of patients who attended after the appointed day or did not attend at all on 25 % or more of the occasions during each three-monthly period were 4 %, 13 %, 19 % and 31 %, respectively.Thus there was an association between irregularity and length of treatment.

Seven patients, who became so uncooperative that they discharged themselves from treatment during the year, have been excluded from the above analyses. Of these, six missed 15 % or more of their scheduled attendances as compared with 14 of the 71 patients who remained under treatment, a difference which attains statistical significance ($P<0.01$). Thus, the particularly uncooperative patients were more irregular even before they stopped treatment.

SUPERVISION OF THE ADMINISTRATION OF ISONIAZID IN THE SHTW SERIES

Since it is known that pills may be expectorated even when given under supervision (Gilroy, 1952), it was desirable to obtain confirmation that isoniazid had been swallowed. For this purpose urine specimens obtained at home visits were tested for isoniazid (Gangadharam et al., 1958), using a test for which a negative result indicates, in a large proportion of patients, that no drug has been taken for at least 24 hours previously (Tuberculosis Chemotherapy Centre, 1963a). Specimens of urine collected from 28 SHTW patients 24 hours after a dose all gave positive results ; 15 of 16 further specimens collected at 24 hours from nine of these patients were also positive.

URINE TEST RESULTS IN THE PH SERIES

The regularity of self-administration of chemotherapy in the PH series was studied by considering the results of tests for PAS on urine specimens obtained at the weekly routine visits to the Centre. A negative result means that no PAS has been taken for 14 hours, so that the equivalent of at least a day's supply of medicine has, in all probability, been missed (Tuberculosis Chemotherapy Centre, 1960). It is likely that the degree of irregularity has been underestimated by using the results of clinic urine specimens, as the fact that a visit was due may have acted as a reminder to take the drug ; also, many patients knew that the specimens were tested for drug. (The results of tests on urine specimens at surprise visits to the home, though useful for supervision, have not been presented because certain factors could have

TABLE 10

REGULARITY OF SELF-ADMINISTRATION OF CHEMOTHERAPY IN PH PATIENTS AS ASSESSED BY TESTS ON CLINIC URINE SPECIMENS

Percentage of urine test results which were negative [a]	Patients [b]	
	No.	%
0	19	*28*
1-4	15	*22*
5-9	6	*9*
10-14	7	*10*
15-24	8	*12*
25-34	5	*7*
35 or more	8	*12*
Total	68	*100*

[a] Excluding periods in hospital or sanatorium. For patients who died or had their chemotherapy terminated on account of deterioration or toxicity, the percentage is based on the test results up to (but not including) 'the month of death or termination.

[b] Excluding one patient who had his prescribed chemotherapy terminated on account of toxicity and one patient who died of tuberculosis. both in the first month. and one patient who had his chemotherapy terminated on account of non-**cooperation.**

introduced bias into the assessment of regularity of drug-taking from such visits : first, the seriously ill patients were more likely to be found at home and, secondly, more frequent visits were often requested by the doctors for patients whose test results were negative.)

The average number of clinic urine tests per month per patient was 3.8. From Table 10 it will be seen that 28 % of 68 patients had no negative urine test results during the year, 31 % had 1-9 % negative results, 22 % had 10-24 %, and 19 % had 25 % or more negative results. The proportions of patients who had no negative test results during the four three-monthly periods were 54 % of 68, 66 % of 67, 60 % of 65 and 47 % of 64, respectively, the corresponding proportions of those who had negative test results on 25 % or more occasions being 16 %, 19 %, 18 % and 23 %, respectively. Thus there was no evidence of an association between duration of treatment and irregularity. The PH patient who became uncooperative and discontinued treatment had negative results for 15 % of specimens.

RESPONSE TO TREATMENT IN RELATION TO THE REGULARITY OF ADMINISTRATION OF CHEMOTHERAPY

SHTW series

Of the three SHTW patients who survived more than one month and had an unfavourable response, one, who had his chemotherapy terminated owing to deterioration in the eleventh month, attended on all of 96 occasions ; the second, who had active disease at one year, missed eight of 104 attendances, and the third, who died in the fifth month, missed one of 36 attendances. Of the 68 patients who had a favourable response, seven (10 %) missed 20 % or more of their scheduled attendances.

PH series

Analyses (not presented here) showed that there was no association between irregularity in self-administration of chemotherapy, either in the first three months or over the whole year, and response to treatment ; thus three (16 %) of 19 patients who had no negative urine test results during the year had an unfavourable response, as compared with two (10 %) of 21 with 1-9 % negative urine test results, and four (16 %) of 25 patients with 10 % or more negative urine test results.

IX. PATIENTS WITH RESISTANT ORGANISMS ON ADMISSION TO STUDY

Fifteen patients (four SHTW, 11 PH), all of whom received the allocated regimen, were exeluded from the main analysis because they had resistant organisms on admission to the study (page 252), seven to isoniazid, five to streptomycin and three to both drugs. These patients were interrogated again during the course of treatment, as their relations with the Centre's staff became more firmly established, to discover whether they had concealed having received previous chemotherapy ; four (three isoniazid-resistant, one resistant to both drugs) admitted to previous chemotherapy. It was presumed that the remaining 11 patients (four isoniazid-resistant,

five streptomycin-resistant and two isoniazid- and streptomycin-resistant) had been infected with resistant organisms.

All four patients (one SHTW, three PH) with acquired isoniazid resistance had an unfavourable response to treatment. The detailed results of sensitivity tests to isoniazid and streptomycin on two pre-study cultures are set out for these patients in the upper part of Table 11.

Of the six patients (two SHTW, four PH) with primary isoniazid resistance, two (one SHTW, one PH) had a favourable response to treatment and the remaining four had an unfavourable response. There was one SHTW patient with primary streptomycin-resistant but isoniazid-sensitive strains, and he had an unfavourable response to treatment. The detailed results of pretreatment sensitivity tests are set out for these seven patients in the lower part of Table 11.

According to the definitions given on page 251, only two patients (both SHTW) yielded organisms resistant to PAS on admission to treatment. These patients were included in the main analysis. A less stringent definition of resistance, similar to that adopted in other studies (East African/British Medical Research Council, 1959, 1960a, 1960b, 1963), is as follows: an RR of 8 or more on one pretreatment culture, or an RR of 4 followed by an RR of 4 or more in a repeat test on the same culture, or an RR of 4 on both cultures irrespective of the results of repeat tests. Using this definition, the organisms from 17 patients (13 SHTW, four PH) would be considered resistant. (Of these, only one patient (SHTW), whose organisms were also resistant to isoniazid on admission, has been excluded from the main analysis.) For reasons to be reported elsewhere, this definition probably overestimates the prevalence of PAS resistance. Of the four PH patients with pretreatment PAS resistance (as defined above), three had a favourable response and the fourth had bacteriologically active disease at 12 months.

TABLE 11

RESPONSE TO TREATMENT RELATED TO SENSITIVITY TEST RESULTS ON ADMISSION IN PATIENTS WITH ACQUIRED OR PRIMARY RESISTANCE TO ISONIAZID AND/OR STREPTOMYCIN

	Serial number	Treatment	Sensitivity on admission						Response to treatment
			Isoniazid			Streptomycin			
			MIC[a] (μg/ml) on two cultures		Classification	Resistance ratio on two cultures		Classification	
Acquired resistance	97	SHTW	50	>50	Resistant	0.5	0.5	Sensitive	Unfavourable [b]
	32	PH	>50	>50	Resistant	2	1	Sensitive	Unfavourable
	41	PH	50	50	Resistant	0.5	1	Sensitive	Unfavourable
	163	PH	5	5	Resistant	8	4,1	Resistant	Unfavourable
Primary resistance	94	SHTW	>50	>50	Resistant	0.5	1	Sensitive	Unfavourable
	33	SHTW	5	50	Resistant	1	0.5	Sensitive	Favourable [c]
	124	PH	131	1,1	Resistant	1	0.5	Sensitive	Unfavourable
	141	PH	>50	0.05	Resistant	0.5	2	Sensitive	Unfavourable
	63	PH	1,1	1,1	Resistant	8	8	Resistant	Unfavourable
	87	PH	50	50	Resistant	>8	>8	Resistant	Favourable
	113	SHTW	1,0.2	0.05	Sensitive	4,2	4,2	Resistant	Unfavourable

[a] Minimal inhibitory concentration.
[b] Tuberculous death or bacteriologically active disease at 12 months including change of chemotherapy for persistent sputum positivity.
[c] Bacteriologically quiescent disease at 12 months.

X. DISCUSSION

In the chemotherapy of pulmonary tuberculosis it is standard practice to give two or more drugs in one or more doses daily; in out-patients the drugs are normally self-administered and irregularity of drug taking, sometimes of a serious degree, is common. Supervised administration of the drugs could overcome this disadvantage but this would be practicable in developing countries only if treatment could be given intermittently–say, twice a week or less frequently. Such intermittent chemotherapy might have additional advantages over daily treatment in being more economical and probably less toxic (and therefore more acceptable) to the patients.

Several forms of intermittent chemotherapy in the treatment of pulmonary tuberculosis have been reported in the literature. Regimens consisting of one drug (usually isoniazid or PAS) given daily plus another (usually streptomycin) given intermittently on two or three days in a week are no longer regarded as adequate by most authorities (Medical Research Council, 1955 ; Crofton, 1960 ; McDermott, 1960 ; Canetti, 1962). Regimens in which both drugs are given intermittently have been used as continuation treatment following a period of daily drug therapy ; thus, intermittent streptomycin plus isoniazid, both drugs being given together every other day, has been used with good results after an initial period of one to three months of daily combined chemotherapy by Mackay-Dick (1954, 1959), Hutton et al. (1956), Todd et al. (1956) and Eade et al. (1959). There have, in addition, been a few reports of intermittent chemotherapy *from the start of treatment.* Frimodt-Møller et al. (1953) in a controlled trial compared isoniazid alone every fourth day with daily isoniazid given as a quarter of the intermittent dosage, and found similar radiographic responses in the two series at 12 weeks. Holmes et al. (1962) treated 29 patients with far advanced disease with a very large dose of isoniazid alone given once a week for periods of up to three months, but only two patients became culture negative. Schaefer (1955) reported on 15 American-Indian patients treated with an intramuscular injection of streptomyclidine isonicotinyl hydrazide-sulfate every three days. Of nine patients who were culture positive on admission, three were culture negative at four months, while at eight months, all of five patients examined were culture negative. Katz et al. (1954) and Chambers et al. (1955) reported on a small group of patients treated with 2 g of streptomycin plus 500 mg of isoniazid twice weekly. They concluded that the response in these patients was inferior to earlier findingswith daily isoniazid plus twice-weekly streptomycin. Tyrrell (1956) gave newly diagnosed patients 1 g of streptomycin plus 400 mg of isoniazid on the same day, twice weekly, half being treated in hospital and half as ambulatory out-patients. At six months sputum conversion had occurred in 78% of 45 in-patients and in 80 % of 46 out-patients.

EFFICACY

The present report confirms the conclusions based on interim findings which were published in a preliminary communication (Tuberculosis Chemotherapy Centre, 1963c). Thus, streptomycin plus high-dosage isoniazid, both drugs being given together twice a week under supervision (SHTW regimen), has proved to be successful in the treatment of newly-diagnosed, far advanced, bacteriologically positive pulmonary tuberculosis, and at least as effective as a standard oral two-drug regimen of PAS plus isoniazid prescribed for self-administration daily (PH regimen). Thus, at one year, 94 % of 72 SHTW patients compared with 85 % of 66 PH patients had bacteriologically quiescent disease (including disease of bacteriologically doubtful status) and 92 % and 94 %, respectively, showed moderate or greater radiographic improvement.

It is of interest to compare the findings in this study with those obtained by the Medical Research Council (1955). In the latter, streptomycin was given intermittently in a dose of 1 g twice a week (about 18 mg/kg body-weight) and isoniazid daily in a dosage of 200 mg. Thus, the total weekly dosage of isoniazid and streptomycin was approximately the same in both studies although the individual dose in the present study was much higher in the case of isoniazid (650 mg) and, because of the light weight of the Indian patients, relatively higher for streptomycin (27 mg/kg body-weight). Considering the results at three months, 98 (74 %) of 132 patients in the Medical Research

Council study yielded a negative culture compared with 62 (82 %) of 76 SHTW patients in the present study. Further, 12 (9 %) patients in the former compared with only three (4 %) in the latter developed resistance to isoniazid by this time. The better results in the present study may be due to the high dose of isoniazid, and perhaps the relatively high dosage of streptomycin, rather than to the effect of giving *both* drugs together intermittently. The findings of Gangadharam et al. (1961b) that high peak serum concentrations of isoniazid play a more important role in the response to treatment than the maintenance of a continuous inhibitory level of isoniazid lend support to such an inference.

TOXICITY

Isoniazid toxicity occurred in two of 78 SHTW patients (convulsions in one and peripheral neuropathy in the other) as compared with none of 70 PH patients. Both patients were treated successfully with 6 mg of pyridoxine twice weekly without reducing the dosage of isoniazid.

With regard to toxic reactions to the drug used with isoniazid, spontaneous complaints of giddiness were made by 27 (35 %) of 78 SHTW patients ; the giddiness, which usually occurred half an hour to two hours after the injection, was mild and of short duration. Further, it is unlikely that the complaints were always due to streptomycin as similar complaints were made by eight (11 %) of the 70 PH patients, in whom they were less likely to have been recorded. None of the SHTW patients had chemotherapy terminated on account of toxicity, but for five who complained of giddiness, the dosage of streptomycin was reduced to approximately 15 mg/kg body-weight, for three of them for the rest of the year and for two for a short period only. In contrast, three (4 %) of the 70 PH patients had chemotherapy terminated on account of hypersensitivity reactions to PAS ; other manifestations of PAS toxicity among patients in this series were unimportant.

It is of interest to compare the incidence of isoniazid toxicity in this study with that in patients in our earlier studies who did not receive any effective prophylactic supplement. Of 60 patients in the earlier studies who received approximately 14 mg/kg body-weight of isoniazid daily, 18 (30 %) developed isoniazid toxicity (Tuberculosis Chemotherapy Centre, 1963b) as compared with only two (3 %) of those who received the same dosage *twice weekly* in the present study; on the other hand, only one of 440 patients who received isoniazid (either alone or in combination with sodium PAS) in a larger total weekly dosage than in the present study–namely, 4 to 6 mg/kg *a day* (Tuberculosis Chemotherapy Centre, 1959, 1960 and the present report)–developed toxicity. There is a similar finding in respect of streptomycin toxicity ; thus, of 69 patients who received a uniform dosage of 1 g of streptomycin *daily* in an earlier study (Velu et al., 1964), 24 (35 %) had to have the dosage reduced to approximately 15 mg/kg body-weight as compared with five (6 %) of 78 patients who received the same dosage *twice weekly* in the present study, and four (6 %) had to have their treatment terminated on account of toxicity in the earlier study as compared with none in the present study. Thus, there has apparently been a considerable reduction in the incidence of toxic reactions, both to isoniazid and to streptomycin, by reducing the frequency of drug-administration from daily to twice weekly (keeping the dose the same).

It is likely that even the small amount of isoniazid toxicity occurring with the intermittent regimen can be prevented by giving 6 mg of pyridoxine twice weekly, since it has been shown that, when given daily in this dosage with 14 mg/kg of isoniazid daily, pyridoxine prevents. peripheral neuropathy (Tuberculosis Chemotherapy Centre, 1963b) ; furthermore, both patients who showed isoniazid toxicity in the present study responded to 6 mg of pyridoxine given twice weekly. The interpretation of the findings on streptomycin toxicity is less clear and special attention is therefore being paid in a current study to the assessment and prevention of such toxicity.

CO-OPERATION

With regard to the co-operation obtained in the two series, seven SHTW patients became so uncooperative as to stop treatment against medical advice. (In four of these, streptomycin toxicity might have been a contributory factor.) As might be expected, these patients were more irregular, even before they stopped treatment, than the 71 who remained on their prescribed chemotherapy. The latter patients attended on the appointed day or earlier on 87 % of the occasions, were late

by one day or more on 5 % of the occasions and missed an attendance altogether on 8 % of the occasions. The late and missed attendances, which caused extra work for the Centre's staff, became more frequent towards the end of treatment ; thus the proportion of patients who, on 25 % or more of the occasions, attended after the appointed day or did not attend at all in each of the four quarters of the year were 4 %, 13%, 19% and 31 %, respectively. Of the PH patients, only one became so uncooperative as to stop treatment; however, 72 % of the remainder were found to be irregular in taking their drugs on one or more occasions, as assessed by urine test results.

It should be remembered that the SHTW patients had to attend the Centre twice a week and receive an injection of streptomycin; thus they came under the special attention of the Centre's staff every time they missed a scheduled injection ; on the other hand, the PH patients had to attend only *once* a week for a supply of the drug, and it would thus have been easy for them to omit doses without the Centre's staff necessarily becoming aware of it. It is therefore difficult to compare the acceptability of the supervised intermittent regimen and the unsupervised daily regimen ; however, despite the irregularities observed, both regimens proved sufficiently robust to achieve high rates of therapeutic success.

CONCLUSION

Summarizing the findings, the SHTW regimen was therapeutically effective ; the incidence of temporary giddiness was rather high but this appeared to have no long-term importance or lasting effects, nor did it appear unduly to affect the co-operation of the patients. However, because of the uncertain significance of the complaints of giddiness in the present study, special attention is being paid in a current trial to investigating the side-effects and the acceptability of intermittent regimens which include streptomycin injections.

The success of intermittent chemotherapy in this trial has suggested a new method of treatment and possibly of the control of tuberculosis in developing countries – namely, changing the regimen from the present daily self-administration to intermittent and fully supervised administration. Although the twice-weekly regimen in this study has been found to be successful, a regimen with a smaller dosage of streptomycin and with longer intervals between the doses would offer still further advantages ; it might be not only less toxic and more acceptable to the patients, thus leading to their greater co-operation, but also more economical and easier to apply in mass treatment. Further studies along these lines are at present in progress at the Centre.

XI. SUMMARY

1. One hundred and sixty-five South Indian patients with pulmonary tuberculosis were allocated by a random procedure to ambulatory out-patient treatment with streptomycin plus isoniazid given together *under supervision twice weekly* (SHTW series, 83 patients) or to a standard unsupervised regimen of PAS plus isoniazid for daily self-administration (PH series, 82 patients).

2. The dosages of the drugs for patients weighing 100 lb (45.5 kg) were 1 g streptomycin plus 650 mg of isoniazid in a single dose for the SHTW regimen and 10 g of PAS (sodium) plus 200 mg of isoniazid in two divided doses for the PH regimen.

The mean initial dosages were :

SHTW series :

Streptomycin	27.0 mg/kg body-weight (range 18.2-53.7 mg/kg)
Isoniazid	13.9 mg/kg body-weight (range 12.5-16.1 mg/kg)

PH series :

PAS	0.22 g/kg body-weight (range 0.18-0.32 g/kg)
Isoniazid	4.4 mg/kg body-weight (range 3.7-6.3 mg/kg)

3. Fifteen patients (four SHTW, 11 PH) were excluded from the main analysis because they had resistant organisms on admission to the study. There remained 79 SHTW and 71 PH patients in the main analysis who *(a)* had, on admission, organisms sensitive to isoniazid and streptomycin,

(b) had had no previous chemotherapy apart from eight, who had had up to two weeks' chemotherapy and *(c)* followed the allocated regimen for 12 months, apart from minor variations, unless it was terminated owing to death, deterioration, toxicity or non-cooperation.

4. The clinical, radiographic and bacteriological condition of the patients in the two series was similar at the time of admission to treatment.

5. During the year there were four deaths, three (two SHTW, one PH) from pulmonary tuberculosis and one (PH) from a non-tuberculous condition ; serious radiographic deterioration necessitating termination of chemotherapy occurred in one patient in each series.

6. At one year, 94 % of 72 SHTW and 85 % of 66 PH patients had bacteriologically quiescent disease or disease of doubtful status. On including the seven uncooperative patients (six SHTW, one PH) whose response could be assessed, the proportions with favourable response became 92 % of 78 SHTW patients and 84 % of 67 PH patients.

7. At 12 months, single collection specimens of sputum were negative on culture for 94 % of 72 SHTW and 89 % of 66 PH patients.

8. The majority of patients showed at least moderate radiographic improvement over the year-namely, 92 % of 72 SHTW and 94 % of 66 PH patients. Cavitation disappeared in 24 % of 70 SHTW patients and 21 % of 63 PH patients.

9. Three (4 %) of 70 PH patients had their originally prescribed chemotherapy terminated because of cutaneous hypersensitivity reactions to PAS for which they could not be desensitized. None of 78 SHTW patients had chemotherapy terminated on account of toxicity although 17 (22%) spontaneously complained of giddiness on one occasion and 10 (13%) on two or more occasions during the year; five of the latter had their dosage of streptomycin reduced to 15 mg/kg bodyweight. Two (3 %) patients (both SHTW) developed toxicity to isoniazid, one having convulsions and the other peripheral neuropathy ; both responded to 6 mg of pyridoxine given with each dose of isoniazid.

10. Seven (9 %) SHTW patients and one (1 %) PH patient became very uncooperative and stopped treatment during the year ; this may have been due partly to toxic effects of streptomycin in four SHTW patients and to reasons unconnected with the regimens in three other patients (two SHTW, one PH) ; the remaining SHTW patient stopped treatment for no apparent reason.

11. Lesser degrees of non-cooperation, manifested by irregularities in taking the prescribed chemotherapy, occurred frequently in both series. Thus, only 10 % of the SHTW patients received all of their prescribed chemotherapy during the year, and as many as 28 % failed to receive their treatment on 10 % or more of the occasions. In the PH series, 72 % of the patients were irregular in taking their drug at some time or other, including 19 % who were irregular on at least a quarter of the occasions. However, there was no evidence that these irregularities were associated with unfavourable response to treatment.

12. The encouraging results of this trial suggest a possible change in the orientation of drug administration for tuberculosis in developing countries. Further investigations are in progress at the Centre.

ACKNOWLEDGEMENTS

It would not have been possible to complete the study reported here without the devoted work of the entire staff–clinical, laboratory, statistical, radiological, secretarial and administrative. The efforts of the public health nurses, health visitors, clinic nurses and social workers made a particularly important contribution to keeping the co-operation of the patients.

RÉSUMÉ

Poursuivant leurs études sur le traitement de la tuberculose, les chercheurs du Centre chimiothérapique de la Tuberculose, de Madras, exposent dans cet article les résultats de l'essai thérapeutique contrôlé, institué pour comparer les résultats de deux regimes thérapeutiques : le premier, bi-hebdomadaire et surveillé, le second, quotidien, non surveillé.

Dans le premier, 165 malades de I'Inde méridio-

nale atteints de tuberculose pulmonaire ont été répartis en deux groupes aléatoires: *a)* 83 malades recevant en dispensaire, deux fois par semaine et sous surveillance, 1 g de streptomycine et 650 mg d'isoniazide en une seule dose (regime SHTW) ; *b)* 82 malades absorbant eux-mêmes, et sans surveillance, 10 g de PAS et 200 mg d'isoniazide, répartis en deux doses (série PH). Ces dosages correspondaient à des sujets pesant 45,5 kg.

Quinze malades (4 SHTW et 11 PH) n'ont pas été pris en considération dans l'analyse générale, car, au debut du traitement, ils présentaient des bacilles résistants. Il restait donc 79 malades SHTW et 71 PH qui *a)* étaient infectés par des bacilles sensibles à l'isoniazide et à la streptomycine ; *b)* n'avaient pas subi de traitement chimiothérapique antérieur, si ce n'est 8 d'entre eux qui avaient reçu des médicaments pendant 2 semaines au plus ; *c)* ont poursuivi leur regime thérapeutique pendant 12 mois sauf quelques minimes derogations, à moins que la mort, l'aggravation, certains effets toxiques ou l'indiscipline, y ait mis prématurément terme. Les données cliniques, radiologiques et bactériologiques étaient à peu près les mêmes pour les malades des 2 séries.

Au cours de l'année, il y eut 4 décès, 3 par tuberculose pulmonaire (2 SHTW et 1 PH) et 1 (PH) d'une maladie non tuberculeuse ; une aggravation révélée par la radiographie nécessita l'interruption du traitement chez 1 malade de chaque série.

A la fin de l'année d'essai, 94 % des 72 malades SHTW et 85 % des 66 malades PH avaient atteint le stade de quiescence bactériologique ou d'état « incertain » de la maladie. Si l'on tient compte des 7 malades (6 SHTW, 1 PH) indisciplinés, on obtient une réponse favorable chez 92 % de 78 malades SHTW et 84 % de 67 malades PH.

Après 12 mois, les crachats, prélevés une seule fois, ont donné 94 % de cultures negatives (sur 72 SHTW) et 89 % (sur 66 PH).

La plupart des malades présentaient une amélioration radiologique fût-elle modeste, soit 92% des 72 SHTW et 94 % des 66 PH. Les cavités ont disparu chez 24 % des 70 malades SHTW et chez 21 % des malades PH qui présentaient des cavités au début de l'essai.

Chez 3 des 70 malades PH (4 %), on a dû interrompre l'administration de médicaments, par suite de l'hypersensibilité cutanée au PAS qui n'a pu être vaincue. Les effets toxiques n'ont pas entraîné d'interruption du traitement dans la série des 78 malades SHTW, bien que 17 d'entre eux (22 %) se plaignirent de vertiges une fois, et 10 (13 %) deux fois ou plus. Cinq de ces derniers reçurent une dose de streptomycine moindre, soit 15 mg par kg de poids corporel. Deux malades SHTW (3 %) présentèrent des phénomènes de toxicité due à l'isoniazide, l'un ayant des convulsions, l'autre une neuropathie périphérique ; les deux se remirent, à la suite de l'administration de 6 mg de pyridoxine avec chaque dose d'isoniazide.

Sept malades SHTW (9 %) et 1 malade PH (1 %), sérieusement indisciplines, interrompirent le traitement au cours de l'année, ce qui, chez 4 malades SHTW au moins pourrait s'expliquer par les effets toxiques de la streptomycine.

Des irrégularités dans la prise des médicaments furent fréquentes dans les deux series. C'est ainsi que 10 % seulement des malades SHTW ont accompli leur cure therapeutique complete, d'une année, et 28 % ont manqué leur tour une fois sur dix ou plus. Dans la série PH, 72 % des malades ont négligé la prise du medicament une fois ou l'autre ; 19 % une fois sur quatre. 11 ne semble pas que ces irrégularités puissent être mises en relation avec les réponses défavorables au traitement.

Les résultats encourageants de cet essai suggèrent une réorientation des principes d'administration des médicaments antituberculeux dans les pays en voie de développement. L'étude de la question se poursuit.

REFERENCES

Angel, J. H., Bhatia, A. L., Devadatta, S., Fox, W., Janardhanam, B., Radhakrishna, S., Ramakrishnan, C. V., Selkon, J. B., Stott, H. & Velu, S. (1963) *Tubercle (Lond.),* **44,** 215

Bloch, H. (1961) *Amer. Rev. resp. Dis.,* **84,** 824

Canetti, G. (1962) *Tubercle (Lond.),* **43,** 301

Chambers, J., Katz, S., McCormick, G., Gimble, A., Leonard, J., Schmidt, W. & Shea, J. (1955) In : *Transactions of the Fourteenth Conference on the Chemotherapy of Tuberculosis held February 7th to 10th, 1955, at Atlanta, Georgia,* Washington, D.C., US Government Printing Office, p. 107

Corper, H. J. & Cohn, M. L. (1947) *Science,* **106,** 446

Crofton, J. W. (1960) *Brit. med. J.,* **2,** 679

Eade, A. W. T., Harrison, G.K., Large, SE., Mackay-Dick, J., Reid, L.McA. & Riddell, R. W. (1959) *Thorax,* **14,** 104

East African/British Medical Research Council, Sulphone Investigation (1959) *Tubercle (Lond.),* **40,** 1

East African/British Medical Research Council, Isoniazid Investigation (1960a) *Tubercle (Lond.),* **41,** 83

East African/British Medical Research Council, Thiacetazone/Diphenylthiourea Investigation (1960b) *Tubercle (Lond.),* **41,** 399

East African/British Medical Research Council, Second Thiacetazone Investigation (1963) *Tubercle (Lond.),* **44,** 301

Fox, W. (1962) *In: Proceedings of the Sixteenth International Tuberculosis Conference, 1961,* Amsterdam, p. 307

Frimodt-Møller, J., Jesudian, K. T., Muthiah, T. S. & Barton, R. M. (1953) *Indian J. Tuberc.,* **1,** 23

Gangadharam, P. R. J., Bhatia, A. L., Radhakrishna, S. & Selkon, J. B. (1961a) *Bull. Wld Hlth Org.,* **25,** 765

Gangadharam, P. R. J., Devadatta, S., Fox, W., Narayanan Nair, C. & Selkon, J. B. (1961b) *Bull. Wld Hlth Org.,* **25,** 793

Gangadharam, P. R. J., Mitchison, D.A., Subbaiah, T. V. & Short, E. I. (1958) *Tubercle (Lond.),* **39,** 191

Gilroy, A. B. (1952) *Ann. trop. Med. Parasit.,* **40,** 333

Grumbach, F., Rist, N. & Riebel, J. (1952) *Ann. Inst. Pasteur,* **83,** 397

Holmes, C. X., Martin, G. E., Fetterhoff, K. I. & Kaiser, J. C. (1962) *Amer. Rev. resp. Dis.,* **86,** 87

Hutton, P. W., Lutalo, Y. K., Williams, A. W., Tonkin, I. M. & Fox, W. *(19.56) Tubercle (Lond.),* **37,** 151

Jensen, K. A. (1955) *Bull. int. Un. Tuberc.,* **25,** 89

Katz, S., McCormick, G., Leon, A. de, Gruver, R., Stanton, J., Bakir, F. & Marshall, E. (1954) In : *Transactions of the Thirteenth Conference on the Chemotherapy of Tuberculosis held February 8th to 11th, 1954, at St. Louis, Missouri,* Washington, D.C., US Government Printing Office, p. 355

McDermott, W. (1960) *Bull. Wld HIth Org.,* **23,** 427

Mackay-Dick, J. (1954) *Lancet,* **2,** 44

Mackay-Dick, J. (1959) *Brit. med. J.,* **2,** 100

Medical Research Council (1955) *Brit. med. J.,* **1,** 435

Palmer, C. E., Ferebee, S. H. & Hopwood, L. (1956) *Amer. Rev. Tuberc.,* **74,** 917

Schaefer, J. H. (1955) *Antibiotic Med.,* **1,** 153

Selkon, J. B., Subbaiah, T. V., Bhatia, A. L., Radhakrishna, S. & Mitchison, D. A. 1960) *Bull. Wld Hlth Org.,* **23,** 599

Simpson. J. H. (1956) *Tubercle (Lond.),* **37,** 333

Stradling, P. (1957) *Proc. roy. Soc. Med.,* **50,** 342

Stradling, P. & Poole, G. W. (1958) *Lancet,* **2,** 1066

Todd, G., Teare, D. & Gordon, W. I. (1956) *Lancet,* **2,** 1

Tuberculosis Chemotherapy Centre (1959) *Bull. Wld Hlth Org.,* **21,** 51

Tuberculosis Chemotherapy Centre (1960) *Bull. Wld Hlth Org.,* **23,** 535

Tuberculosis Chemotherapy Centre (1963a) *Bull. Wld Hlth Org.,* **28,** 455

Tuberculosis Chemotherapy Centre (1963b) *Bull. Wld Hlth Org.,* **29,** 457

Tuberculosis Chemotherapy Centre (1963c) *Lancet,* **1,** 1078

Tyrrell, W. F. (1956) *Lancet,* **1,** 821

Velu, S., Andrews, R. H., Angel, J. H., Devadatta, S., Fox, W., Gangadharam, P. R. J., Narayana, A. S. L., Ramakrishnan, C. V., Selkon, J. B. & Somasundaram, P. R. (1961a) *Bull. Wld Hlth Org.,* **25,** 409

Velu, S., Andrews, R. H., Angel, J. H., Devadatta, S., Fox, W., Jacob, P. G., Narayanan Nair, C. & Ramakrishnan, C. V. (1961b) *Tubercle (Lond.),* **42,** 136

Velu, S., Andrews, R. H., Devadatta, S., Fox, W., Radhakrishna, S., Ramakrishnan, C. V., Selkon, J. B., Somasundaram, P. R. & Subbaiah, T. V. (1960) *Bull. Wld Hlth Org.,* **23,** 511

Velu, S., Dawson, J. J. Y., Devadatta, S., Fox, W., Kulkarni, K. G., Mohan, K., Ramakrishnan, C. V. & Stott, H. (1964) *Tubercle (Lond.),* **45,** 144

PRINTED IN SWITZERLAND