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Isoniazid plus Thioacetazone * compared with Two Regimens of Isoniazid plus PAS in the Domiciliary Treatment of Pulmonary Tuberculosis in South Indian Patients

TUBERCULOSIS CHEMOTHERAPY CENTRE, MADRAS [1]

Previous reports from the Tuberculosis Chemotherapy Centre, Madras, have established that ambulatory treatment of pulmonary tuberculosis with a standard daily regimen of isoniazid plus PAS for one year yields satisfactory results. However, this regimen may be unsuitable for large-scale use in many developing countries, because PAS is expensive, bulky and unpleasant to take, and has poor keeping qualities, especially in tropical countries. It might be possible to overcome these disadvantages, by substituting for the PAS a drug which is equally effective but less expensive and more acceptable, or by reducing the daily dosage of PAS and the period for which it is prescribed.

This paper presents the results over a II-month period of a controlled comparison of (a) *the standard regimen of isoniazid (average 4.5 mg/kg body-weight) plus sodium PAS (average 0.22 g/kg), daily in two divided doses ;* (b) *a regimen of isoniazid (average 6.9 mg/kg) plus thioacetazone (average 3.4 mg/kg), daily in one dose ; and* (c) *a 2-phase regimen of isoniazid (average 5.5 mg/kg) plus sodium PAS (average 0.17 g/kg), daily in one dose for 6 months, followed by isoniazid alone (average 6.8 mg/kg), daily in one dose for the second 6 months. The regimen of isoniazid plus thioacetazone was found to be therapeutically as effective as the standard regimen of isoniazid plus PAS ; however, it was associated with a higher incidence of minor side-effects, and three cases of exfoliative dermatitis. The 2-phase regimen of isoniazid plus PAS followed by isoniazid alone was less effective.*

These findings are encouraging for the large-scale use in developing countries of the relatively inexpensive regimen of isoniazid plus thioacetazone ; however, any such step should be preceded by carefully planned studies to investigate, under local conditions, the toxicity and the efficacy of the regimen.

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* Thioacetazone is the recommended international non-proprietary name (see World Health Organization, 1962) for 4'-formylacetanilide thiosemicarbazone (thiacetazone, Tb I-698).

[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 (BMRC). 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), and Dr S. P. Tripathy (ICMR), Bacteriologists; Dr P. R. J. Gangadharam (ICMR), Dr K. V. Nageswara Rao (ICMR) and Mr C. Narayanan Nair (ICMR), Assistant Bacteriologists; Dr D. V. Krishnamurthy (ICMR), Biochemist; Mr C. V. Jacob (ICMR), Miss S. Joseph (ICMR), Mrs S. Subbammal (ICMR) and Mr P. Venkataraman (ICMR), Laboratory Research Assistants; Mr P. Hinchliffe (WHO), Laboratory Technician; Dr S. Radhakrishna (Madras Government), Senior Statistician; Mr K. Ramachandran (ICMR) and Mr P. R. Somasundaram (ICMR), Statisticians; and Mr B. Janardhanam (ICMR) and Mr A. S. L. Narayana (ICMR), Senior Assistant Statisticians.

The research of the Centre is guided by a Project Committee consisting of three ICMR representatives (Dr P. V. Benjamin, Convener, 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, succeeded by Col. B. L. Taneja in August 1964), the Director of Medical Services, Madras State (Dr A. B. Marikar), a WHO representative (appointed for each meeting), a BMRC representative (appointed for each meeting), the Director of the Centre (Dr N. K. Menon) and the Senior Medical Officer

[continued overleaf]

I. INTRODUCTION

In many developing countries, the resources available for the control of tuberculosis are very limited (Canetti, 1962; Fox, 1964). Therefore, the development of inexpensive but effective, acceptable and non-toxic drug regimens for mass treatment of patients is of great importance. Chemotherapy with a daily regimen of isoniazid plus p-aminosalicylic acid (PAS) is too expensive for large-scale use in many countries; furthermore, PAS is bulky and unpleasant to take, and its keeping properties, especially in tropical countries, are not good. Isoniazid alone is inexpensive and small in bulk, but is not sufficiently effective even in its optimal therapeutic dosage of 8-9 mg/kg given in one daily dose (Tuberculosis Chemotherapy Centre, Madras, 1960, 1963b).

Preliminary results in 1961 from East Africa suggested that an inexpensive regimen of 300 mg of isoniazid plus 150 mg of thioacetazone[1] in a single daily dose was therapeutically as effective and of the same order of toxicity as isoniazid plus PAS (J. Heffeman, personal communication ; subsequently published as East African/British Medical Research Council Second Thiacetazone Investigation, 1963). It was therefore decided to compare the value of this regimen in India with a standard daily regimen of 200 mg of isoniazid plus 10 g of sodium PAS for one year.

Since the latter regimen is expensive, largely owing to the PAS, a reduction in the daily dosage of sodium PAS from 10 g in two divided doses to 6 g in one dose was also investigated. It was decided to give the total daily dosage of 6 g in one rather than two doses for the following reasons. First, Bridge & Carr (1958) had reported that, in combination with isoniazid, 7 g of sodium or calcium PAS in a single daily dose was as effective as, and better tolerated than, 9-12 g given in three or four doses a day. Secondly, Karlson & Carr (1958) had demonstrated that a single daily dose of PAS was as effective in guinea-pigs as the same dosage or twice the dosage given daily in two doses. Finally, there is evidence that a single high daily dose of PAS results in higher blood concentrations of free PAS than repeated small doses, because a larger margin of free PAS remains after acetylation (Lehmann, 1959; Wagner, Fajkosova & Simane, 1960). In order to reduce the cost of the regimen further and since, when the study was planned, there was some evidence (subsequently published as Great Britain, Medical Research Council, 1962) that it is the early phase of chemotherapy that is crucial to the outcome of treatment, the reduced dosage of 6 g of sodium PAS was given with isoniazid for the first 6 months only, and was followed by isoniazid alone for the second 6 months of treatment.

II. PLAN AND CONDUCT OF THE STUDY

The great majority of patients came from the poorest sections of the population of Madras City and were admitted on the same criteria as in previous investigations (Tuberculosis Chemotherapy Centre, Madras, 1959, 1960, 1964); in particular, they were aged 12 years or more, had bacteriologically confirmed pulmonary tuberculosis, had either received no antituberculosis chemotherapy or had received it for not more than two weeks, and were judged to be co-operative, that is, prepared to have at least one year of domiciliary chemotherapy and willing to attend the Centre subsequently for follow-up investigations.

[Continued from previous page]

of the Centre (Dr Hugh Stott). The joint secretaries have been Mr. D Chakravarti, and Mr B. S. Verma succeeded by Mr V. S. Talwar in April 1962. The BMRC, acting through its Tuberculosis and Chest Diseases Research Unit, is responsible for advising WHO on the research in accordance with plans prepared by the Project Committee. Close contact is maintained between the Centre and Dr Wallace Fox (BMRC Tuberculosis and Chest Diseases Research Unit), Dr Ian Sutherland (BMRC Statistical Research Unit) and Dr D. A. Mitchison (BMRC Unit for Research on Drug Sensitivity in Tuberculosis). The analyses were undertaken at the Tuberculosis Chemotherapy Centre, Madras, and the report prepared by Dr H. Stott and Dr S. Radhakrishna in collaboration with the medical and statistical staff of the Centre.

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

[1] See footnote * on preceding page.

TABLE 1
MEAN DOSAGE AND RANGE OF ISONIAZID, SODIUM PAS AND THIOACETAZONE IN THE THREE SERIES

	Regimen	Isoniazid		Sodium PAS		Thioacetazone	
		Mean dosage	Range	Mean dosage	Range	Mean dosage	Range
At start of treatment	PH	4.5	3.7-6.6	0.22	0.19-0.33	–	–
	TH	6.9	4.6-8.0	–	–	3.4	2.3-4.0
	P_6H/H	5.5	4.0-9.2	0.17	0.12-0.28	–	–
At 6 months	P_6H/H	6.8	6.2-7.7	–			–

PRETREATMENT INVESTIGATIONS

The pretreatment investigations included among others :

1. A full clinical examination, assessment of the general clinical condition, the weight (lb), examination of the urine for albumin, sugar, bilirubin (Sobotka, Luisada-Opper & Reiner, 1953) and spectroscopic examination for urobilin (Harrison, 1957).

2. A full-plate postero-anterior radiograph of the chest.

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, PAS and thioacetazone on two cultures.

5. The estimation of the haemoglobin, packed cell volume (PCV) and a total and differential leucocyte count.

6. The determination of the whole blood L-aspartate: 2-oxoglutarate aminotransferase [1] (glutamic-oxaloacetic transaminase, GOT) level by the method of Yatzidis (1960) and of the serum GOT level by the procedure described by the Sigma Chemical Company, St. Louis, MO., USA (1961), for patients in two of the series, TH and P_6H/H (see below).

[1] 'Terminology recommended by the Commission on Enzymes of the International Union of Biochemistry (1961).

CHEMOTHERAPEUTIC REGIMENS

Three chemotherapeutic regimens were studied; the details of chemotherapy and the dosages for patients weighing 100 lb (45.4 kg) were as follows:

PH. Isoniazid 200 mg plus sodium PAS 10 g, daily for one year; the two drugs were prescribed together in cachets, four to be taken in the morning and four in the evening.

TH. Isoniazid 300 mg plus thioacetazone 150 mg, daily for one year; the two drugs were prescribed together as a single morning dose of six tablets.

P_6H/H. Isoniazid 200 mg plus sodium PAS 6 g, daily for the first 6 months; the two drugs were prescribed together as a single morning dose of four cachets. For the second 6 months, isoniazid alone in a dosage of 300 mg daily was prescribed as a single morning dose of six tablets.

The dosages of drugs were related to the patient's weight (see Appendix Table A) with the exception of the P_6H/H regimen in the first 6 months, when both isoniazid and PAS were prescribed in the uniform dosage mentioned above. Table 1 shows the mean dosages and the ranges at the start of treatment for each of the three treatment series and, in addition, at six months for the P_6H/H series.

ALLOCATION OF CHEMOTHERAPY

On the basis of the smear result of the first collection specimen of sputum, which was 3-plus, 2-plus,

l-plus or negative, the patients were classified into four categories. Treatment was allocated by the statisticians from four series of sealed envelopes (one for each category), based on random sampling numbers. Nobody had prior knowledge of the chemotherapy which any individual patient would receive. The first allocation was made on 15 January 1962 and the last on 21 March 1963.

GENERAL MANAGEMENT

The patients were treated at home with supervision of their progress at the Centre; they attended the Centre once a week to collect drugs, which were to be taken at home. Two visits, at approximately fortnightly intervals, were usually made by a health visitor to the patient's home every month. At one visit, which was unannounced, the stock of cachets or tablets was counted and a specimen of urine was collected, to check whether the patient was taking the drugs; the other visit, towards the end of each month of treatment, was to deliver a sputum specimen bottle.

If a patient was too ill to attend the Centre at the start of treatment, the drugs were delivered to the home, weekly. This was done for only a very few patients, and as soon as they improved sufficiently, which was usually by the end of one month of treatment, they were put on to the ordinary routine of clinic and home visits.

ASSESSMENTS OF PROGRESS

Assessments made at monthly intervals after the start of chemotherapy included (1) the weight, (2) a postero-anterior chest radiograph, (3) the examination of two collection specimens and one supervised spot specimen of sputum by smear and culture, and (4) tests of sensitivity to the allocated drugs on one positive culture. (However, in the case of PH and P_6H/H patients, tests of sensitivity to PAS were set up only on one 6-month culture and one 12-month culture.)

As anaemia, agranulocytosis and hepatitis may occur as toxic manifestations of thioacetazone (Hinshaw & McDermott, 1950; Bunn, 1950), the haemoglobin, PCV, total and differential leucocyte counts, and serum GOT estimations were performed at 3, 9 and 12 months in the TH series, and also in the P_6H/H series as a control. As a further control, the haematological examinations were undertaken at 12 months in the PH series. Whole blood GOT estimations were undertaken for pyridoxine deficiency (Krishnamurthy et al., in preparation) at 3, 9 and 12 months in the TH series, and in the P_6H/H series as a control, as a measure of isoniazid toxicity. Unless they were urgently required for the management of the patients, the results of these tests were withheld from the clinicians in order to avoid possible bias in the assessment and interpretation of clinical signs and symptoms. A specimen of urine was examined spectroscopically for urobilin each week for every patient.

In order to check the self-administration of drugs, a urine specimen was obtained at each weekly visit of the patient to the Centre and at the unannounced monthly visit to the home by the health visitor, The specimens from patients in the PH and P_6H/H series were tested for the presence of PAS by the ferric chloride test (Simpson, 1956), and those from patients in the TH and P_6H/H series for isoniazid by the combined naphthoquinone-mercuric chloride test (Gangadharam et al., 1958).

III. BACTERIOLOGICAL PROCEDURES

SMEARS, CULTURES AND SENSITIVITY TESTS

The methods used for examining sputum specimens are similar to those described previously (Tuberculosis Chemotherapy Centre, Madras, 1959). In brief, sputum smears were examined by fluorescence microscopy (Hoist, Mitchison & Radhakrishna, 1959) and were classified as 3-plus, 2-plus, l-plus or negative. Sputum specimens were cultured, after treatment with 4% NaOH for 20 minutes, on Löwenstein-Jensen medium which did not contain potato starch (Jensen, 1955). The cultures were examined weekly for 8-9 weeks and were reported as negative if no growth was present by that time.

Sensitivity tests were set up on Löwenstein-Jensen medium slopes containing the drug concentrations (expressed as the amounts added before

inspissation) set out below, as well as on a drug-free slope as control.

Drug	*Drug concentration (μg/ml)*	
	Test strain	*H37Rv*
Isoniazid	0.2, 1, 5, 50	0.025, 0.05, 0.1, 0.2, 1
Sodium PAS dihydrate	0.5, 1, 2, 4, 8, 16	0.125, 0.25, 0.5, 1, 2
Thioacetazone	0.25, 0.5, 1, 2, 4, 8, 16, 32	0.25, 0.5, 1, 2, 4, 8, 16, 32

A standard suspension of the culture (inoculum of approximately 0.01 mg (moist weight) of bacilli on each slope) was used in the isoniazid sensitivity test, a 1 : 10 dilution of this suspension for the PAS test as recommended by Selkon et al. (1960), and both the standard suspension and a 1:20 dilution for the thioacetazone test. (In the case of the thioacetazone test, the drug was dissolved in triethylene glycol before incorporation in the medium, the final concentration of triethylene glycol being 0.5% in all slopes; also, an additional drug-free slope containing 0.5 % triethylene glycol was set up.) The standard sensitive strain, H37Rv, was set up with every batch of tests. The results of all the tests were read at the end of four weeks of incubation at 37°C.

DEFINITIONS OF DRUG RESISTANCE

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

Isoniazid

Pretreatment :

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

(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.

During treatment : growth on 0.2 μg/ml.

PAS

Pretreatment and during treatment. A culture was defined as PAS-resistant if it yielded a resistance ratio (that is, minimal inhibitory concentration (MIC) of the test strain expressed as a proportion of the MIC of the standard sensitive strain, H37Rv) of 8 or more, or 4 followed by 4 or more in a repeat test.

Thioacetazone

On the available evidence, it has not been possible to define thioacetazone resistance (see page 495).

RATE OF INACTIVATION OF ISONIAZID

On admission to treatment, the rate of inactivation of isoniazid was determined for each patient by the microbiological assay method of Gangadharam et al. (1961).

IV. PATIENTS ADMITTED TO TREATMENT

In all, 240 patients were admitted to treatment, 79 to the PH, 80 to the TH and 81 to the P_6H/H series. Of these, 17 (6 PH, 2 TH, 9 P_6H/H) were subsequently found to have been excreting isoniazid-resistant organisms on admission, 1 (PH) had anomalous pretreatment sensitivity results and 2 (1 TH, 1 P_6H/H) had had anonymous mycobacterial infections. These 20 patients have been excluded from the main analysis and are considered in section IX. There remain 220 patients (72 PH, 77 TH, 71 P_6H/H) in the main analysis who, on admission to the study, *(a)* had organisms sensitive to isoniazid and *(b)* had had, so far as is known, no previous chemotherapy, apart from 6 patients (2 PH, 3 TH, 1 P_6H/H) who had had up to two weeks of chemotherapy.

No attempt has been made to exclude from the analysis patients with PAS- or thioacetazone-resistant strains at the start of treatment because of the difficulty of identifying such patients with certainty.

COMPARISON BETWEEN THE THREE SERIES ON ADMISSION TO TREATMENT

Of the 72 patients in the PH series, 71% were males, as compared with 68 % of 77 in the TH series

and 58 % of 71 in the P_6H/H series. More than half the patients were between the ages of 15 and 34—namely, 57 % of the PH, 55 % of the TH and 54 % of the P_6H/H series. The weight distributions of the patients were similar (Table 2); the mean weights were 84, 86 and 82 lb, respectively.

TABLE 2

CONDITION ON ADMISSION TO TREATMENT

Condition on admission to treatment	PH patients		TH patients		P_6H/H patients	
	No.	%	No.	%	No.	%
Weight (lb [a]):						
100 or more	9	*12*	12	*16*	11	*15*
80-99	38	*53*	36	*47*	32	*45*
Under 80	25	*35*	29	*38*	26	*39*
Extent of cavitation:						
Nil	26	*36*	33	*43*	24	*34*
Slight	14	*19*	12	*16*	15	*21*
Moderate	30	*42*	32	*42*	29	*41*
Extensive	2	*3*	0	*0*	3	*4*
Total extent of disease:						
Slight	1	*1*	2	*3*	3	*4*
Limited	36	*50*	36	*47*	36	*51*
Moderate	26	*36*	30	*39*	23	*32*
Extensive	7	*10*	8	*10*	6	*8*
Gross	2	*3*	1	*1*	3	*4*
Number of long zones involved in disease:						
1, 2 or 3	16	*22*	23	*30*	23	*32*
4, 5 or 6	56	*78*	64	*70*	46	*68*
Bacterial content of sputum : [b]						
Direct smear negative	7	*10*	10	*13*	7	*10*
Direct smear positive:						
1-plus (scanty)	23	*32*	24	*31*	26	*37*
2-plus (moderate)	34	*47*	35	*45*	30	*42*
3-plus (heavy)	8	*11*	8	*10*	8	*11*
Total patients	72	*100*	77	*100*	71	*100*

[a] 1 lb = 0.45 kg.

[b] First or only collection specimen.

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, Madras, 1960), from a single full-plate radiograph by an independent assessor (Dr Raj Narain), who was unaware of the treatment series or any other detail of any patient (Table 2). Cavitation was present in 64 % of the PH, 57 % of the TH and 66 % of the P_6H/H patients, being extensive or moderate in 44%, 42% and 45 %, respectively. Gross or extensive disease was present in 13% of the PH, 12 % of the TH and 13 % of the P_6H/H patients, and 4 or more lung zones were involved in disease in 78 %, 70 % and 68 %, respective1y.[1]

Considering the direct smear result of the first or only collection specimen of sputum (Table 2), 58% of the PH, 56% of the TH and 54% of the P^6H/H patients had a 3-plus or 2-plus result; only 10%, 13 % and 10%, respectively, had a negative result.

It may be concluded that the three series of patients were similar on admission to treatment.

PLAN OF THE REST OF THE REPORT

The next section (section V) compares the response to treatment of patients during the 12-month period in the three series. Section VI studies the prognostic importance of various characteristics at the start of treatment. Section VII deals with drug toxicity and other complications of treatment, section VIII with the acceptability of the regimens and the co-operation of patients and section IX with the 20 patients not included in the main analysis. This presentation of the results is followed by a discussion (section X) and a summary (section XI).

[1] Of the 220 patients in the main analysis of this study, 62% were assessed as having cavitation on admission to treatment and 12% as having extensive or gross disease. These proportions are considerably smaller than those quoted in earlier reports and give the impression that patients in this study had less severe radiographic lesions than those in earlier studies. However? there is evidence that these differences are due to variations in the standards of interpretation of radiographs. Thus, the 220 radiographs in the present study had been assessed *along with* 324 other pre-treatment radiographs (random sample) from previous studies by the same independent assessor, who was unaware of the study to which any individual patient belonged. He reported cavitation in 63 % of the 324 patients and extensive or gross disease in 15 %, proportions which are very similar to those in the present study. Confirmatory evidence that no change had occurred in the type of disease encountered is provided by the finding that 89% of the patients in the present study had a positive smear from a single collection specimen of sputum on admission to treatment, as compared with 85 % in the random sample from earlier studies.

V. COMPARISON OF THE RESPONSE TO TREATMENT OF PATIENTS IN THE THREE SERIES

DEATHS

Two patients died of tuberculosis, one (PH) in the first week from pulmonary disease and the other (TH), who had positive cultures with isoniazid-resistant organisms at 3, 5 and 7 months, in the eighth month from a space-occupying intracranial lesion, believed to be a tuberculoma.

Six patients (2 PH, 4 TH) died of non-tuberculous causes. Two chronic asthmatics (both PH), who were under treatment for this condition, died in *status asthmaticus;* of these, one died in the third month having had positive cultures at two months, and the other in the eleventh month having had negative cultures persistently since the first month. Three others (all TH) died of non-tuberculous bronchopneumonia, bacillary dysentery and carcinoma of the oesophagus, respectively, in the fourth, seventh and seventh months, having had only negative cultures since the second, third and fourth months, respectively. The sixth patient (TH) died suddenly in the third month, the cause of death being uncertain (see page 502); she had had only negative cultures since the first month. An autopsy was not performed on any of the patients.

PREMATURE TERMINATION OF THE ALLOCATED CHEMOTHERAPY OWING TO SERIOUS RADIOGRAPHIC OR CLINICAL DETERIORATION

If a patient was considered by the Centre's medical staff to have, in the presence of a positive sputum, definite radiographic extension of the disease which had not been present at one month, a 10-day course of penicillin was given. If the lesion persisted or spread, the complete radiographic series was shown to an independent assessor (Dr K. S. Sanjivi), who decided whether a change of chemotherapy was necessary. Eleven patients had their allocated chemotherapy prematurely terminated on account of serious radiographic deterioration, 3 PH patients in the tenth, eleventh and twelfth months, 2 TH patients in the fifth and ninth months and 6 P_6H/H patients in the sixth, eighth, tenth, eleventh, eleventh and twelfth months, respectively.

Serious clinical deterioration was regarded as a reason for termination of the allocated chemotherapy without recourse to the independent assessor, and two patients (1 TH, 1 P_6H/H), both with a positive sputum, had chemotherapy terminated for this reason in the ninth and eleventh months, respectively.

DEPARTURES FROM THE ALLOCATED CHEMOTHERAPY ON ACCOUNT OF TOXICITY

In three patients (1 PH, 1 TH, 1 P_6H/H) the allocated chemotherapy was terminated on account of cutaneous hypersensitivity in the second, second and third months, respectively. In three other patients (all TH) there were departures from the prescribed chemotherapy on account of hypersensitivity, which started in the second, second and third months and lasted for more than six weeks—namely, for 43, 64 and 54 days, respectively. A further patient (P_6H/H) developed hypersensitivity in the third month and, although he was successfully desensitized, he subsequently became uncooperative and had a departure from the allocated chemotherapy for more than six weeks.

DEPARTURE FROM THE ALLOCATED CHEMOTHERAPY ON ACCOUNT OF NON-COOPERATION

Five patients (1 PH, 2 TH, 2 P_6H/H) became uncooperative and stopped treatment completely, two (both TH) in the first, one (P_6H/H) in the fourth, one (P_6H/H) in the sixth and one (PH) in the twelfth month. Eight other patients (2 PH, 2 TH, 4 P_6H/H) did not collect drugs for periods of more than six weeks.

POLICY FOR INCLUSION IN THE ANALYSES OF PATIENTS WHO DID NOT RECEIVE THE ALLOCATED CHEMOTHERAPY THROUGHOUT THE YEAR

Patients who died of tuberculosis and those whose allocated chemotherapy was terminated owing to deterioration have, in general, been included in the analyses throughout the year except in theanalyses of toxicity (Appendix Tables B and C) and regularity of attendance (Table 15), where they have been included only up to the time of death or termination; furthermore, patients who died of tuberculosis have been included only up to the time of death in analyses of isoniazid-sensitivity test results (Table 6). Patients who died of non-tuberculous causes, and those who had their allocated chemotherapy terminated or had a departure of more than six weeks owing to

TABLE 3
CHANGES IN RADIOGRAPHIC APPEARANCES IN THE 12-MONTH PERIOD[a]

		PH patients	TH patients	P$_6$H/H patients
Improvement	Exceptional	3	5	4
	Considerable	22 (83 %)	26 (77 %)	18 (70 %)
	Moderate	30	19	22
	Slight	6	6	8
No change		1	2	2
Deterioration	Slight	0	1	1
	Moderate	0	2	1
Termination of allocated chemotherapy owing to serious radiographic deterioration		3	2	6
Termination of allocated chemotherapy owing to serious clinical deterioration, or tuberculous death		1	2	1
Total patients [b]		66	65	63

[a] Assessment on standard radiographs taken on admission to treatment and at 12 months.
[b] The policy for including in the analyses patients who did not receive the allocated chemotherapy throughout the 12-month period is described in the text.

toxicity or noncooperation have, in general, been included only up to the time of death, termination of the chemotherapy or first major departure; however, those who had a departure of more than six weeks for any reason have been included throughout in the analyses of toxicity (Appendix Tables B and C). The policy set out above relates to Tables 3-6, Table 15 and Appendix Tables B and C. The policy for analyses relating response to treatment to factors on admission (Tables 9 and 14) and for analyses of PAS-sensitivity test results (Table 11) is described in footnotes.

WEIGHT CHANGES

The average change in weight during the first 6 months was a gain of 9.4 lb for the PH, 5.3 lb for the TH and 9.8 lb for the P_6H/H patients and, over the full 12-month period, 10.6 lb, 6.0 lb and 10.3 lb, respectively. (As many as 18% of the TH patients lost weight over the 12-month period, as compared with 3 % of the PH patients and 6% of the P_6H/H patients.) The difference between the TH series and the other two series attains statistical significance, both in the first 6 months and over the 12-month period ($P<0.01$).

RADIOGRAPHIC CHANGES

The changes in radiographic appearances were evaluated by an independent assessor, Dr Raj Narain, who was unaware of the treatment or any other detail of any individual patient (Table 3). Viewing the postero-anterior films taken. on admission and at 12 months, he assessed the improvement as moderate or greater in 83% of the PH patients, 77 % of the TH and 70% of the P_6H/H patients. Serious radiographic deterioration (necessitating termination of the allocated chemotherapy) occurred in 5 %, 3 % and 10 %, respectively. Thus, the radiographic progress appeared to be best in the PH series and least satisfactory in the P_6H/H series. However, none of the differences is statistically significant.

Table 4 presents the changes in cavitation for the 12-month period as assessed by the independent assessor on the basis of postero-anterior films taken on admission and at 12 months. Cavitation disappeared in 70% of the PH patients, 69 % of the TH patients and 61% of the P_6H/H patients and had become less in 7 %, 18 % and 15 %, respectively. Of 70 patients (22 PH, 26 TH, 22 P_6H/H) who had no cavitation on admission to treatment, 5 (2 PH,

TABLE 4
CHANGES IN CAVITATION IN THE 12-MONTH PERIOD IN PATIENTS WITH CAVITATION ON ADMISSION TO TREATMENT[a]

Treatment series[b]	Total patients	Cavitation at 12 months in relation to cavitation on admission						Termination of allocated chemotherapy owing to serious radiographicoclinicaldeterioration or tuberculous death
		Disappeared		Less		Same	More	
		No.	%	No.	%			
PH	44	31	*70*	3	*7*	1	5	4
TH	39	27	*69*	7	*18*	0	2	3
P_6H/H	41	25	*61*	6	*15*	2	2	6

[a] Assessment on standard radiographs taken on admission to treatment and at 12 months.

[b] The policy for including in the analyses patients who did not receive the allocated chemotherapy throughout the 12-month period is described on page 489.

2 TH, 1 P6H/H) had cavitation at 12 months and 2 (1 TH, 1 P6H/H) had their allocated chemotherapy terminated on account of serious deterioration during the year. Thus, the differences between the three series were small, the response seeming to be most satisfactory in the TH series and least satisfactory in the P6H/H series.

SMEAR AND CULTURE RESULTS

The findings of smear and culture examination of multiple specimens of sputum at monthly intervals during treatment are presented in Table 5. The intensity of the examination was similar in the three series at every month of the year, the average number of results per patient at each month varying from 2.7 to 2.9, as compared with the planned number of 3 (only specimens collected within a week of the set date have been included).

It can be seen that there was a rapid and similar increase during the first 4 months in the proportion of patients with all cultures negative; thus, at 4 months, 79% of the patients in each of the three series produced only negative cultures. Thereafter, there was comparatively little change in the PH and the TH series; however, in the P6H/H series, there was evidence of a decline at 6 months, a point discussed further on page 499. Thus, the proportion of patients with all cultures negative at 6 months was 79 % for the PH series, 81% for the TH series and 71% for the P6H/H series; the corresponding proportions were 81%, 80 % and 63 % at 9 months and 82%, 82% and 66% at 12 months. Although the differences between the P6H/H series and the other two were fairly large at the end of the year of chemotherapy, they did not attain statistical significance ($0.05<P<0.1$).

SENSITIVITY TESTS

Isoniazid

In Table 6, the results of isoniazid-sensitivity tests are set out monthly for the first 9 months, and for 12 months. (Results were not available in only 12 (1.7%) of 709 cultures.) From the fifth month onwards, an increasing number of patients had their allocated chemotherapy terminated on account of a serious radiographic or clinical deterioration. In all, there were 13 such patients, 12 of whom were excreting isoniazid-resistant organisms at the time of the termination (all 12 had produced a resistant culture on at least four occasions); excluding them thereafter would have the effect of underestimating the incidence of isoniazid resistance at later months with the allocated chemotherapy. Consequently, the assumption has been made that the 12 patients with resistant organisms at the time of termination of the allocated chemotherapy would have continued to excrete resistant organisms subsequently had their treatment not been changed. A consolidated total of patients with resistant strains was therefore obtained at each month by adding the number of patients with a resistant culture (column C) to the number who had chemotherapy terminated on account of deterioration (column D). This total has then been expressed as a percentage of (1) the total patients with sensitivity results available (column B) plus the patients whose chemotherapy was terminated (column D), and (2) the total patients under study (column A).

TABLE 5

PRESENCE OF TUBERCLE BACILLI IN MULTIPLE SPECIMENS OF SPUTUM TAKEN AT MONTHLY INTERVALS

Months after start of chemo-therapy	Treatment series	Total patients [a]	Termination of allocated chemotherapy owing to serious radiographic or clinical deterioration or tuberculous death	At least me culture positive	All cultures negative [b]	
					No.	%
1	PH	72	1	63	8	*11*
	TH	75	0	65	10	*13*
	P_6H/H	69	0	60	9	*13*
2	PH	11	1	41	29	*41*
	TH	72	0	40	32	*44*
	P_6H/H	69	0	40	29	*42*
3	PH	69	1	22	46	*67*
	TH	70	0	22	48	*69*
	P_6H/H	68	0	20	48	*71*
4	PH	68	1	13	54	*79*
	TH	66	0	14	52	*79*
	P_6H/H	66	0	14	52	*79*
5	PH	68	1	14	53	*78*
	TH	67	1	8	58	*87*
	P_6H/H	65	0	14	51	*78*
6	PH	68	1	13	54	*79*
	TH	67	1	12	54	*81*
	P_6H/H	63	1	17	45	*71*
7	PH	68	1	15	52	*76*
	TH	65	1	10	54	*83*
	P_6H/H	63	1	16	46	*73*
8	PH	68	1	9	58	*85*
	TH	65	2	14	49	*75*
	P_6H/H	63	2	18	43	*68*
9	PH	68	1	12	55	*81*
	TH	65	4	9	52	*80*
	P_6H/H	63	2	21	40	*63*
10	PH	68	2	10	56	*82*
	TH	64	4	7	53	*83*
	P_6H/H	63	3	17	43	*68*
11	PH	67	3	9	55	*82*
	TH	65	4	8	53	*82*
	P_6H/H	63	6	12	45	*71*
12	PH	66	4	8	54	*82*
	TH	65	4	8	53	*82*
	P_6H/H	62	7	14	41	*66*

[a] The policy for including in the analyses patients who did not receive the allocated chemotherapy throughout the 12-month period is described on page 489.

[b] Even If the smears were positive.

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 with sensitivity test results: Total results available (B)	Sensitive: No growth on 0.2 μg/ml	Resistant: Growth on 0.2 but not on 1 μg/ml	Resistant: Growth on 1 but not on 5 μg/ml	Resistant: Growth on 5 but not on 50 μg/ml	Resistant: Growth on 50 μg/ml	Resistant: Total (C)	Termination of allocated chemotherapy owing to serious radiographic or clinical deterioration (D)	Consolidated total resistant: No. (C+D)	Consolidated total resistant: % of (B+D)	Consolidated total resistant: % of (A)
1	PH	71	63	61	0	1	1	0	2	0	2	*3*	*3*
	TH	75	65	62	2	1	0	0	3	0	3	*5*	*4*
	P_sH/H	69	60	58	0	0	1	1	2	0	2	*3*	*3*
2	PH	70	40	39	0	1	0	0	1	0	1	*2*	*1*
	TH	72	40	33	1	3	1	2	7	0	7	*18*	*10*
	P_sH/H	69	39	35	1	2	1	0	4	0	4	*10*	*6*
3	PH	68	21	18	0	2	1	0	3	0	3	*(14)* [c]	*4*
	TH	70	22	13	0	4	3	2	9	0	9	*(41)*	*13*
	P_sH/H	68	20	15	0	2	2	1	5	0	5	*(25)*	*7*
4	PH	67	13	7	3	3	0	0	6	0	6	*(46)*	*9*
	TH	66	13	8	0	3	2	0	5	0	5	*(38)*	*8*
	P_sH/H	66	14	7	2	1	3	1	7	0	7	*(50)*	*11*
5	PH	67	14	5	3	2	2	2	9	0	9	*(64)*	*13*
	TH	67	8	3	0	2	2	1	5	1	6	*(67)*	*9*
	P_sH/H	65	14	3	0	7	0	4	11	0	11	*(79)*	*17*
6	PH	67	12	1	4	2	1	4	11	0	11	*(92)*	*16*
	TH	67	11	4	2	1	3	1	7	1	8	*(67)*	*12*
	P_sH/H	63	17	3	1	7	4	2	14	1	15	*(83)*	*24*
7	PH	67	14	4	3	1	2	4	10	0	10	*(71)*	*15*
	TH	65	10	4	0	3	3	0	6	1	7	*(64)*	*11*
	P_sH/H	63	16	1	2	8	1	4	15	1	16	*(94)*	*25*
8	PH	67	8	0	2	4	1	1	8	0	8	*(100)*	*12*
	TH	64	12	4	3	3	1	1	8	1	9	*(69)*	*14*
	P_sH/H	63	18	0	1	6	4	7	18	2	20	*(100)*	*32*
9	PH	67	12	2	2	3	2	3	10	0	10	*(83)*	*15*
	TH	63 [d]	8	3	0	2	2	1	5	2 [d]	7	*(70)*	*11*
	P_sH/H	63	21	1	2	6	4	8	20	2	22	*(96)*	*35*
12	PH	65	8	0	1	2	2	3	8	3	11	*(100)*	*17*
	TH	63 [d]	8	3	1	3	0	1	5	2 [d]	7	*(70)*	*11*
	P_sH/H	62	14	0	0	3	3	8	14	7	21	*(100)*	*34*

[a] All patients had strains sensitive to isoniazid on admission to treatment.
[b] The policy for including in the analyses patients who did not receive the allocated chemotherapy throughout the 12-month period is described on page 489.
[c] The parentheses indicate percentages based on fewer than 25 observations.
[d] Excluding one patient who was persistently excreting isoniazid-sensitive organisms and had the allocated chemotherapy terminated owing to serious deterioration.

Considering first the former percentages, there was a higher incidence of resistant strains in the early months in the TH series, increasing from 5% at 1 month to 18 % at 2 months and 41% at 3 months. The corresponding proportions for the PH series were 3 %, 2% and 14% respectively, and for the P_6H/H series 3%, 10% and 25%, respectively. By 4 months, however, the proportions in the PH and the P_6H/H series had overtaken that in the TH series; thus the proportion with resistant cultures was 46 % for the PH series, 38 % for the TH series and 50% for the P_6H/H series. At the end of 6 months of treatment, 92% of 12 cultures in the PH series were resistant, as compared with 67 % of 12 in the TH series and 83 % of 18 in the P_6H/H series. Subsequently, the great majority of cultures in the PH and the P_6H/H series were resistant, the figures being 88 % of a total of 67 and 97% of a total of 118, respectively (including results at 10 and 11 months which have not been tabulated here for reasons of space). In contrast, only 67% of a total of 63 cultures in the TH series were resistant, the proportion ranging between 60% and 70 % at the individual months; this difference was largely due to three patients in the TH series who persistently had positive cultures with sensitive organisms (see below).

Considering next the incidence of isoniazid resistance expressed as a percentage of total patients in the study, the findings in the early months were similar-namely, a higher incidence in the TH series. Thus, the proportion with resistant cultures was 1 % in the PH series, 10 % in the TH series and 6 % in the P_6H/H series at 2 months, and 4 %, 13 % and 7 %, respectively, at 3 months. Thereafter, this proportion continued to increase in the PH series up to 6 months, remained fairly constant in the TH series, and increased in the P_6H/H series up to 9 months. At 12 months, the proportions were 17%, 11% and 34 %, respectively.

In summary, isoniazid resistance emerged earlier in the TH series than in the PH or the P_6H/H series. The proportions of patients with a resistant culture at 6 months were 16 % in the PH, 12 % in the TH and 24 % in the P_6H/H series. Thereafter, the proportion remained fairly constant for the PH and the TH series, but continued to increase in the P_6H/H series.

Emergence of resistance. Resistance to isoniazid emerged during treatment in 22 (31%) of the 72 PH patients, 25 (32%) of the 77 TH patients and 27 (38%) of the 71 P_6H/H patients. Of these 74 patients, 26 (8 PH, 14 TH, 4 P_6H/H) produced a resistant culture on only one occasion; the resistant culture was produced after sputum conversion (that is, three consecutive months of culture negativity) in 11 patients (4 PH, 7 TH) and before sputum conversion in the remaining 15 (4 PH, 7 TH, 4 P_6H/H). At least two resistant cultures were produced by 14 (19%) PH, 11 (14%) TH and 23 (32%) P_6H/H patients. This was followed by sputum conversion in 2, 3 and 1 patients, respectively; however, one patient in each series subsequently had a bacteriological relapse with isoniazid-resistant organisms. There were 146 patients (50 PH, 52 TH, 44 P_6H/H) who did not produce even one resistant culture during the year. Of these, three (all TH) persistently had positive cultures with isoniazid-sensitive organisms; one produced positive cultures at each month throughout the year except the third and the twelfth, another from the fifth to the twelfth month inclusive, and the third from the first to the eighth month inclusive when treatment was changed on account of serious radiographic deterioration. All three patients had been veb irregular in taking their drugs, as 56 %, 90% and 82 %, respectively, of their clinic urine specimens, and 78%, 57 % and 75 %, respectively, of urine specimens collected at surprise visits to the home, yielded a negative result when tested for the presence of isoniazid.

Thioacetazone

Pretreatment sensitivity results. Thioacetazone-sensitivity test results were available on duplicate pretreatment cultures from each of

(a) 209 patients (71 PH, 75 TH, 63 P_6H/H), using the standard inoculum, and

(b) 168 patients (55 PH, 64 TH, 49 P_6H/H), using a dilute inoculum (1 : 20).

The correlation between the results of duplicate cultures is summarized in Table 7 for both types of test. Identical results or results differing by a single 2-fold dilution step were obtained for 82% of the patients using the standard inoculum, as compared with 86% using the dilute inoculum. Further, the difference was 4 dilution steps or greater in 7% of the former tests, as compared with 1% of the latter. Thus, the correlation was slightly less good with the standard inoculum than with the dilute inoculum—the mean difference between results of duplicate cultures being just less than 1 dilution step with the standard inoculum as compared with approximately two-thirds of a dilution step with the dilute inoculum; the contrast attains statistical significance ($P = 0.02$). (This conclusion was confirmed in the subgroup of

TABLE 7. COMPARISON OF THIOACETAZONE-SENSITIVITY TEST RESULTS IN DUPLICATE PRETREATMENT CULTURES FROM THE SAME PATIENT

Difference between results of duplicate cultures (No. of 2-fold dilution steps)	Standard inoculum		Dilute inoculum (1 : 20)	
	No. of patients	%	No. of patients	%
0	92	*44*	84	*50*
1	79	*38*	61	*36*
2	16	*8*	15	*9*
3	7	*3*	6	*4*
4	8	*4*	1	*1*
5	4	*2*	1	*1*
6	3	*1*	0	0
Total	209	*100*	168	*101*
Mean	0.97		0.70	

TABLE 8. RESULTS OF THIOACETAZONE-SENSITIVITY TESTS IN ALL PATIENTS ON ADMISSION TO TREATMENT

Geometric mean of MICs for two pretreatment cultures (μg/ml)	Standard inoculum		Dilute inoculum (1 : 20)	
	No. of patients	%	No. of patients	%
Less than 0.5	17	*8*	24	*14*
0.5-	23	*11*	26	*15*
1.0-	53	*25*	70	*42*
2.0-	69	*33*	40	*24*
4.0-	18	*9*	6	*4*
8.0-	10	*5*	2	*1*
16.0-	10	*5*	0	*0*
32.0-	5	*2*	0	*0*
64.0 or more	4	*2*	0	*0*
Total	209	*100*	168	*100*

168 patients, who had sensitivity test results for two cultures, *both* with the standard inoculum and with the dilute inoculum tests.) Examination of the results by analysis of variance indicated that both types of test were capable of distinguishing variation from patient to patient in the thioacetazone sensitivity of their strains; the standard inoculum test appeared slightly more efficient than the dilute inoculum test in this differentiation.

In view of the wide variability in the results of duplicate cultures from the same patient, the geometric mean of the MICs of two pretreatment cultures was calculated for each patient. Table 8 sets out the distribution of patients according to these means, both for the standard inoculum and for the dilute inoculum. Neither of the distributions suggests any obvious definition of thioacetazone resistance.

Pretreatment thioacetazone sensitivity and response to treatment in the TH series. Table 9 relates pre-

TABLE 9. RESPONSE TO TREATMENT IN THE TH SERIES RELATED TO THIOACETAZONE SENSITIVITY ON ADMISSION TO TREATMENT[a]

Geometric mean of MICs for two pretreatment cultures (μg/ml)	Standard inoculum			Dilute inoculum (1 : 20)		
	Total patients [b]	Favourable response [c]	Unfavourable response [c]	Total patients [d]	Favourable responses	Unfavourable response [c]
Less than 1.0	16	14	2	22	18	**4**
1.0-	11	9	2	23	19	**4**
2.0-	19	16	3	17	16	**1**
4.0-	9	9	0	0	0	**0**
8.0-	4	2	2	1	0	**1**
16.0-	3	2	1	0	0	**0**
32.0 or more	3	1	2	2	0	**2**
Total	65	53	12	65	53	12

[a] Excluding patients who died of a non-tuberculous cause and those who had a termination of the allocated chemotherapy, or a departure of over six weeks, on account of toxicity or non-cooperation.
[b] Including two patients for whom only one pretreatment sensitivity result was available.
[c] For definition, see page 497. [d] Including 10 patients for whom only one pretreatment sensitivity result was available.

treatment thioacetazone sensitivity, expressed as the geometric mean of the MICs of two pretreatment cultures, to response to treatment in the TH series. There was a tendency for patients with initially less sensitive strains to respond unsatisfactorily to treatment. Thus, with the standard inoculum results, the patients with an unfavourable response had a pretreatment geometric mean of 3.98 µg/ml, as compared with 1.83 µg/ml for patients with a favourable response, the contrast just attaining statistical significance (P = 0.05). With the dilute inoculum results, the corresponding figures were 1.94 µg/ml and 0.98 µg/ml, respectively (P = 0.04).

Sensitivity results during treatment in the TH series. Owing to difficulties in identifying patients with pretreatment thioacetazone-resistant strains, the results of sensitivity tests at monthly intervals during treatment are not presented here for *all* TH patients, as has been done in the case of isoniazid. However, the detailed findings of tests with the standard inoculum are presented in Table 10 for those TH patients who had an unfavourable response to treatment, since they are the patients in whom resistance is most likely to have emerged.

An examination of these findings suggests that resistance to thioacetazone *emerged* in only one patient (R 231), and possibly in another (R 146). Thus, there was little evidence of the emergence of resistance in strains from individual patients in the TH series. (Similar conclusions were drawn from the results (not tabulated here) of the dilute inoculum tests.)

PAS

The first pretreatment culture was considered to be PAS-resistant for 11 (8%) of 142 patients—namely, 4 of 72 in the PH series and 7 of 70 in the P_6H/H series (Table 11). Of these, 5 cultures (4 with a resistance ratio (RR) of 8 and 1 with an RR of 16) were retested and all yielded an RR of 2 or less. Of the above 11 patients, 9 (82%) were classified at 6 months as having a favourable response to treatment (for definition, see Table 13), as compared with 95 (78%) of 122 patients with sensitive organisms whose response could be assessed. Further, both pretreatment cultures were considered to be resistant in only two patients, both of whom were classified as having a favourable response at 6 months. These findings suggest that, in all likelihood, most or all of the 11 patients really had PAS-sensitive strains on admission to treatment.

TABLE 10

THIOACETAZONE SENSITIVITY TEST RESULTS (STANDARD INOCULUM), EXPRESSED AS MICs (µg/ml), IN PATIENTS IN THE TH SERIES WHO HAD AN UNFAVOURABLE RESPONSE[a]

Serial No.	On admission to treatment			Months after start of treatment											
	First culture	Second culture	Geometric mean	1	2	3	4	5	6	7	8	9	10	11	12
R146	0.25	0.25	0.25	0.25	0.5	—[b]	—	1	0.5	—	—	—	1	2	—
R85	0.25	0.5	0.35	0.5	0.25	—	NT[c]	0.25	0.25	0.25	0.25	0.25	0.25	0.25	—
R170	1	1	1.0	—	1	—	1	—	—	—	—	—	—	NT	2
R231	1	2	1.4	2	—	—	2	32	>32	>32	NT	Allocated chemotherapy terminated			
R181	4	2	2.8	2	—	—	—	2	>32	1	2	2	NT	2	4
R166	4	2	2.8	>32	2	NT	2	2	2	2	2	Allocated chemotherapy terminated			
R174	2	4	2.8	2	4	—	—	—	—	2	—	NT	NT	2	2
R97	2	>32	11.3	8	1	2	8	8	8	8	>4	16	2	4	16
R112	>32	2	11.3	2	>32	8	>32	Allocated chemotherapy terminated							
R4	>32	4	16.0	2	2	2	NS[d]	2	—	1	Tuberculous death				
R84	32	>32	45.3	8	8	8	8	>8	2	8	NT	8	4	2	8
R164	>32	NT	64.0	>32	—	—	—	—	>32	>32	—	NT	>32	>32	>32

[a] For definition, see opposite page.
[b] — = negative.
NT = culture positive, but no sensitivity test result available.
[d] NS = no specimen.

TABLE 11
RESULTS OF PAS-SENSITIVITY TESTS ON ADMISSI0N, [a] AT 6 AND AT 12 MONTHS

Months after start of chemotherapy	Treatment series	Total patients receiving allocated chemotherapy with sensitivity test results available [b]	PAS-sensitive	PAS-resistant	
				No.	%
0	PH	72	68	4	6
	P_6H/H	70	63	7	10
	Both series	142	131	11	8
6 (or 7 or 5)	PH	16	17	1	(6) [c]
	P_6H/H	19	17 [d]	2	(11)
	Both series	37	34	3	8
12 (or 11)	PH	10	7	3 [d]	(30)
	P_6H/H	15	12 [d]	3	(20)
	Both series	25	19	6	24

[a] Based on the results of the first specimen.

[b] Patients who died, those who had a termination of the allocated chemotherapy and those who had a departure of over six weeks, for any reason, have been included up to the time of death, termination and the first major departure, respectively.

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

[d] Including one patient whose allocated chemotherapy was terminated at this month owing to serious radiographic-deterioration.

Considering next the results at 6 months, 3 (8 %) of 37 patients had a resistant culture. At 12 months, the corresponding figures were 6 (24%) of 25; all of these six had had PAS-sensitive strains on admission. Thus, PAS resistance had not emerged at 6 months but had emerged in a small proportion of patients at 12 months.

CLASSIFICATION OF PATIENTS AT 12 MONTHS ACCORDING TO THEIR RESPONSE TO TREATMENT

Table 12 presents a classification of all the patients at 12 months, based primarily on the bacteriological response to treatment. The proportion of patients who had bacteriologically quiescent disease at one year was 77% for the PH series, 78% for the TH series and 65 % for the P_6H/H series. There were six patients (3 PH, 2 TH, 1 P_6H/H) who had disease of bacteriologically doubtful status at one year. In view of the intensity with which sputum specimens are examined at the Centre (see page 486) and previous experience with similar groups of patients (Velu et al., 1960, 1961; Devadatta et al., 1961; Dawson et al., 1966 [1]), these patients have been regarded as having a favourable response to treatment. (A follow-up of the patients showed that all six produced only negative cultures in the six months immediately following the single positive culture.) Thus, 82 % of 66 PH patients, 82% of 65 TH patients and 67% of 63 P_6H/H patients had a favourable response. The difference between the P_6H/H series and the other two, although fairly large (15 %), does not attain statistical significance ($0.05<P<0.1$).

An unfavourable response to treatment-that is, death from tuberculosis, or bacteriologically relapsed or active disease at 12 months (including premature termination of the allocated chemotherapy for serious radiographic or clinical deterioration)– occurred in 18 % of the PH patients, 18 % of the TH patients and 33% of the P_6H/H patients.

In the above totals, 26 patients (6 PH, 12 TH, 8 P_6H/H) have not been included for reasons given in the lower part of the table. It was not possible to assess the therapeutic efficacy of the regimens in 10 of these patients, namely, six who died of non-tuberculous causes (see page 489), three whose chemotherapy was terminated on account of

[1] See article on page 533 of this issue.

TABLE 12

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					
		PH		TH		P_6H/H	
		No.	%	No.	%	*No.*	*%*
	First month of persisting culture negativity						
Patients with bacteriologically quiescent disease: **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	4		6		5	
	2	13		15		14	
	3	12		6		11	
	4	6		10		5	
	5	4		3		1	
	6	2		0		0	
	7	3		2		2	
	3	4		0		1	
	9	1		6		0	
	10	2		3		2	
	Total	51	*77*	51	*78*	41	*65*
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 last three monthly examinations–i.e., at 10, 11 or 12 months		3	*5*	2	*3*	1	
Total patients with a favourable response		54	*82*	53	*82*	42	*67*
Patients with bacteriologically relapsed disease: that is, patients whose cultures were all negative at three or more consecutive monthly examinations, but who produced a total of two or more positive cultures in the last three monthly examinations-i.e., at 10, 11 and 12 months		2	*3*	5	*8*	6	*13*
Patients with bacteriologically active disease:							
that is, *(a)* patients whose cultures were never all negative at three consecutive monthly examinations		6	*9*	3	*5*	6	*10*
or *(b)* patients who had their allocated chemotherapy terminated on account of serious radiographic or clinical deterioration		3	*5*	3	*5*	7	*11*
Tuberculous deaths		1	*2*	1	*2*	0	*0*
Total patients with an unfavourable response		12	*18*	12	*18*	21	*33*
Total		66	*100*	65	*100*	63	*100*
Patients who became uncooperative and:							
(a) refused further treatment		1	–	2	–	2	–
or *(b)* received no treatment for more than six weeks		2	–	2	–	4	–
Patients who, on account of toxicity, had:							
(a) their allocated chemotherapy terminated		1	–	1	–	1	–
or *(b)* a departure from the allocated chemotherapy for more than six weeks		0	–	3	–	1	–
Non-tuberculous deaths		2	–	4	–	0	–
All patients		72	–	77	–	71	–

toxicity within three months of starting treatment and one (TH) who refused to attend the clinic after the first month. Of the remaining 16 patients (3 PH, 6 TH, 7 P_6H/H), one (TH) died of tuberculosis in the ninth month; for the other 15, it was possible to assess the response on the basis of 2-9 (average of 7) culture results in the last 3 months of the year, a favourable response being observed in 8 patients (1 PH, 3 TH, 4 P_6H/H). If these 16 patients are taken into consideration in assessing the therapeutic efficacy of the three regimens, the proportion of patients with a favourable response becomes 80% for the PH, 79 % for the TH and 66% for the P_6H/H series; again, the differences between the P_6H/H series and the other two are not statistically significant ($P \simeq 0.1$).

In summary, the therapeutic efficacies of the PH and TH regimens were very similar. The P_6H/H regimen was inferior, although the difference was not statistically significant.

RESPONSE TO TREATMENT IN THE PH AND THE P_6H/H SERIES DURING THE FIRST 6 MONTHS

In the preceding pages, it has been reported that the response to the P_6H/H regimen over the 12-month period was inferior to that to the PH regimen, both radiographically and bacteriologically. The extent to which this finding was influenced by the differences between the regimens in drug-composition in the first 6 months (see Table 1 and Appendix Table A) is studied below.

Considering radiographic changes, there was moderate or greater improvement in 79% of 68 PH patients, as compared with 76% of 63 P_6H/H patients, including considerable or exceptional improvement in 9 % and 22 %, respectively. Serious radiographic deterioration (necessitating termination of the allocated chemotherapy) occurred in 0% and 2 %, respectively. Cavitation disappeared in 66 % of 44 PH patients, as compared with 78 % of 41 P_6H/H patients, while it became less in 18 % and 17 %, respectively.

The proportions of patients who produced only negative cultures from multiple specimens of sputum (usually 3) were very similar for the two series at each month up to five months (see Table 5), at which time 78 % of the patients in both series had only negative cultures. While this proportion was practically the same at six months in the PH series, there was a fall to 71% in the P_6H/H series. The

TABLE 13
RESPONSE TO TREATMENT DURING THE FIRST SIX MONTHS

Response to treatment		PH patients		P_6H/H patients		TH patients	
		No.	%	No.	%	No.	%
Favourable	All cultures (usually 6) negative at five and six months	49	72	46	70	54	81
Doubtful	All cultures negative at six months but at least one positive culture at five months	5 [a]	12	1 [b]	8	0	4
	One positive culture at six months but all cultures negative at five	3 [a]		4 [a]		3 [c]	
Unfavourable	Total of two or more positive cultures at five and six months, at least one of these being at six months	10	16	14	23	9	15
	Termination of allocated chemotherapy owing to serious radiographic deterioration, or tuberculous death	1		1		1	
	Total	68	100	66	101	67	100
Patients who died of a non-tuberculous cause or who, on account of toxicity or non-cooperation, had a prolonged departure from or termination of the allocated chemotherapy		4	–	5	–	10	–
All patients		72	–	71	–	77	–

[a] Including three patients whose response was finally classified as favourable (see text).
[b] This patient was finally classified as having a favourable response.
[c] Including two patients whose response was finally classified as favourable.

decrease in the P_6H/H series was accounted for by six patients having all cultures negative at five months and at least one positive culture at six months, as compared with only one patient having all cultures negative at six months and at least one positive culture at five months (the corresponding numbers in the PH series were four and five, respectively). Further examination of the data showed that in four of the seven P_6H/H patients, the result observed was unusual-for example, an isolated positive result among a series of negative results (this was also the case in five of the nine patients in the PH series). In order to obtain a clearer picture of the findings, a more comprehensive classification of response, based on culture results at five and six months, was therefore undertaken; the findings are presented in Table 13.

In all, 72% of 68 PH patients had a bacteriologically favourable response, as compared with 70 % of 66 P_6H/H patients. In 13 patients (8 PH, 5 P_6H/H), the response was classified as doubtful; however, a consideration of the results at 7 months suggested that 10 (6 PH, 4 P_6H/H) of these patients could also be classified as having had a favourable response, so that the over-all numbers of patients with favourable response are 55 (81%) for the PH series and 50 (76 %) for the P_6H/H series.

In summary, the response of the PH and the P_6H/H patients during the first 6 months was fairly similar, the latter showing slightly better radiographic response but slightly inferior bacteriological response. These findings, taken in conjunction with those over the 12-month period, suggest that the relatively poor therapeutic response in the P_6H/H series at 12 months was due to giving only isoniazid in the second 6 months of treatment.

The findings for the TH patients have also been included in Table 13 for the sake of completeness.

TABLE 14

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

Condition on admission to treatment	PH series			TH series			P_6H/H series		
	Total patients	Unfavourable response [b]		Total patients	Unfavourable response [b]		Total patients	Unfavourable response [b]	
		No.	%		No.	%		No.	%
Extent of cavitation:									
Extensive or moderate	31	10	*32*	28	5	*18*	29	14	*48*
Slight or nil	35	2	*6*	37	7	*19*	34	7	*21*
Total extent of disease:									
Gross, extensive or moderate	32	11	*34*	32	6	*19*	30	15	*50*
Limited or slight	34	1	*3*	33	6	*18*	33	6	*18*
Number of lung zones:									
6, 5 or 4	52	12	*23*	45	11	*24*	42	16	*38*
3, 2 or 1	14	0	*(0)* [c]	20	1	*(5)*	21	5	*(24)*
Bacterial content of sputum: [d]									
3-plus or 2-plus	41	10	*24*	38	5	*13*	34	14	*41*
1-plus or negative	25	2	*8*	27	7	*26*	29		*24*
Total patients	*66*	12		65	12		63	21	

[a] Excluding patients who died of a non-tuberculous cause, and those who had a termination of the allocated chemotherapy or a departure of over six weeks, on account of toxicity or non-cooperation.

[b] For definition, see page 497.

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

[d] Direct smear result on first or only collection specimen.

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

Of 39 PH patients who were under 35 years of age, 10% had an unfavourable response to treatment, as compared with 30 % of 27 who were aged 35 years or above; the corresponding proportions were 11% of 37 and 29 % of 28 in the TH series, and 29 % of 34 and 38 % of 29 in the P_6H/H series. Thus, the older patients in all three series had a relatively poor response to treatment; however, the association attained statistical significance only in the PH series, in which further analysis showed that the patients aged 35 years or above had more extensive disease initially than those below 35 years, as assessed by the total extent of disease, extent of cavitation and number of lung zones involved in disease. There was no association between sex and response to treatment in any of the series.

Table 14 relates other assessments of condition on admission to the response to treatment. It can be seen that, both in the PH and in the P_6H/H series, the likelihood of an unfavourable response was greater for patients with extensive or moderate cavitation, for those with gross, extensive or moderate disease, for those with 4 or more lung zones involved in disease and for those with a moderately or heavily positive smear on a single collection specimen of sputum; however, in both series, the association was statistically significant only for cavitation and total extent of disease. In contrast, in the TH series, neither cavitation nor total extent of disease was of prognostic value, although patients with 4 or more lung zones involved in disease had a greater likelihood of unfavourable response; this association was not statistically significant ($P>0.1$).

VII. TOXICITY AND OTHER COMPLICATIONS

DRUG TOXICITY

Of the 220 patients in the main analysis, one (PH) who died in the first week of treatment and two (both TH) who refused further treatment in the first and third weeks have been excluded from the analysis of drug toxicity as they had been under treatment for so short a period; none of these three patients had complained of toxicity. There remain 71 PH, 75 TH and 71 P_6H/H patients in the analyses.

Gastrointestinal and other complaints

Only spontaneous complaints were recorded and patients were not questioned to elicit symptoms. A complaint of vomiting, with or without diarrhoea, was recorded on at least one occasion in 8% of the 71 PH patients, 23 % of the 75 TH and 15 % of the 71 P_6H/H patients; the difference between the PH and the TH series attains statistical significance ($P=0.03$). In 2 PH, 2 TH and 2 P_6H/H patients, the complaints were so persistent that treatment had to be interrupted for 7, 35, 7, 35, 15 and 38 days, respectively. Anorexia occurred in 7 % of the PH patients, 17 % of the TH and 4% of the P_6H/H patients; the difference between the TH and the P_6H/H series was statistically significant ($P=0.02$) while that between the TH and the PH series was not ($P>0.1$). Complaints of giddiness were made by 4% of the PH, 28 % of the TH and 10 % of the P_6H/H patients, the differences between the TH series and the other two being highly significant ($P \leq 0.01$).

Cutaneous hypersensitivity

Cutaneous hypersensitivity reactions occurred in 4 (6 %) of the 71 PH patients (3 in the second and 1 in the third mouth), 5 (7 %) of the 75 TH patients (3 in the first and 2 in the second month) and 1 (1%) of the 71 P_6H/H patients (in the second month). Desensitization was successful in three of the PH and four of the TH patients but unsuccessful, even under cover of corticosteroids, in one of the PH patients and in the P_6H/H patient; in one TH patient it was not attempted, since the rash persisted even after thioacetazone was stopped.

Of the five TH patients, two had a Stevens-Johnson syndrome including one with very extensive exfoliative dermatitis; both were extremely ill and required

urgent hospital admission. Two other TH patients had early exfoliative dermatitis. The fifth TH patient, the four PH patients and the P_6H/H patient had discrete papular rashes.

Liver toxicity

Jaundice occurred in 2 (3%) of the PH patients (1, with concurrent urticaria (not included under cutaneous hypersensitivity), in the second month and 1 in the eleventh month), in 2 (3 %) of the TH patients (in the seventh and eighth months), and in none of the P_6H/H patients. The two PH patients resumed treatment after interruptions of 14 and 37 days and one of the TH patients after 29 days. The other TH patient had also a serious clinical deterioration warranting a change of treatment; however, on account of the jaundice and a high serum GOT (132 Karmen units), the change was not effected until after 18 days.

In order to study the effect of thioacetazone on hepatic function, serum GOT levels were determined on admission to treatment and at 3, 9 and 12 months in the TH series, and also in the P_6H/H series as a control. (The detailed findings are presented in the upper half of Appendix Table B.) The average serum GOT levels (Karmen units) on admission were similar in the two series, namely, 21.3 (range 8-41) and 21.8 (range 6-51), respectively. The average levels were 22.9 for the TH series and 24.3 for the P_6H/H series at 3 months, 23.2 and 28.9 at 9 months, and 28.2 (range 10-68) and 29.9 (range 16-54) at 12 months, respectively. Thus, at the end of the year of treatment, there was a similar and statistically highly significant ($P<0.001$) rise in both series. Although the great majority of routine serum GOT values during treatment lay well within the range of pretreatment values, 2 TH patients and 8 P_6H/H patients had a value between 51 and 75 units on a single occasion, but none had clinical evidence of liver damage. One patient (TH) had a value of 90 units at 3 months and developed jaundice in the seventh month; another (P_6H/H) had a serum GOT level of 115 units at 9 months while receiving isoniazid alone, but had no clinical evidence of liver toxicity.

A urine test for urobilin was performed weekly and produced a positive result in three (4%) of the PH patients, none of the TH patients and three (4 %) of the P_6H/H patients, each on one occasion.

Haemopoietic side-effects

To study the effect of thioacetazone on haemopoiesis, certain haemotological examinations were undertaken on admission to treatment and at 3, 9 and 12 months for patients in the TH series and, as a control, for those in the P_6H/H series. For patients in the PH series, the investigations were undertaken only on admission and at 12 months. (The detailed findings are presented in Appendix Table C.)

Haemoglobin and packed cell volume (PCV) . The average haemoglobin value on admission was low, being 11.7 g per 100 ml for the PH, 11.5 g per 100 ml for the TH and 10.9 g per 100 ml for the P_6H/H series. At 12 months, it had increased by 1.6 g in the PH series ($P<0.001$), 0.9 g in the TH ($P<0.05$) and 2.1 g in the P_6H/H series ($P<0.01$). The PCV values showed similar trends, the increase over the 12-month period being statistically highly significant in all three series ($P \leq 0.01$).

Leucocytes. The average total leucocyte counts on admission were similar in the three series, namely, 9800 cells/mm^3 in the PH, 9700 in the TH and 9500 in the P_6H/H series. During the year, the average count fell in all three series ($P<0.001$), being 8100, 7700 and 7100, respectively, at 12 months. This fall was due to a decrease in the average number of polymorphonuclear cells, from 6300 to 4300 in the PH, from 6900 to 4800 in the TH and from 6800 to 4000 in the P_6H/H series.

One patient (TH) complained of a sore throat and a swollen ankle seven weeks after the start of treatment and had by that time lost 11 lb (5 kg) in weight. She was diagnosed as having acute filariasis and continued with her initial chemotherapy. The differential leucocyte count was later reported as polymorphonuclear cells 390 (5%), lymphocytes 4600 (59 %), eosinophils 2400 (31%) and monocytes 390 (5 %) cells/mm^3. She died suddenly at home nine weeks after admission, having coughed up a " mass of sputum " and become very dyspnoeic. Although the clinical course was unusual, in the absence of an autopsy, agranulocytosis due to thioacetazone cannot be excluded.

Glycosuria

Urine specimens of all patients were tested for the presence of sugar (Benedict's test) before admission to the study; only two (1 TH, 1 P_6H/H) had a positive result, both being trace reactions. During the year of treatment, some TH patients gave positive results (in a sample of three patients, the sugar was identified chemically as glucose), and it was therefore decided subsequently to examine, at 6, 11 and 12 months, urine specimens for sugar from

patients in the TH series and, as a control, from those in the P_6H/H series. The average number of specimens examined per patient was 1.6 in the TH series and 1.7 in the P_6H/H series, the number of patients with one or more routine examinations during treatment being 65 and 61, respectively. The test result was positive in at least one specimen during treatment in 20 (31%) of the TH patients, as compared with 8 (13 %) of the P_6H/H patients, a statistically significant difference ($P = 0.03$); there was more than a trace in 8 (12 %) of the TH patients, as compared with 2 (3%) of the P_6H/H patients ($P > 0.1$). Glucose tolerance tests performed on three TH patients who had a strongly positive urine test result for sugar were within normal limits.

Of the 20 TH patients in whom sugar was detected during treatment, only 15 had a positive result at the last test during the year of treatment. Urine tests were undertaken in 14 of these after the thioacetazone had been stopped; 13 had negative results while one produced a trace result on two occasions.

Neurological side-effects

Neurological side-effects attributed to isoniazid were not encountered in the PH series, but one TH patient (slow inactivator of isoniazid) had a sudden loss of consciousness for about one hour in the seventh month and one P_6H/H patient (slow inactivator) developed symptoms of peripheral neuropathy in the third month. (One patient (TH), a slow inactivator of isoniazid who has been excluded from the main analysis on account of primary isoniazid resistance, developed peripheral neuropathy in the fourth month.)

GOT levels on whole blood were performed routinely in the TH and the P_6H/H series on admission and at 3, 9 and 12 months to study if there was any evidence of isoniazid toxicity manifested by depression of the blood transaminase activity (Krishnamurthy et al., in preparation). (The detailed findings are presented in the lower half of Appendix Table B.) The average levels of blood GOT on admission to treatment were similar, namely, 598 units (range 271-1223) for the TH patients and 602 units (range 308-1043) for the P_6H/H patients. In the TH patients, there was a fall of 69 units in the average level at 3 months, followed by a gradual rise at 9 and at 12 months. Even so, the level at 12 months was still significantly lower than that on admission ($P<0.05$). In the P_6H/H series, there was a fall of 27 units in the average GOT level at 3 months, but in contrast to the findings in the TH series, the average level at 9 months and at 12 months was similar to the level at the start of treatment. Six patients had GOT levels of less than 300 units during treatment (each on one occasion), namely, 261, 261 and 298 at 3 months and 287 at 9 months in 4 TH patients, and 298 at 3 months and 287 at 12 months in 2 P_6H/H patients. The TH patient with a level of 298 at 3 months had the transient loss of consciousness referred to above. In summary, there was a significant depression of the mean blood GOT level over the 12 months in the TH series, which was greatest at 3 months; although the P_6H/H series also showed a depression of the mean level at 3 months, full recovery to the pretreatment level had occurred by 12 months.

COMPLICATIONS REQUIRING ADMISSION TO HOSPITAL OR SANATORIUM

Sixteen patients were admitted to hospital or sanatorium on one or more occasions on account of pulmonary tuberculosis. Of these, 10 (1 PH, 7 TH, 2 P_6H/H) were admitted, on account of serious clinical deterioration, for total periods of 6 weeks, 5 days, and 3, 4, 9, 11, 12, 14, 10 and 13 weeks, respectively. Five others (1 TH, 4 P_6H/H) were admitted for 4, 5, 7, 8 and 18 weeks, respectively, on account of spontaneous pneumothorax. The 16th patient (P_6H/H) was admitted for 2 weeks following severe haemoptysis.

Seven patients were admitted on one or more occasions on account of toxicity to the antituberculosis drugs; of these, 4 (3 TH, 1 P_6H/H) were admitted for total periods of 1, 2, 15 and 3 weeks, respectively, on account of severe skin reactions. The remaining 3 (2 PH, 1 TH) were admitted for 7, 10 and 22 weeks, respectively, for intractable vomiting and diarrhoea ascribed to drug intolerance; the TH patient had a spontaneous pneumothorax also.

Sixteen other patients (3 PH, 8 TH, 5 P_6H/H) were admitted for non-tuberculous illnesses for total periods ranging from 1 day to 6 weeks (average 2 weeks).

VIII. ACCEPTABILITY OF REGIMENS AND CO-OPERATION OF PATIENTS

ACCEPTABILITY OF REGIMENS

In previous studies at the Centre (Tuberculosis Chemotherapy Centre, Madras, 1959, 1960, 1963a, 1963b), two methods were used to check whether patients were taking their drugs regularly, and to compare the regularity of self-administration of drugs in the different series. These were:

(1) tests to detect the presence of the drugs in urine specimens collected at routine visits to the Centre and at surprise visits to the home, and

(2) counts of the patient's stock of cachets or tablets at surprise visits to the home.

Both methods were undertaken in the present study also (see page 486).

Urine tests

On account of the differences in the daily dosages of both isoniazid and PAS and the different rhythms in which the drugs were administered, the interpretation of the test results varied for the three regimens. It has therefore not been possible to compare the regularity of self-administration of drugs in the three series.

Despite these difficulties, the urine test results can be used to compare degrees of irregularity between patients in the *same* series. In all three series, there was considerable variation between the patients in the regularity with which they took their drugs (as assessed by the results of tests on clinic urine specimens collected at *routine* weekly visits); however, there was no clear evidence in any of them that this was associated with the outcome of treatment (the results have not been tabulated here).

Counts of cachets or tablets

Although counts of stocks of cachets or tablets are a valuable means of checking on the co-operation of individual patients, the findings are not suitable for purposes of analyses (for reasons, see Tuberculosis Chemotherapy Centre, Madras, 1960) and are therefore not presented here.

TABLE 15
REGULARITY OF WEEKLY ATTENDANCE FOR COLLECTION OF DRUGS DURING THE YEAR OF TREATMENT=

Percentage of occasions on which patients attended on the appointed day of the week or earlier [b]	PH patients		TH patients		P_6H/H patients	
	No.	%	No.	%	No.	%
90 or more	44	*65*	36	*49*	41	*63*
80-89	9	*13*	19	*25*	11	*17*
70-79	8	*12*	8	*11*	6	*9*
60-69	4	*6*	8	*11*	5	*8*
50-59	3	4	2	*3*	2	*3*
Less than 50	0	*0*	1	*1*	0	*0*
Total	68	*100*	73	*100*	65	*100*
Patients who became uncooperative and						
(a) received no treatment for more than six weeks	2	–	2	–	4	–
(b) refused further treatment	1	–	2	–	2	–
All patients	71[c]	–	77	–	71	–

[a] The policy for including In the analyses patients who did not receive the allocated chemotherapy throughout the 12-month period Is described on page 489.

[b] Excluding periods during which patient was In hospital or sanatorium or under desensitization.

[c] Excluding one patient who died In the first month.

CO-OPERATION OF PATIENTS

There were 13 patients (3 PH, 4 TH, 6 P_6H/H) who became very uncooperative, including 5 (1 PH, 2 TH, 2 P_6H/H) who refused further treatment. Table 15 sets out the regularity with which the remaining 68 PH, 73 TH, and 65 P_6H/H patients (excluding 1 PH patient who died in the first month) attended on the appointed day of the week (or earlier). Regularity on 90% or more of the occasions was observed in 65 % of the PH, 49 % of the TH and 63% of the P_6H/H patients; the proportions who were regular on less than 70% of the occasions were 10%, 15 % and 11 %, respectively. Thus, the PH and the P_6H/H series had very similar distributions for regularity of attendance. There was some evidence that the TH patients were, on the average, less regular in attending the clinic to collect their drugs; indeed, the difference between this series and the PH series is statistically significant ($P = 0.03$).

An analysis (not tabulated here) was undertaken to study whether the regularity of attendance was affected by the passage of time. In the PH series, the proportion who attended on the appointed day (or earlier) on all occasions was 60 % in the first quarter, 42 % in the second, 38 % in the third and 42 % in the fourth quarter. The corresponding proportions were 45 %, 37 %, 24 % and 18 % in the TH series and 51%, 34 %, 42 % and 37 % in the P_6H/H series. Thus, in all three series, the patients attended less regularly in the later nine months of treatment, there being a noticeably strong trend in the proportions for the four quarters in the TH series.

IX. PATIENTS NOT INCLUDED IN THE MAIN ANALYSIS

This section describes the progress during treatment of 20 patients (7 PH, 3 TH, 10 P_6H/H) who were excluded from the main analysis, 17 because they had had isoniazid-resistant strains of tubercle bacilli at the start of treatment, one because his pretreatment sensitivity test results were anomalous and two because they had anonymous mycobacterial infections. All continued on the allocated regimen.

PATIENTS WITH ISONIAZID-RESISTANT ORGANISMS AT THE START OF TREATMENT

The 17 patients with isoniazid-resistant strains of tubercle bacilli on admission were interrogated again during the course of treatment, as their relation with the Centre's staff became established, to discover whether they had concealed a history of previous chemotherapy. Two (1 PH, 1 TH) admitted to previous treatment with isoniazid for approximately three weeks and two months, respectively; they are regarded as having acquired resistance from previous chemotherapy. It is presumed that the remaining 15 patients (5 PH, 1 TH, 9 P_6H/H), with no history of previous chemotherapy, had been infected with isoniazid-resistant organisms-that is, had primary isoniazid resistance (an incidence of 6.4 %).

The detailed results of isoniazid-sensitivity tests on two pretreatment cultures and the response to treatment are set out for all 17 patients in Table 16. Both the patients with acquired isoniazid resistance had an unfavourable response, as did 12 of 15 patients with primary isoniazid resistance.

There were 15 patients who, on admission, had primary or acquired isoniazid resistance and who received isoniazid plus PAS (PH or P_6H/H); none had a history of previous treatment with PAS although one had received isoniazid. On the basis of a single pretreatment culture, all (except one who had no test) were classified as having a PAS-sensitive infection on admission. At six months, 10 patients had positive cultures of which six were classified as resistant to PAS. Thus, there is clear evidence that the PAS-sensitivity test, as carried out in this study, was able to detect the emergence of resistance to PAS in patients with isoniazid-resistant organisms initially.

PATIENTS WITH ANOMALOUS PRETREATMENT SENSITIVITY TEST RESULTS

One patient (PH) has been excluded from the analysis because he had one pretreatment culture resistant to isoniazid, streptomycin and PAS (MIC of 50 µg/ml, an RR of 8 and an RR of 4, respectively), although two other pretreatment cultures were sensitive to all three drugs; a discrepancy of this type is very unusual at the Centre and suggests that one of the pretreatment specimens was incorrectly labelled.

PATIENTS WITH ANONYMOUS MYCOBACTERIAL INFECTIONS

For two patients (1 TH, 1 P_6H/H), the cultures from specimens obtained on admission were pure growths of photochromogenic organisms;[1] these were

[1] Subsequently identified as *Mycobacterium kansasii.*

TABLE 16
RESPONSE TO TREATMENT IN PATIENTS WITH ISONIAZID-RESISTANT ORGANISMS ON ADMISSION

Isoniazid resistance	Serial No.	Treatment series	MIC [a] of isoniazid on 2 cultures on admission		Response to treatment at 12 months
Acquired	R72	PH	5	5	Unfavourable [b]
	R9	TH	5	5	Unfavourable
Primary	R193	PH	50	50	Unfavourable
	R198	PH	5	5	Unfavourable
	R143	PH	1, 1	1, 1	Unfavourable
	R58	PH	1, 1	1, 1	Unfavourable
	R78	PH	1, 5	0.2	Favourable [c]
	R153	TH	5	0.2	Unfavourable
	R128	P_6H/H	50	5	Unfavourable
	R171	P_6H/H	5	5	Unfavourable
	R203	P_6H/H	5	5	Unfavourable
	R94	P_6H/H	5	> I	Favourable
	R236	P_6H/H	1, 1	1, 1	Favourable
	R67	P_6H/H	1, 1	1, 1	Unfavourable
	R91	P_6H/H	1, 1	1, 1	Unfavourable
	R221	P_6H/H	1, 1	1, 0.2	Unfavourable
	R127	P_6H/H	1, 1	0.2	Unfavourable

[a] Minimal inhibitory concentration.
[b] Bacteriologically active disease at 12 months including termination of allocated chemotherapy owing to persistent sputum positivity or serious radiographic or clinical deterioration.
[c] Bacteriologically quiescent disease at 12 months.

niacin-negative and highly resistant to isoniazid and PAS. The TH patient had positive cultures from 1 to 6 months and at 8 and 9 months. The P_6H/H patient had positive cultures at the first month only. All positive cultures during treatment from both these patients were pure growths of photochromogenic organisms.

X. DISCUSSION

The cost of chemotherapy is a major consideration in planning antituberculosis programmes in many developing countries and, therefore, studies at the Centre continue to be directed towards finding regimens which are inexpensive, effective, non-toxic and acceptable to the patients, and hence suitable for application on a wide scale. Isoniazid alone, given in its optimal dosage of approximately 8-9 mg/kg body-weight as a single daily dose, is inexpensive and, if given with 6 mg of pyridoxine, non-toxic (Tuberculosis Chemotherapy Centre, Madras, 196313); however, it is not as effective as a standard daily regimen of 200 mg of isoniazid plus 10 g of sodium PAS, given in two divided doses (Tuberculosis Chemotherapy Centre, Madras, 1960)—the PH regimen of the present study. The present study was designed to compare for a year two dual-drug oral regimens, less expensive and smaller in bulk, with the standard PH regimen. One of these was the TH regimen, that is, 300 mg of isoniazid plus 150 mg of

thioacetazone given in one dose daily for the whole year. This regimen has been found to be as effective as the PH regimen in East African patients (East African/British Medical Research Council Second Thiacetazone Investigation, 1963). The other was a 2-phase regimen of 200 mg of isoniazid plus 6 g of sodium PAS given daily in one dose for the first 6 months, followed for the second 6 months by isoniazid alone in one daily dose of 300 mg–the P_6H/H regimen.

THERAPEUTIC EFFICACY

The therapeutic efficacies of the PH and TH regimens were the same, 82 % of the patients in each series having a favourable response to treatment, and this confirms the findings in East Africa (East African/British Medical Research Council Second Thiacetazone Investigation, 1963). The P_6H/H patients, however, fared less well, only 67 % having a favourable response.

The PH regimen

The efficacy of the PH regimen in this study was of the same order as in three previous studies by the Centre (Tuberculosis Chemotherapy Centre, Madras, 1959, 1960, 1964), in which 86%, 91% and 85% of the patients had a favourable response (average of 87 %), and was within the expected range (95 % confidence limits) of 79 % to 95 %. The severity of the disease on admission was broadly similar in the four studies.

The TH regimen

The therapeutic results with thioacetazone plus isoniazid in the present study are encouraging. Favourable results with this combination have also been reported from other parts of India (Deshmukh, Master & Kulkarni, 1963; Sikand, Goyal & Mathur, 1964; Menon, 1965).

It is of interest to compare the findings in the present study with those in East Africa. Mitchison & Lloyd (1964) have reported, on the basis of a concurrent comparison, that cultures of tubercle bacilli from previously untreated patients are more often resistant to thioacetazone in Madras than in East Africa. In a further unpublished concurrent comparison, an MIC of 2 µg/ml has been found in 83 % of patients at Madras and in 39 % of patients in East Africa (Mitchison, personal communication, 1966). (Supporting evidence from the present study that Madras strains are more often resistant before treatment is derived from the fact that resistance emerged during treatment less frequently in Madras than in East African patients.) Further, an association between pretreatment thioacetazone sensitivity and unfavourable response to treatment was found in East Africa in patients receiving isoniazid plus thioacetazone; it might therefore be expected that the TH regimen in Madras would be less effective. However, thioacetazone-resistant strains from untreated Madras patients are frequently of low virulence (Joseph et al., 1964), and it has been shown by Ramakrishnan et al. (1961) that Madras patients with strains of low virulence progress slightly more satisfactorily when treated with *isoniazid alone* than patients with strains of high virulence. Thus, the therapeutic disadvantage of pretreatment thioacetazone-resistant strains may be offset to some extent by the possible advantage gained from their low virulence.

The P_6H/H regimen

Bowerman (1957) has reported a controlled comparison in which a daily dosage of 10-12 g of PAS, given in divided doses, was slightly more effective in combination with isoniazid than was 5-6 g also given in divided doses. However, there is subsequent evidence that a *single* high dose of PAS can saturate the acetylating process of the body more effectively than a series of small doses and thus result in higher concentrations of therapeutically active PAS in the blood (Lehmann, 1959; Wagner, Fajkosova & Simane, 1960; Bang et al., 1962). In the present study, the proportion of patients with a favourable response at six months was 81% for the PH and 76% for the P_6H/H series. There was therefore only a suggestion that at six months the PH patients had responded better bacteriologically. Reisner & Shaw (1963) and Reisner (1964, 1965) reported on a controlled study comparing (a) a regimen of 300 mg of isoniazid plus 6 g of PAS (equivalent to 8.3 g of sodium PAS) given in one dose daily with (6) a regimen of 300 mg of isoniazid in one dose plus 12 g of PAS in three divided doses and (c) a regimen of 300 mg of isoniazid plus 12 g of PAS, both drugs being given in three divided doses. They found at four months that the regimen containing 6 g of PAS was as effective as the other two regimens in all respects.

The proportions of patients with an unfavourable response to treatment in the P_6H/H series increased from 24 % at six months to 33 % at one year, whereas the corresponding proportions for the PH series were 19 % and 18 %, respectively. It has been

observed in the Centre that when any regimen, irrespective of its therapeutic effectiveness, is given for a year, the results at one year closely resemble those at six months, a finding that was observed in the PH series (and also the TH series) in the present study. It is therefore likely that the same would have applied to the regimen containing 200 mg of isoniazid plus 6 g of PAS had it been continued for the full year. If this is so, it follows that isoniazid alone in the second six months was unable to maintain the progress attained by patients in this series at the end of the first six months. However, the efficacy of maintenance chemotherapy with isoniazid alone may well depend on the intensity of the initial treatment as, in the International Union against Tuberculosis Investigation (1964), it was found that in patients who had had 28 weeks of *triple*- drug chemotherapy (streptomycin, isoniazid and PAS), all of 33 who were allocated at random to isoniazid alone had all cultures negative at 52 weeks (and 35 of 37 patients who were allocated isoniazid plus PAS).

TOXICITY

Severe toxic reactions, requiring an interruption or termination of chemotherapy, occurred to similar extents in the PH and TH series, but were rather less frequent in the P_6H/H series, the proportions being 11% of 71 PH, 12% of 75 TH and 4% of 71 P_6H/H patients.

Cutaneous hypersensitivity was the commonest serious reaction and occurred in 4 PH, 5 TH and 1 P_6H/H patients, all of whom were affected in the first 3 months, 3 of them (all TH) in the first month. Hypersensitivity due to PAS was less common in patients receiving the 6-g dosage than in those on the 10-g dosage, in keeping with the report of Bowerman (1957). Although the incidence of cutaneous hypersensitivity in the PH and the TH series was similar, the reactions were more severe in the TH patients, two of whom required urgent hospital admission, one for a Stevens-Johnson syndrome and the other for a Stevens-Johnson syndrome and extensive exfoliative dermatitis; two other patients had early exfoliative dermatitis. Other cases of exfoliative dermatitis due to thioacetazone have recently been reported in India and elsewhere (Raj Narain, personal communication, 1963; Mehrotra et al., 1965; East African/British Medical Research Council Third Thiacetazone Investigation, 1966); it is therefore important that clinicians giving thioacetazone should exercise particular caution when skin hypersensitivity occurs.

Thioacetazone, when administered in a daily dosage of 200 mg or more, has been reported to be particularly toxic to the liver and haemopoietic system (Hinshaw & McDermott, 1950; Bunn, 1950). In the present study, in which it was given in a single daily dose of 150 mg, there was no evidence of a greater incidence of serious liver toxicity than with sodium PAS in a dosage of 10 g daily, since jaundice. (not necessarily due to drug toxicity) occurred in two PH and two TH patients. Also, at the end of the year of treatment, there was a similar rise in the serum GOT level in patients receiving TH and P_6H/H (no estimations were undertaken for patients receiving PH). It is possible that this rise was due to an improvement in the nutritional state of the patients as Babcock, Brush & Sostman (1960) have reported a rise in the average serum GOT levels after the administration of vitamin B_6 to 15 college students who had been deprived of this vitamin in their diets.

Considering the toxic effect on the haemopoietic system, the average total leucocyte and polymorphonuclear cell counts fell to a similar extent during the year in all three series. A neutropenia of less than 1000 cells/mm^3 was observed in only one TH patient and might have been due to thioacetazone. However, the average haemoglobin level rose only by 0.9 g per 100 ml over 12 months in the TH series, as compared with 1.6 g per 100 ml in the PH series and 2.1 g per 100 ml in the P_6H/H series; the corresponding increases in the PCV values were 2.5%, 4.1% and 4.7%, respectively; all the increases are statistically significant. These findings are similar to those reported from East Africa (East African/British Medical Research Council Thiacetazone/Diphenylthiourea Investigation, 1960).

Gastrointestinal disturbances due to thioacetazone have been reported to occur commonly (Deshmukh & Master, 1962). In the present study, two patients in each of the three series had severe gastrointestinal complaints necessitating an interruption of chemotherapy. Minor complaints of anorexia, vomiting and giddiness, not requiring any interruption of chemotherapy, were recorded much more frequently among the TH patients. However, since isoniazid plus thioacetazone was being used for the first time in the Centre, it is possible that the clinicians were more assiduous in recording complaints from patients treated with this regimen. (Nevertheless, it is of interest that the TH patients gained, on the average, only 6.0 lb during the year, as compared with 10.6 lb for the PH and 10.3 lb for the P_6H/H

patients; the differences being highly significant ($P<0.01$).) Glycosuria occurred in 31% of 65 TH patients, as compared with 13 % of a control group of 61 P_6H/H patients ($P=0.03$); it was, however, not a persisting feature as the test results were negative in all but one patient after cessation of chemotherapy. Three patients were investigated further and found to have a normal glucose tolerance curve. However, Haynes (1952) has reported two East African patients who, on each occasion thioacetazone was administered, developed episodes of glycosuria with a diabetic-type glucose tolerance result. Escovitz (1952) has also reported two patients with pulmonary tuberculosis who showed demonstrable impairment of carbohydrate metabolism associated with prolonged administration of Amithiozone (thioacetazone) and Mitra (1964) has noted glycosuria and hyperglycaemia in 3 of 50 patients treated with Tebafen (nicotinaldehyde thiosemicarbazone+isonicotinic acid hydrazide).

The frequency of minor side-effects in the TH regimen might prove to be important in that the acceptability of the regimen might be adversely affected. There is some evidence in the present study that patients in the TH series were less regular in attending the clinic to collect their weekly supply of drugs, as compared with patients in the PH and the P_6H/H series. It has been claimed (Deshmukh & Master, 1962) that vitamins and antihistamine additives reduce the incidence of side-effects, and this is to be the subject of an investigation by the Medical Research Council of Great Britain in a number of countries, including India. It is also possible that a reduction in the incidence might be achieved by giving the thioacetazone in two doses daily, without necessarily impairing the therapeutic effect (Sikand, Goyal & Mathur, 1964).

BACTERIAL RESISTANCE TO THE DRUGS

In previous studies in the Centre, the PAS-sensitivity test, using an undiluted inoculum, was not found to be satisfactory for classifying strains as sensitive or resistant (Tuberculosis Chemotherapy Centre, Madras, 1959, 1960). In the present study, a smaller inoculum (obtained from a 1 in 10 dilution) was therefore used (for reasons, see Selkon et al., 1960), and although there was some improvement the test was still not very satisfactory. Thus, in patients with *isoniazid-sensitive* organisms on admission, the sensitivity to PAS of the pretreatment cultures did not appear to influence the response to treatment either in the PH or in the P_6H/H series. However, there was evidence that the test measures acquired resistance, but that resistance emerged infrequently during treatment with isoniazid plus PAS. The occurrence of PAS-sensitive strains during treatment is presumably because PAS, as has been shown *in vitro*, may not inhibit but only delay the growth of PAS-sensitive organisms (Singh, 1954; Mitchison, 1965). On the other hand, there is evidence from both the present study and the East African studies (East African/British Medical Research Council Pretreatment Drug Resistance Report, 1963) that in patients with initially *isoniazid-resistant* organisms who are treated with isoniazid plus PAS (and in whom PAS may therefore be acting alone), PAS resistance emerged more frequently; there is also some evidence that PAS resistance emerges in patients treated with PAS alone (Great Britain, Medical Research Council, 1950).

Finally, there is some evidence in the present study that the emergence of isoniazid resistance occurred earlier in the TH series than in either of the two isoniazid plus PAS series, although it should be noted that in the later months of treatment the proportion of patients with isoniazid-resistant organisms in the TH and PH series were similar. The explanation for this may be that PAS may delay the growth of isoniazid-resistant mutants in the same manner as it delays the growth of isoniazid-sensitive organisms *in vitro* (see above).

CONCLUSION

This study has shown that isoniazid in a dosage of 300 mg plus thioacetazone in a dosage of 150 mg given together in one dose daily is as effective as the standard regimen of isoniazid plus PAS. However, there is conflicting evidence on the incidence of thioacetazone toxicity and, further, there is evidence of geographical variations in the prevalence of naturally occurring thioacetazone-resistant strains of tubercle bacilli (Mitchison & Lloyd, 1964); these suggest that it would be advisable to establish the toxicity and therapeutic efficacy of thioacetazone under local conditions by conducting careful preliminary trials before introducing it on a large scale in any country (see also World Health Organization Expert Committee on Tuberculosis, 1964). Finally, there is also some suggestion that 200 mg of isoniazid plus 6 g of PAS, given in one dose daily for one year, might prove as effective as 200 mg of isoniazid plus 10 g of PAS, given daily in two divided doses for one year.

XI. SUMMARY

1. Two hundred and forty South Indian patients with advanced pulmonary tuberculosis were allocated at random to treatment for one year with one of three regimens of daily, oral, chemotherapy; the patients were treated on an out-patient basis and required to administer the drugs themselves at home.

2. The three regimens and the daily dosages for a patient weighing 100 lb (45.4 kg) were:

PH: Isoniazid 200 mg plus sodium PAS 10 g, in two divided doses

TH: Isoniazid 300 mg plus thioacetazone 150 mg, in one dose

P_6H/H: Isoniazid 200 mg plus sodium PAS 6 g, in one dose for the first 6 months, followed by isoniazid 300 mg in one dose for the second 6 months.

3. The main analysis of this report concerns 220 of the 240 patients-namely, the 72 PH, 77 TH and 71 P_6H/H patients who had organisms sensitive to isoniazid on admission; of these, 214 had received no previous chemotherapy while the remaining 6 had received it for not more than 2 weeks.

4. The clinical, radiographic and bacteriological condition of the patients in the three series were similar at the time of admission.

5. During the year there were 8 deaths, 2 (1 PH, 1 TH) from tuberculosis, and 6 (2 PH, 4 TH) from non-tuberculous causes; serious clinical or radiographic deterioration necessitating termination of the allocated chemotherapy occurred in 3 PH, 3 TH and 7 P_6H/H patients.

6. At one year, 82 % of 66 PH, 82 % of 65 TH and 67% of 63 P_6H/H patients were classified as having a favourable response, mainly on the basis of culture results at 10, 11 and 12 months.

7. The majority of patients showed at least moderate radiographic improvement over the year–namely, 83 % of the PH, 77 % of the TH and 70 % of the P_6H/H patients. Cavitation disappeared in 70% of 44 PH, 69% of 39 TH and 61% of 41 P_6H/H patients with initial cavitation and became less in 7 %, 18 % and 15 %, respectively.

8. Chemotherapy was interrupted or terminated on account of toxicity in 8 (11%) PH, 9 (12 %) TH and 3 (4%) P_6H/H patients; this was due to cutaneous hypersensitivity in 4, 5 and 1, jaundice in 2, 2 and 0, and severe gastrointestinal complaints in 2, 2 and 2, respectively. Exfoliative dermatitis was observed in 3 patients (all TH).

9. Complaints of vomiting were recorded in 8% of the PH, 23 % of the TH and 15 % of the P_6H/H patients, of anorexia in 7 %, 17 % and 4% respectively, and of giddiness in 4%, 28% and 10%, respectively. Glycosuria during treatment occurred in 31% of the TH patients, as compared with 13 % of the P_6H/H patients. Neurological complications due to isoniazid occurred in 1 TH and 1 P_6H/H patient.

10. The average haemoglobin value in the PH series increased from 11.7 g per 100 ml on admission to treatment to 13.3 g per 100 ml at 12 months; the corresponding figures were 11.5 and 12.4 g in the TH series, and 10.9 and 13.0 g in the P_6H/H series.

11. Major non-cooperation was encountered in 13 patients (3 PH, 4 TH, 6 P_6H/H) including 5 (1 PH, 2 TH, 2 P_6H/H) who refused further treatment. In all three series, patients attended the Centre less regularly to collect their drugs in the later months of treatment.

12. This study has shown that the regimen of isoniazid plus thioacetazone (TH) was as effective as the standard regimen of isoniazid plus PAS (PH) in the treatment for one year of patients with advanced pulmonary tuberculosis. However, the thioacetazone regimen had a higher incidence of side-effects. A 2-phased regimen of isoniazid plus 6 g of PAS for the first 6 months followed by isoniazid alone for the second 6 months (P_6H/H) was less effective.

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RÉSUMÉ

Au cours de cette enquête du Centre de Chimiothérapie de la Tuberculose, à Madras (Inde), 240 malades atteints de tuberculose pulmonaire avancée ont été traités ambulatoirement suivant l'un de trois schémas de traitement déterminé par randomisation. Chaque schéma a été administré par voie orale par auto-médication, durant 12 mois, aux dosages quotidiens suivants correspondant à un malade pesant 45,4 kg: *a*) 200 mg d'isoniazide et 10 g de PAS, en deux doses séparées (traitement PH); *b*) 300 mg d'isoniazide et 150 mg de thio-acétazone, en une dose unique (traitement TH); *c*) 200 mg d'isoniazide et 6 g de PAS, en une dose unique, durant les six premiers mois, et une dose unique de 300 mg d'isoniazide, pendant les six derniers mois (traitement P_6H/H).

L'analyse des résultats porte essentiellement sur 220 patients (72 PH, 77 TH et 71 P_6H/H) porteurs, au début du traitement, de bacilles sensibles à l'isoniazide; 214 d'entre eux n'avaient reçu aucun traitement chimiothérapique et 6 avaient été traités pendant 2 semaines au plus. Quant aux données cliniques, radiologiques et bactériologiques, elles étaient, avant le traitement, similaires dans les trois groupes.

Durant les 12 mois d'observation, on enregistra 2 décès par tuberculose (1 PH et 1 TH) et 6 décès par cause non tuberculeuse (2 PH et 4 TH); chez 13 malades (3 PH, 3 TH et 7 P_6H/H), la chimiothérapie dut être interrompue en raison d'une aggravation, clinique ou radiographique, de leur état.

Après un an, sur la base des résultats de cultures effectuées aux 10e, 11e et 12e mois, on notait une réponse favorable au traitement chez respectivement 82% des 66 PH, 82% des 65 TH et 67% des 63 P_6H/H. Au cours de cette période, la majorité des malades (83% des PH, 77% des TH et 70% des P_6H/H) bénéficièrent d'une amélioration, au moins légère, de leur état décelable radiologiquement. Chez les patients atteints initialement de lésions cavitaires (44 PH, 39 TH et 41 P_6H/H), celles-ci disparurent dans 70%, 69% et 61% des cas respectivement, ou s'atténuèrent (respectivement 7%, 18% et 15% des cas).

La chimiothérapie dut être interrompue ou définitivement supprimée chez certains malades (8 (11%) PH, 9 (12%) TH et 3 (4%) P_6H/H) en raison de l'action toxique des médicaments déterminant de l'hypersensibilité cutanée (4; 5 et 1 cas, respectivement), de l'ictère (2; 2 et 0 cas) et des troubles gastro-intestinaux graves (2; 2 et 2 cas). Une dermatite exfoliative se déclara chez 3 patients, tous TH. Certains malades se plaignirent de vomissements (8% des PH, 23% des TH et 15% des P_6H/H), d'anorexie (7%, 17% et 4%) et de vertiges (4%, 28% et 10%). Au cours du traitement, de la glycosurie fut décelée chez 31% des TH et 13% des P_6H/H. Deux malades (1 TH et 1 P_6H/H) présentèrent des complications neurologiques à la suite du traitement par l'isoniazide.

A l'issue des 12 mois de traitement, la teneur du sang en hémoglobine, initialement de 11,7 g/100 ml chez les malades PH, atteignait 13,3 g/100 ml; les chiffres correspondants étaient de 11,5 g et 12,4 g chez les TH, et de 10,9 g et 13 g chez les P_6H/H.

On eut à déplorer un sérieux manque de coopération chez 13 malades (3 PH, 4 TH et 6 P_6H/H) dont 5 (1 PH, 2 TH et 2 P_6H/H) refusèrent de poursuivre le traitement. Dans tous les groupes, les malades se présentèrent au Centre pour y retirer leurs médicaments avec une assiduité moindre durant les derniers mois.

Les résultats de cette enquête montrent que, en traitement d'un an, l'association isoniazide-thio-acétazone (TH) est aussi active que le schéma standard isoniazide-PAS (PH) chez les malades atteints de tuberculose pulmonaire avancée. Cependant, les effets secondaires sont plus fréquents en cas d'emploi de thio-acétazone. Les résultats les moins concluants ont été observés avec le traitement en deux stades (P_6H/H) comportant l'administration d'isoniazide et de 6 g de PAS pendant les six premiers mois, et d'isoniazide seul pendant les six derniers mois.

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APPENDIX TABLE A
DOSAGE OF DRUGS IN RELATION TO BODY-WEIGHT

Regimen		Body-weight (lb [a])	Total daily dosage			Dosage in relation to body-weight			No. of cachets or tablets to be taken daily	
			Isoniazid mg	Sodium PAS (g)	Thioacetazone	Isoniazid m	Sodium PAS (g/kg)	Thioacetazone m	Morning	Evening
PH		50-79	150	7.50	—	6.6-4.2	0.33-0.21		3	3
		80-99	175	8.75		4.8-3.9	0.24-0.20	–	3	4
		100 or more	200	10.00	—	4.4 or less	0.22 or less		4	4
TH		50-69	200		100	8.8-6.4		4.4-3.2	4	0
		70-89	250		125	7.9-6.2		3.9-3.1	5	0
		90 or more	300		150	7.3 or less	–	3.7 or less	6	0
P_6H/H	First months	50-79	200	6	–	8.8-5.6	0.26-0.17		4	0
		80-99	200	6		5.5-4.4	0.16-0.13		4	0
		100 or more	200	6	—	4.4 or less	0.13 or less	-	4	0
	Second months	50-69	200	–	—	8.8-6.4	–		4	0
		70-89	250			7.9-6.2			5	0
		90-109	300	–	—	7.3-6.1			6	0
		110 or more	350		—	7.0 or less	–		7	0

[a] 1 lb = 0.45 kg.

APPENDIX TABLE B. SERUM AND BLOOD GOT VALUES ON ADMISSION AND AT 3, 9 AND 12 MONTHS

		TH patients								P_6H/H patients							
		On admission		At 3 months		At Q months		At 12 months		On admission		At 3 months		At 9 months		At 12 months	
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Serum GOT	Less than 10	3	4	5	7	3	5	0	0	2	3	3	4	0	0	0	0
	10-	28	39	18	25	18	28	10	16	30	44	19	28	13	21	5	9
	20-	32	45	39	53	30	47	27	44	26	38	30	43	28[a]	45	30	56
	30-	6	8	7	10	11	17	17	27	5	7	10	14	13	21	9	17
	40 or more	2	3	4	5	2	3	8	13	5	7	7	10	0	13	10	19
	Total [b]	71	99	73	100	64	100	62	100	68	99	69	99	62	100	54	101
	Average	21.3		22.9		23.2		28.2		21.8		24.3		28.9		29.9	
	No result available	4	–	0	–	2	–	4	–	3	–	1	–	4	–	7	–
Blood GOT	Less than 400	7	10	16	23	3	5	4	7	3	5	7	10	1	2	2	4
	400-	8	11	13	18	21	33	10	16	6	9	13	19	4	6	5	9
	500-	43	61	37	52	37	58	41	67	44	67	40	58	44[a]	70	39	74
	700 or more	13	18	5	7	3	5	6	10	13	20	9	13	14	22	7	13
	Total [b]	71	100	71	100	64	101	61	100	66	101	69	100	63	100	53	100
	Average	598		529		545		565		602		575		620		600	
	No result available	4	–	2	–	2	–	5	–	5	–	1	–	3	–	8	–
Patients who had their allocated chemotherapy terminated on account of toxicity		–	–	1	–	1	–	1	–	–	–	1	–	1	–	1	–
Patients who had their allocated chemotherapy terminated owing to death, serious radiographic or clinical deterioration, or non-cooperation		–	–	1	–	8	–	8	–	–	–	0	–	4	–	9	–
All patients		75	–	75	–	75	–	76	–	71	–	71	–	71	–	71	–

[a] Including one specimen at 8 months.
[b] The policy for including In the analyses patients who did not receive the allocated chemotherapy throughout the 12-month period is described on page 489.

APPENDIX TABLE C

HAEMOGLOBIN, PACKED CELL VOLUME AND LEUCOCYTE COUNT VALUES ON ADMISSION TO TREATMENT AND AT 3, 9 AND 12 MONTHS

	PH patients				TH patients								P_6H/H patients							
	On admission		At 12 months		On admission		At 3 months		At 9 months		At 12 months		On admission		At 3 months		At 9 months		At 12 months	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Haemoglobin (g/100 ml):																				
Less than 9	11	*15*	5	*8*	9	*12*	9	*12*	0	*0*	2	*3*	11	*16*	4	*6*	4	*6*	1	*2*
9-	13	*18*	6	*10*	21	*29*	10	*14*	8	*12*	9	*14*	25	*36*	21	*30*	5	*8*	9	*17*
11-	25	*35*	13	*21*	21	*29*	39	*53*	30	*47*	31	*48*	22	*32*	15	*21*	19 [a]	*29*	13	*24*
13-	20	*28*	20	*32*	19	*26*	14	*19*	22	*34*	20	*31*	10	*14*	22	*31*	19	*29*	19	*35*
15 or more	2	*3*	18	*29*	3	*4*	1	*1*	4	*6*	3	*5*	1	*1*	8	*11*	18	*28*	12	*22*
Average	11.7		13.3		11.5		11.7		12.7		12.4		10.9		12.2		13.4		13.0	
Packed cell volume (%):																				
Less than 30	6	*8*	3	*5*	7	*10*	8	*11*	2	*3*	2	*3*	7	*10*	2	*3*	3	*5*	2	*4*
30-	10	*14*	6	*10*	21	*29*	14	*19*	8	*12*	11	*17*	24	*35*	15	*21*	4	*6*	9	*17*
35-	29	*41*	14	*23*	26	*36*	35	*48*	29	*45*	28	*43*	24	*35*	22	*31*	18 [a]	*28*	11	*20*
40-	22	*31*	15	*24*	14	*19*	12	*16*	19	*30*	12	*18*	12	*17*	23	*33*	22	*34*	19	*35*
45 or more	4	*6*	24	*39*	5	*7*	4	*5*	6	*9*	12	*18*	2	*3*	8	*11*	18	*28*	13	*24*
Average	37.4		41.5		36.1		36.8		38.5		38.6		35.2		36.4		40.8		39.9	
Leucocyte count (cells/mm³):																				
Less than 4 000	0	*0*	1	*2*	0	*0*	0	*0*	0	*0*	3	*5*	0	*0*	0	*0*	0	*0*	2	*4*
4 000-	4	*6*	9	*15*	5	*7*	9	*12*	14	*22*	9	*14*	2	*3*	4	*6*	13	*20*	15	*28*
6 000-	16	*23*	25	*40*	21	*29*	17	*23*	19	*30*	31	*48*	20	*29*	27	*39*	28	*43*	21	*39*
8 000-	21	*30*	15	*24*	15	*21*	26	*36*	17	*27*	14	*22*	24	*35*	22	*31*	13 [a]	*20*	12	*22*
10 000-	17	*24*	8	*13*	17	*23*	9	*12*	11	*17*	4	*6*	10	*14*	11	*16*	7	*11*	3	*6*
12 000 or more	13	*18*	4	*6*	15	*21*	12	*16*	3	*5*	4	*6*	13	*19*	6	*9*	4	*6*	1	*2*
Average	9 800		8 100		9 700		9 300		8 100		7 700		9 500		8 400		7 900		7 100	
Total [b]	71	*100*	62	*100*	73	*100*	73	*100*	64	*100*	65	*100*	69	*100*	70	*100*	65	*100*	54	*100*
No results available	0	–	2	–	2	–	0	–	2	–	1	–	2	–	o	-	I	-	7	-
Patients who had their allocated chemotherapy terminated on account of toxicity	—	—	1	–	—	—	1	–	1	–	1	–	–	–	1	–	1	–	1	–
Patients who had their allocated chemotherapy terminated owing to death, serious radiographic or clinical deterioration, or non-cooperation	—	—	6	–	—	—	1	–	8	–	8	–	–	–	0	–	4	–	9	–
All patients	71	–	71	–	75	-	75	-	75	–	75	-	71	–	71	–	7 1	–	7 1	–

[a] Including one specimen at 8 months.

[b] The policy for Including In the analyses patients who did not receive the allocated chemotherapy throughout the 12-month period Is described on page 489.