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A Concurrent Comparison of Isoniazid plus PAS with Three Regimens of Isoniazid Alone in the Domiciliary Treatment of Pulmonary Tuberculosis in South India

TUBERCULOSIS CHEMOTHERAPY CENTRE, MADRAS

Recent studies have shown that treatment of pulmonary tuberculosis with isoniazid plus p-aminosalicylic acid (PAS) at home is, in the majority of cases, as satisfactory as treatment with the same combination of drugs in sanatorium and does not appear to expose the patient's contacts to any special risk. Before mass domiciliary chemotherapy can be introduced, however, a question that has to be decided is what drug or drugs and what dosage and rhythm of administration will be most effective.

This paper presents the results of a controlled comparison of four chemotherapeutic regimens : (a) 3.9-5.5 mglkg body-weight of isoniazid plus 0.2-0.3 g/kg body-weight of PAS (sodium salt) daily in two doses (the standard combined chemotherapy) ; (b) 7.8-9.6 mglkg body-weight of isoniazid alone daily in one dose ; (c) 7.8-9.6 mg/kg body-weight of isoniazid alone daily in two doses ; (d) 3.9-5.5 mg/kg body-weight of isoniazid alone daily in two doses. Isoniazid plus PAS proved to be the most satisfactory regimen; it was clinically effective and there were very few toxic manifestations.

I. INTRODUCTION

GENERAL

A controlled comparison of the merits of four different chemotherapeutic regimens in the domiciliary treatment of pulmonary tuberculosis for a period of 12 months has been completed at the Tuberculosis Chemotherapy Centre, Madras, and the following is a report of the results. The patients are being studied for a second and a third year, some receiving further chemotherapy. These findings will be reported later.

The formation of the Centre and its general objects have been described in an earlier report (Tuberculosis Chemotherapy Centre, 1959). The principles were agreed upon in October 1955 at a joint meeting in New Delhi of the Tuberculosis Sub-Committee of the Indian Council of Medical Research (ICMR) and representatives of the World Health Organization (WHO) and the Medical Research Council of Great Britain (MRC). It was decided that there were a number of problems in the chemotherapy of tuberculosis, relevant to the launching of mass campaigns in under-developed countries, which urgently required scientific investigation. The first and most important need was for an investigation of the efficacy of treatment at home as compared with treatment in sanatorium, including a study of the risks to which treatment of patients at home might expose their contacts. Secondly, because chemotherapy with isoniazid alone was being used on an increasing scale in India, it was important to investigate closely the efficacy of isoniazid when used alone, compared with standard combined chemotherapy, as well as the epidemiological consequences of an increase in the number of patients in the community excreting isoniazid-resistant organisms. The study of isoniazid alone has since become of even greater importance, for a number of authorities have either recommended the use of isoniazid alone in the conditions that obtain in many parts of India (McDermott, 1956) or have considered its use justifiable pending further research of the type reported here (World Health Organization Study Group on Chemotherapy and Chemoprophylaxis in Tuberculosis Control, 1957). Also, in 1957, UNICEF made substantial supplies

of isoniazid available, through the Indian Government, for use, alone, in a number of selected tuberculosis clinics. The considerable controversy concerning the use of isoniazid alone has been reviewed in a recent report (East African/British Medical Research Council Isoniazid Investigation, 1960).

The 1955 meeting in New Delhi recommended that a special research centre be established; the Madras Government elected to co-operate in the project and agreed to its being located in Madras City. The Centre opened in May 1956 and began its first major study, the comparison of home and sanatorium treatment, in September 1956. Some of the findings of this study, both for patients and their contacts, have already been reported (Tuberculosis Chemotherapy Centre, 1959; Andrews et al., 1960; [1] Velu et al., 1960[2]). The present report is concerned with the second major issue, that is, the efficacy of isoniazid alone, and gives the findings of a study of the merits of three different regimens of isoniazid alone compared with isoniazid plus p-aminosalicylic acid (PAS). This standard form of oral combined chemotherapy, when given for a year, has already been shown to be effective in the domiciliary treatment of patients in Madras City (Tuberculosis Chemotherapy Centre, 1959).

The members of the senior scientific staff of the Centre with major responsibility for the work reported here are: Dr Wallace Fox (WHO), Senior Medical Officer; Dr R. H. Andrews (WHO), Dr C. V. Ramakrishnan (ICMR) and Dr S. Velu (Madras Government), Medical Officers; Dr S. Devadatta (ICMR), Assistant Medical Officer; Dr A. L. Bhatia (ICMR) and Dr J. B. Selkon (WHO), Bacteriologists; Dr P. R. J. Gangadharam (ICMR), Assistant Bacteriologist; Mr T. V. Subbaiah (ICMR), Laboratory Research Assistant; Mr S. Radhakrishna (Madras Government), Statistician.

The research of the Centre is guided by a Project Committee consisting of three ICMR representatives (Dr P. V. Benjamin, Convenor, Dr J. Frimodt-Møller and Dr K. S. Sanjivi), the Director of the ICMR (Dr C. G. Pandit), the Director of Medical Services, Madras State (Dr V. R. Thayumanaswamy), a WHO representative (appointed for each meeting), an MRC representative (appointed for each meeting) and the Senior Medical Officer of the Centre (Dr Wallace Fox). The joint secretaries are Mrs K. Daniels and Mr B. S. Verma.

The MRC, through its Tuberculosis Research Unit, is responsible for the scientific direction of the research, in accordance with plans prepared by the Project Committee. Dr Wallace Fox of the Tuberculosis Research Unit has been seconded to WHO to serve as the Senior Medical Officer and the Director of Research at the Centre. Close contact is maintained between the Centre in Madras, the MRC Tuberculosis Research Unit (Dr P. D'Arcy Hart) and the MRC Group for Research on Drug Sensitivity in Tuberculosis (Dr D. A. Mitchison and Dr J. G. Wallace) in London. Dr Ian Sutherland of the MRC Statistical Research Unit has advised on statistical aspects.

The great majority of the patients in the present study were referred to the Centre from the Government Tuberculosis Institute, Madras, the Director of which during the period of intake was first Dr P. R. Mudaliar and then Dr M. A. Hamid, and the Corporation Tuberculosis Clinic, Pulianthope, the Medical Officer in Charge of which was Dr K. Narayana Murthi. The analysis was undertaken and the report was prepared in the Tuberculosis Chemotherapy Centre by the Centre's medical and statistical staff, Dr Wallace Fox and Mr S. Radhakrishna being the co-ordinators.

GENERAL OBJECTS OF THE STUDY

The study reported here was designed to yield information on the following aspects of the treatment of pulmonary tuberculosis among patients living in an adverse urban environment in South India.

(1) The progress of patients treated in their homes with three alternative regimens of isoniazid alone in comparison with the progress of patients treated with standard combined chemotherapy.

(2) The extent to which the infectivity of patients treated at home can be reduced by these different regimens of chemotherapy.

(3) The prevalence of tuberculosis in close family contacts at the time of diagnosis of the patient admitted to the study and the subsequent incidence of tuberculosis among them, with particular reference to the drug sensitivity and the guinea-pig virulence of the strains isolated from both the index cases and their contacts.

(4) The identity and the virulence in the guinea-pig of the strains isolated before treatment, and the relation of the virulence to the response of the patients to treatment.

[1] See article on page 463 of this issue.

[2] See article on page 511 of this issue.

(5) The relationship between the emergence of isoniazid resistance and the guinea-pig virulence, the catalase activity and the hydrogen peroxide susceptibility of the resistant strains, and their relation to the response of the patients to treatment.

(6) The rate of inactivation of isoniazid and its relation to isoniazid toxicity and the response of the patients to treatment.

The present report is concerned principally with the first and second of these points. The other subjects will be reported fully elsewhere.

II. GENERAL PLAN AND CONDUCT OF THE STUDY

SOURCE OF CASES

All the patients presented at local clinics with symptoms. Mass miniature radiography was not used as a source of cases. (For further details see the 1959 report.) The great majority of patients came from the poorest sections of the population of Madras City.

AREA OF INTAKE

Madras City has a population of approximately 1 750 000. The area of intake for the present study was approximately 20 square miles (50 km^2) and included 750 000 of this population.

DEFINITION OF ELIGIBLE CASES

With certain exceptions listed below, a patient with pulmonary tuberculosis was eligible for the study if all the following conditions were satisfied:

(1) The patient had either had no previous antituberculosis chemotherapy, or antituberculosis chemotherapy had been administered for not more than two weeks.

(2) The sputum was positive for tubercle bacilli either on direct smear examination or on culture.

(3) The patient was aged 12 years or more.

(4) The patient was living in Madras City in the defined area of intake (and was thus accessible for home visiting) and was likely to remain there for several years.

(5) The patient was prepared to :

(a) accept treatment at home for at least one year;

(b) accept treatment whether with tablets or injections;

(c) permit home visiting.

(6) The family was judged to be co-operative.

By adopting these criteria it was hoped to admit both newly diagnosed cases and old cases which had had no (or very little) previous chemotherapy, to be able to treat them for at least 12 months, and to follow them up for five years. In addition, it was the intention to examine all the close family contacts of each patient, by both radiography and tuberculin testing, at regular intervals over the 5-year period. (Findings on these contacts will be published separately.)

A patient was considered ineligible for the study if any of the following applied at the time of assessment :

(1) The patient was too ill to be treated at home (e.g., was nearly moribund, had a spontaneous pneumothorax or had had a severe haemoptysis).

(2) The patient had a pleural effusion obscuring more than one-third of a lung field, as seen on a postero-anterior chest radiograph.

(3) The patient had a non-respiratory form of tuberculosis which it was considered would complicate treatment.

(4) The patient was known to have leprosy.

(5) The patient was known to have a serious concomitant disease, such as diabetes.

(6) The patient was known to be pregnant.

PRETREATMENT INVESTIGATIONS

The following investigations were made before the start of chemotherapy in the present study:

(1) Clinical examination and assessment of the general clinical condition.

(2) A full-plate postero-anterior chest radiograph.

(3) Weight (lb.)

(4) Erythrocyte sedimentation rate (ESR Westergren 200 mm, reading in mm at one hour).

(5) An intracutaneous tuberculin (Mantoux) test with 5 tuberculin units (TU) of a purified protein derivative (PPD, batch RT22) on the left arm. If the greatest diameter of induration was less than 10 mm at 48 hours (sometimes 72 hours), a 100 TU test was undertaken on the right arm and this was also read at 48 hours (sometimes 72 hours).

(6) Examination of the urine for albumin and for sugar.

(7) The examination by direct smear and culture of a minimum of four sputum specimens, two produced on demand and within a matter of minutes in the Centre (" spot " specimens) and two produced overnight in the home (" collection " specimens).

(8) Tests of sensitivity to isoniazid, PAS and streptomycin on two cultures, usually one from a spot specimen and the other from a collection specimen.

(Other bacteriological investigations are referred to on page 542.)

In addition to the above, a detailed inquiry was made into previous chemotherapy.

Before accepting a patient for treatment the co-operation to be expected both from the patient and from the family was assessed both in the Centre and in the home by the health visitors, public health nurses, social workers and doctors.

THE CHEMOTHERAPEUTIC REGIMENS

Four chemotherapeutic regimens were studied (Table 1). These were a standard oral combination –namely, isoniazid plus PAS (PH)–and three regimens of isoniazid alone. One of these three regimens (H) contained the same dosage of isoniazid, in the same rhythm, as the combination isoniazid plus PAS; the other two contained the largest dose of isoniazid which it seemed likely could be given by itself without an unduly high proportion of the patients developing peripheral neuritis. The high dosage of isoniazid was studied because of the possibility that it would have greater efficacy than the low dosage. It was administered in one regimen (HI-2) as two doses a day and in the other (HI-1) as a single daily dose (at the suggestion of Dr J. Holm), to see whether the rhythm was important either in acceptability for self-administration or in therapeutic effectiveness. It was decided not to use pyridoxine as a preventative of peripheral neuritis (Biehl & Vilter, 1954; Tchertkoff et al., 1956) because this vitamin is expensive (it has subsequently been shown that it may possibly interfere with the therapeutic effectiveness of isoniazid (McCune et al., 1957)). The details of the chemotherapy and the dosage *for patients weighing 100 lb. (45.4 kg)* were as follows :

PH. Isoniazid 200 mg plus PAS (sodium salt) 10 g daily to be taken as eight cachets, four in the morning and four in the evening; each cachet was white and contained 25 mg of isoniazid and 1.25 g of PAS (sodium salt).

HI-1. Isoniazid 400 mg daily to be taken as eight tablets in a single dose in the morning; each tablet was blue, weighed 0.5 g and contained 50 mg of isoniazid.

HI-2. Isoniazid 400 mg daily to be taken as eight tablets, four in the morning and four in the evening; the same tablets were used as in the HI-1 regimen.

H. Isoniazid 200 mg daily to be taken as eight tablets, four in the morning and four in the evening; each tablet was pink, weighed 0.5 g and contained 25 mg of isoniazid.

The daily dosage was related to the patient's weight (Table 1). The mean daily dosage of isoniazid at the start of chemotherapy was 4.6 mg/kg for the PH series, 8.7 mg/kg for the HI-1 series, 8.7 mg/kg for the HI-2 series and 4.5 mg/kg for the H series. The mean daily dosage of PAS at the start of chemotherapy for the PH series was 0.23 g/kg.

If, at a monthly examination, it was found that a patient had gained weight and had moved into a higher weight category, the dosage was increased appropriately; however, if a patient lost weight and moved into a lower weight category, the dosage was not reduced.

PRESCRIBED DURATION OF CHEMOTHERAPY

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

ALLOCATION OF CHEMOTHERAPY

The allocation of chemotherapy was made from a pre-arranged list, prepared by the MRC Statistical Research Unit, which was based on random sampling numbers and which had been incorporated in a series of numbered sealed envelopes before the start of the study. The allocation was made by the Centre's statistical staff from the next envelope in the series. Neither the medical nor the statistical staff nor anybody else in the Centre had prior knowledge of the chemotherapy which any individual patient would receive. The patients were allocated to the treatment series in approximately the following proportions : 5 PH to 4 HI-1 to 4 HI-2 to 5 H, The HI-1 and HI-2 series were allocated smaller numbers because it was thought likely that the responses in these two series would be similar, and that the findings might therefore be amalgamated.

The first allocation was made on 5 October 1957 and the intake was stopped on 6 December 1958, by which date 342 patients had been allocated to the treatment series. One patient allocated to the HI-1 series left the district immediately and never commenced chemotherapy. Of the remaining 341 patients, 96 were allocated to the PH, 75 to the HI-1, 75 to the HI-2 and 95 to the H series.

It was originally intended to admit at least 360 patients to this study, but the intake was stopped as soon as it became evident from a preliminary analysis that enough patients had been admitted to permit the relative merits of the four chemotherapeutic regimens to be determined.

GENERAL MANAGEMENT

The patients were treated in their own homes, with supervision at the Centre of their progress. The great majority attended the Centre weekly throughout the 12 months for supplies of medicine. Further, a visit was usually paid to the home each week during the first month by a health visitor, and, less regularly, by a doctor or a public health nurse. Less frequent visits were made in later months, though the number was not usually less than two per month. The object of one of these visits was to deliver a sputum specimen bottle and that of the other, an unexpected visit, was to count the stock of medicament and collect a specimen of urine for testing, to check whether the patient was taking the medicine.

Patients who were initially too ill to attend weekly rested at home for the first month and were then brought to the Centre by ambulance for examination and re-assessment. As soon as they had improved sufficiently, which was usually after one month of treatment, they were changed to the ordinary routine of clinic and home visits. The patients were advised, if working, to stop work initially and to rest, and the majority did so, although rest was rarely strictly observed except by patients feeling really ill. The majority of the patients were ambulant much of the time and were quite often not at home when visited, especially at surprise visits. Patients were encouraged to return to work when they were considered medically fit. A number of patients returned to work before the Centre's staff considered them medically fit to do so.

ASSESSMENT OF PROGRESS

All the patients had examinations and assessments at monthly intervals after the start of chemotherapy, which included *(a)* a postero-anterior radiograph, *(b)* examination of two sputum specimens by smear and culture, *(c)* in addition, from three months onwards, a pair of laryngeal swabs for culture, *(d)* tests of sensitivity to the allocated drug or drugs on one positive culture, *(e)* measurement of the weight (lb.), and *(f)* assessment of the degree of ambulation and working capacity. The ESR was determined every three months.

URINE TESTING FOR ISONIAZID OR PAS

In order to check the self-administration of the medicine, a urine specimen was obtained at every visit to the Centre and also at surprise visits to the home, which the health visitor usually made once a month. A napthoquinone-mercuric chloride test for isoniazid (Short & Case, 1957; Gangadharam et al., 1958) was performed on the specimens from patients in the HI-1, HI-2 and H series. For patients in the PH series, a ferric chloride test for PAS (Simpson, 1956) was performed.

POWDERED MILK

Powdered milk was issued once a month to the families of all the patients; the quantities, which were the same as those supplied in the earlier study (Tuberculosis Chemotherapy Centre, 1959), were small.

III. BACTERIOLOGICAL PROCEDURES

BACTERIAL CONTENT OF SPUTUM SPECIMENS AND LARYNGEAL SWABS

Before the start of treatment a minimum of four sputum specimens was obtained–namely, two overnight (collection) specimens and two clinic (spot) specimens. At the end of every month of treatment two collection specimens of sputum were obtained from each patient. At the end of three months, and monthly thereafter, a pair of laryngeal swabs was also obtained, In all, therefore, a patient was scheduled to have 38 specimens examined by the end of 12 months. All the sputum specimens were examined by smear and culture and the laryngeal swabs by culture only. The reasons for this pattern of bacteriological investigation and the details of

the method of examination of the smears and the procedures for culture of sputum and laryngeal swabs have been described in the earlier report (Tuberculosis Chemotherapy Centre, 1959). In brief, smears were examined by fluorescence microscopy and were graded as 3-plus, 2-plus, 1-plus and negative. It was estimated that a 3-plus smear contained more than 5000 bacilli per mm^2, that is, about 100 bacilli per field examined with a total magnification of x 700. A 1-plus smear was recorded when there were fewer than about 300 bacilli per mm^2, that is, 6 bacilli per field under the same magnification; a 2-plus smear, therefore, contained between approximately 5000 and 300 bacilli per mm^2. Cultures were set up on Löwenstein-Jensen medium without potato starch (Jensen, 1955), and were examined weekly for between eight and nine weeks; they were reported as negative if no growth was present by that time. Positive cultures were graded when they first showed growth as 3-plus if the growth was confluent, as 2-plus if there were innumerable discrete colonies and as 1-plus if there were 100-20 colonies; the number of colonies was recorded if this was less than 20.

SENSITIVITY TESTS

Tests of sensitivity to isoniazid, PAS and streptomycin were performed on two cultures obtained before the start of treatment, one from a spot and one from a collection specimen. After the start of treatment tests of sensitivity to the allocated drug or drugs were performed on one positive culture at every month in which positive cultures were obtained. sensitivity tests were set up on Löwenstein-Jensen medium slopes containing the concentrations of drug set out below, as well as on a drug-free slope as a control. The standard sensitive strain, H37Rv, was also set up with each batch of tests. The details of the procedures have been given in the earlier report *(op. cit.)*

The drug concentrations used were as follows:

	Drug concentrations in µg/ml
lsoniazid :	
Test strain	0.2, 1, 5, 50
H37Rv	0.025, 0.05, 0.1, 0.2, 1
Sodium PAS dihydrate :	
Test strain	2, 4, 8, 16, 64
H37Rv	0.25, 0.5, 1, 2, 4
Streptomycin:	
Test strain	4, 8, 16, 32, 1024
H37Rv	1, 2, 4, 8

DEFINITIONS OF BACTERIAL DRUG RESISTANCE

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

Isoniazid

Pretreatment tests. Resistance was defined as:

(a) growth on 1 µg/ml or a higher concentration, even if the result of a test on a second culture was sensitive ;

(b) growth on 0.2 µg/ml, followed by the same result on a repeat test on the same culture, even if the result of a test on a second culture was sensitive; or

(c) growth on 0.2 µg/ml for two separate cultures (irrespective of the results of repeat tests).

Tests during treatment. Resistance was defined as: growth on 0.2 µg/ml or a higher concentration. This definition differs slightly from that used in the earlier report (Tuberculosis Chemotherapy Centre, 1959) in that growth on 0.2 µg/ml has now been classified as indicating resistance, irrespective of the results of any repeat tests. This modification has been introduced in the present study because in a series of 89 such repeat tests in the present study, only 12 failed to show growth on 0.2 µg/ml or a higher concentration. Moreover, in 10 of these 12 instances, resistant results were obtained at the succeeding month or at both the preceding and the succeeding months.

Streptomycin

Pretreatment tests. Resistance was defined as:

(a) a resistance ratio of 8 or more, or a resistance ratio of 4 followed by a ratio of 4 or more on a repeat test on the same culture, even if the result of a test on a second culture was sensitive; or

(b) a resistance ratio of 4 for each of two separate cultures.

The resistance ratio was defined as the minimal drug concentration inhibiting growth of the test strain divided by the minimal drug concentration inhibiting growth of strain H37Rv.

PAS

The definitions of PAS resistance used in the 1959 report are not appropriate to the present study. The findings for the present study are considered in section VIII.

OTHER INVESTIGATIONS

A number of other tests were undertaken on strains isolated from specimens obtained before the start of chemotherapy :

(1) Estimation of the catalase activity of all strains from each patient by a qualitative method.

(2) Estimation of the catalase activity of a sample of strains by a semi-quantitative method (Kreis, Le Joubioux & Pariente, 1956).

(3) A series of identification tests on one strain from each patient.

(4) Estimation of the virulence in the guinea-pig of one strain from each patient.

(5) Estimation of the susceptibility to hydrogen peroxide of a small sample of strains.

During chemotherapy the following estimations were made monthly :

(1) The qualitative catalase activity of all the strains on which sensitivity tests were performed.

(2) The semi-quantitative catalase activity of all the isoniazid-resistant strains.

The following tests were made on one strain from each patient at six, nine and 12 months after the start of chemotherapy:

(1) A series of identification tests.

(2) A guinea-pig virulence test.

(3) A hydrogen peroxide susceptibility test.

The results of these other bacteriological investigations will be fully reported elsewhere. The pre-treatment virulence findings are summarized in section VI.

IV. THE PATIENTS ADMITTED TO TREATMENT

CLASSIFICATION

In all, 341 patients were admitted to treatment, 96 to the PH, 75 to the HI-1, 75 to the HI-2 and 95 to the H series. Of these, 22 (6 PH, 3 HI-1, 7 HT-2, 6 H) were subsequently found to have been excreting isoniazid-resistant organisms before treatment. These patients have been separated from the main analysis and are considered in section XII. Only four other patients were removed from the main analysis. Of these, one patient (H) who had organisms sensitive to isoniazid had received more than two weeks of previous chemotherapy (probably including isoniazid). Another patient (H) died from a carcinoma of the bronchus which had complicated the interpretation of the course of the tuberculosis. One patient in the HI-1 series took his own discharge from treatment in the second month, and another HI-1 patient was advised, in error, by a member of the staff to take his medication in two doses a day instead of one and did so for two months. There remain 315 patients (90 PH, 70 HI-1, 68 HI-2, 87 H) who contribute to the main analysis. These patients conformed to the following especially important criteria :

(a) of having, on admission to the study, organisms sensitive to isoniazid;

(b) of having had, as far as is known, no previous chemotherapy or, in 2 PH, 3 HI-1, 4 HI-2 and 2 H patients, up to two weeks' chemotherapy; and

(c) of having followed the prescribed regimen for 12 months with, at most, minor variations, unless chemotherapy was stopped or changed owing to death, tuberculous deterioration or major toxicity.

Six patients (1 PH, 1 HI-1, 2 HI-2, 2 H) who had streptomycin-resistant strains before treatment have been left in the main analysis since none of the regimens included streptomycin.

No attempt has been made to exclude from the analysis any patients who may have had PAS-resistant strains before the start of treatment because of the difficulty in the present study identifying such patients with certainty (see section VIII). The test results suggest (see page 567) that between four and eight of the 315 patients in the main analysis (and not more than four in the PH series) had primary PAS-resistant strains. Their inclusion in the analysis may have put the PH series at a minor disadvantage.

PRETREATMENT COMPARISON BETWEEN THE FOUR SERIES

Age, sex and religion

The age and sex distributions are given in Table 2. Of the 90 patients in the PH series 63 % were males, compared with 54% of 70 in the HI-1 series, 72% of 68 in the HI-2 series and 63 % of 87 in the H series. The distributions of estimated age were reasonably

TABLE 3
CLINICAL AND RADIOGRAPHIC CONDITION ON ADMISSION TO TREATMENT

	PH		HI-1		HI-2		1 H	
	No.	%	No.	%	No.	%	No.	%
General condition :								
Good	16	18	15	21	15	22	15	17
Fair	53	59	44	63	37	54	53	61
Poor	18	20	11	16	15	22	19	22
Very poor	3	3	0	0	1	1	0	0
Weight (lb.*) :								
Under 60	5	6	0	0	1	1	2	2
60-69	9	10	12	17	10	15	10	11
70-79	26	29	16	23	10	15	16	18
so-39	28	31	20	29	20	29	32	37
90-99	15	17	14	20	17	25	14	16
100-109	6	7	5	7	9	13	11	13
110 or more	1	1	3	4	1	1	2	2
ESR (mm in 1 hour):								
0-10	0	0	1	1	1	7	1	7
11-20	3	3	2	3	4	6	2	2
21-50	24	27	16	23	14	21	20	23
51-100	44	49	40	57	36	53	52	60
101 or more	19	21	11	16	13	19	12	14
Extent of cavitation :								
Nil	8	9	1	1	5	7	8	9
Slight	24	27	26	37	19	28	25	29
Moderate	41	46	36	51	39	57	46	53
Extensive	17	19	7	10	5	7	8	9
Total extent of disease :								
Trivial	5	6	1	1	2	3	4	5
Slight	3	3	3	4	3	4	5	6
Limited	16	18	20	29	19	28	17	20
Moderate	33	37	29	41	28	41	34	39
Extensive	18	20	12	17	14	21	19	22
Gross	15	17	5	7	2	3	8	9
Number of lung zones involved in disease :								
1	1	1	3	4	2	3	4	5
2	15	17	10	14	13	19	13	15
3	14	16	13	19	13	19	15	17
4	19	21	23	33	15	22	14	16
5	22	24	12	17	16	24	32	37
6	19	21	9	13	9	13	9	10
Total patients	90	100	70	100	68	100	87	100

* 1 lb.=0.45 kg.

It will be seen from Table 3 that the four series of patients had very similar distributions in respect of the general condition, the weight and the ESR. Considering the radiographic features, the PH series was at a disadvantage, for 19% had extensive cavitation compared with 10 % in the HI-1, 7 % in the HI-2 and 9 % in the H series. Also, 17 % of the PH series had gross disease compared with 7 %, 3 % and 9 % for the other three series, respectively, and 21% of the PH series had six lung zones involved compared with 13 %, 13 % and 10 %, respectively. Considering extensive cavitation and gross disease (not tabulated here), 24 (27%) of the PH, nine (13 %) of the HI-1, five (7 %) of the HI-2 and 14 (16 %) of the H series had one or both of these undesirable features. The occurrence of such large pretreatment differences between four series, with random allocation, is most unusual ($P < 0.01$).

Table 4 presents the condition of the patients on admission to treatment as reflected by the bacterial content of four sputum specimens (two collection and two spot specimens). (Owing either to failure to collect all the required specimens or to contamination of cultures, complete results were not available for a small proportion of the patients. However, all the patients had at least one spot specimen and allexcept three (2 PH, 1 H) had at least one collection specimen.) Considering the findings on the first (or only) collection specimen, 74% of 88 PH patients, 91% of 70 HI-1, 88 % of 68 HI-2 and 85% of 86 H patients had a positive smear. The corresponding proportions were 78%, 83 %, 83 % and 84 % for the second collection specimen, 68% 74%, 76 % and 79 % for the first spot specimen and 70%, 77 %, 73 % and 78 % for the second spot specimen. The differences are greatest for the first collection specimen. Although the patients in the PH series had a smaller bacterial content of sputum on admission to treatment than those in the other three series, the differences between the four series are unusually large ($P<0.02$) only for the first collection specimen.

To summarize, the PH series was at a disadvantage radiographically and at an advantage bacteriologically. The pretreatment condition of the PH series has therefore been regarded, on balance, as similar to that of the other three series.

(A special analysis–not tabulated here–was made to study the effect upon the results of these pretreatment differences between the PH and the other three series. Measures of radiographic and bacteriological response to treatment in each of the four

TABLE 4

BACTERIAL CONTENT OF SPUTUM ON ADMISSION TO TREATMENT

Bacterial content of sputum		First (or only) collection specimen								Second collection specimen								First (or only) spot specimen								Second spot specimen							
		PH		HI-1		HI-2		H		PH		HI-1		HI-2		H		PH		HI-1		HI-2		H		PH		HI-1		HI-2		H	
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
	Culture negative	6	7	0	0	2	3	2	2	5	6	1	2	1	2	1	1	9	10	3	4	3	4	4	5	8	9	3	5	4	6	4	5
Direct smear negative	Culture less than 20 colonies	5	6	2	3	3	4	5	6	6	7	2	3	2	3	4	5	3	3	6	9	4	6	5	6	10	11	4	6	3	5	2	2
	Culture 20 colonies or more	12	14	4	6	3	4	6	7	7	9	7	12	8	12	7	9	17	19	9	13	9	13	9	10	8	9	8	12	11	17	12	14
	Smear l-plus (scanty)	14	16	19	27	13	19	11	13	10	12	11	18	9	14	11	14	28	31	20	29	25	37	36	41	26	30	24	37	21	32	25	30
Direct smear positive *	Smear 2-plus (moderate)	24	27	17	24	22	32	30	35	28	35	16	27	24	36	25	33	25	28	24	34	22	32	23	26	26	30	17	26	20	30	28	34
	Smear 3-plus (heavy)	27	31	28	40	25	37	32	37	25	31	23	38	22	33	28	37	8	9	8	11	5	7	10	11	10	11	9	14	7	11	12	14
	Total patients tested	88	101	70	100	68	99	86	100	81	100	60	100	66	100	76	99	90	100	70	100	68	99	87	99	88	100	65	100	66	101	83	99

* Even if the culture was negative.

treatment series during the 12 months were standardized statistically for pretreatment differences both in the extent of cavitation and in the bacterial content of the sputum. The results were practically unaltered by the standardization. In other words, the net effect on the results of the radiographic disadvantage and the bacteriological advantage before treatment in the PH series was negligible.)

CO-OPERATION OF THE PATIENTS

The co-operation obtained from the 341 patients admitted to treatment in the present study was excellent, only one patient absconding during the year. He and all the other survivors were examined at 12 months, so that information on the entire group of 341 patients was available at the end of the period.

PLAN OF THE REST OF THE REPORT

The next section (section V) describes the progress of the 315 patients in the main analysis. Section VI reports the study of virulence in the guinea-pig of the strains isolated before treatment and its bearing on the results of treatment. Section VII evaluates the prognostic importance of various characteristics at the start of treatment. Certain additional bacteriological findings are presented in section VIII. Analyses of toxicity and other clinical complications of treatment are given in section IX. Sections X and XI deal, respectively, with the self-administration of the medicine, and with rest and activity of the patients and the financial status of their families. The findings for the 26 patients not included in the main analysis are considered in section XII. This presentation of the results is followed by a discussion (section XIII) and a summary (section XIV).

V. COMPARISON OF THE FOUR TREATMENT SERIES

CLINICAL

Deaths

There were 11 deaths among the 315 patients during the 12-month period-namely, three (3 %) of the 90 PH patients, one (1%) of 70 HI-1, two (3 %) of 68 HI-2 and five (6 %) of 87 H patients.

Of the three PH patients, one (a female, aged 20) died of smallpox in the fifth month of treatment. The second (a female, aged 30) died in the seventh month of treatment. There had been considerable resolution of the lesion radiographically and all the 14 cultures examined from the first month of treatment onwards were negative for tubercle bacilli. She was admitted to hospital for investigation of diarrhoea associated with oedema of the face and legs, but passed into coma and died. The lumbar puncture findings were normal. Permission for a post-mortem examination was not obtained and the cause of death was not established, but, in view of the satisfactory response to treatment, it seems unlikely to have been connected with the tuberculosis. The third patient (a male, aged 30) died in the third month of treatment. Although he was responding radiographically and bacteriologically (the two culture results at two months being negative and two colonies, respectively, compared with 3-plus and 2-plus positive findings before treatment), the patient developed symptoms of a secondary respiratory infection with a pleurisy and was admitted to sanatorium; he died the same day. It is possible that his pulmonary tuberculosis, although responding, was at least a contributory cause of death.

The HI-1 patient (a female, aged 23) died in the third month. She had evidence of both a radiographic and a bacteriological response, but had had a chronic diarrhoea for a number of months. This led to generalized oedema. She died in hospital, and the cause of death was considered by the hospital physician to be idiopathic tropical steatorrhoea, permission for a post-mortem examination was not obtained.

One HI-2 patient (a male, aged 65), who was responding both radiographically and bacteriologically to treatment, died in his sleep in the second month. A cardiovascular catastrophe was considered to be the most likely cause of death. The other HI-2 patient (a male, aged 54) died of pulmonary tuberculosis in the fourth month of treatment.

Of the five H patients, one (a female, aged 20), with extensive disease and cavitation, died of pulmonary tuberculosis in the third week of treatment, and another (a male, aged 45), with gross disease and moderate cavitation, died in the fourth week. The third (a male, aged 38) died in the second month of treatment. At the start of treatment he had a moderately extensive lesion with moderate

cavitation which, at one month, showed a definite improvement both radiographically and bacteriologically. However, he had had diarrhoea at intervals for the previous nine months, associated with anaemia. He developed oedema of the feet, and was admitted to hospital for further investigation and treatment after five weeks of chemotherapy, but died suddenly. It was considered unlikely that the tuberculosis contributed to his death. The fourth patient (a female, aged 21) died early in the fourth month of treatment. She showed no bacteriological response, and the radiograph just before the end of the third month of treatment showed a radiographic spread, confirmed by an independent assessor (see next subsection), and it was decided to admit her to sanatorium and change her chemotherapy. Within two days she had developed a spontaneous pneumothorax and, despite intercostal drainage and daily streptomycin plus pyrazinamide, she died a week later. The fifth patient (a female, aged 55) died in the eighth month of treatment. She had failed to respond to her therapy and at the end of four months the independent assessor considered that there was a radiographic spread and recommended a change of chemotherapy; daily streptomycin plus pyrazinamide was commenced. The patient subsequently developed a gastro-enteritis which led to a vitamin B deficiency state, with oedema, ascites, anaemia, glossitis and angular stomatitis. She received vitamin B complex injections and packed cell transfusions but failed to improve and died early in the eighth month of treatment, there having been light resolution of the radiographic spread, although the sputum was still heavily positive. The primary cause of death was pellagra, but the tuberculosis may have been a contributory factor. (This patient has been classified in the rest of the report as having had her chemotherapy changed owing to a deterioration, and not as a tuberculous death.)

In the absence of post-mortem examinations it is difficult to be certain of the precise cause of death in several of these patients. Considering all the evidence, it seems probable that one PH, one HI-2 and four H patients either died of pulmonary tuberculosis or that the tuberculosis was a factor contributing to death. With the exception of the H patient who died more than three months after a change of chemotherapy (see above), these patients have been regarded as tuberculous deaths throughout the rest of the report. It should be noted that two of the deaths (in H patients) occurred in the first month of therapy.

Change of chemotherapy due to radiographic or clinical deterioration

Radiographic spread of the disease is not uncommon in the first month of treatment, even in patients whose subsequent progress is very satisfactory. For this reason a radiographic spread in the first month was not regarded as an indication to change the chemotherapy. In the course of a series of radiographic assessments, an independent assessor (Dr Raj Narain) was shown the radiographs on admission and at one month for each patient and he reported on definite spreads of disease, *no matter how localized,* and even if the over-all picture was one of improvement. Such spreads, many of which were minor, occurred in 26% of the 90 PH patients, 27% of the 70 HI-1, 28 % of the 68 HI-2 and 21% of the 85 H patients (two H patients had died in the first month).

If, during the course of the study, a patient was considered by the Centre's medical staff to have a definite radiographic extension of the disease which was not present at the first month, the following procedure was adopted. The supervision of the patient was intensified, a 7- to 10-day course of penicillin was given and a further radiograph was taken at the end of two weeks or at the next monthly examination. A careful supervision for possible radiographic evolution of the lesion was maintained. If the new lesion was persisting or spreading, and was more than minor, the complete radiographic series was shown to an independent assessor, Dr K. S. Sanjivi, who was unaware of the treatment the patient was receiving. (This procedure was adopted because of the observation of Oestreicher et al. (1955) that the radiographic spreads which occur under treatment with isoniazid alone frequently resolve without change of chemotherapy.) All the patients had a positive sputum when reviewed by the assessor. The assessor sometimes decided that the disease had deteriorated radiographically to such an extent that chemotherapy should be changed; sometimes he considered that, although a deterioration had occurred, it did not warrant a change of chemotherapy. In the latter circumstances he indicated when he wished to see the radiographic series again. It will be appreciated that a number of patients who changed chemotherapy because of a localized radiographic deterioration still showed, at that time, general radiographic improvement since the start of treatment.

Serious clinical deterioration was also regarded as a ground for changing the chemotherapy, without recourse to an assessor.

During the course of the 12 months 35 patients (1 (1%) PH, 5 (7%) HI-1, 14 (21%) HI-2 and 15 (17 %) H) had their treatment changed because of definite deterioration (Table 5). The differences between the PM series and the HI-2 and H series each attain significance at the 0.1% level, and the difference between the HI-1 and HI-2 series at the 5% level. In the majority of these patients (83 %) the treatment was changed in the second six months. Radiographic deterioration was confirmed by the independent assessor in 33 patients. The remaining two patients (both HI-2) had their chemotherapy changed because of serious clinical deterioration in one and an haemoptysis in the other.

One patient (HI-2) requires particular mention. His chemotherapy was changed in the twelfth month; he had peripheral neuritis as well as a radiographic deterioration. Except in the section on toxicity (section IX), this patient has been classified throughout the report as having the chemotherapy changed owing to deterioration.

TABLE 5

DISTRIBUTION OF CHANGES OF CHEMOTHERAPY DUE TO DETERIORATION ACCORDING TO THE NUMBER OF MONTHS OF CHEMOTHERAPY COMPLETED

Number of months of chemotherapy completed	Treatment series			
	PH	HI-1	HI-2	H
1	0	0	0	0
2	0	0	0	0
3	0	0	0	1
4	0	1	0	1
5	0	0	1	2
6	1	0	4	2
7	0	0	1	1
8	0	1	3	2
9	0	0	1	3
10	0	2	2	1
11	0	1	2	2
Total changes of chemotherapy	1 (1 %) **	5 (7 %)	14 (21 %)	15 * (17 %)

* One more patient, who deteriorated radiographically after completing two months of treatment, then had a spontaneous pneumothorax, and died within a week of a change of chemotherapy. She has been classified as a tuberculous death throughout this report (see page 547).

** The percentages are based on the total number of patients in each treatment series in the main analysis.

Changes of chemotherapy due to toxicity

In seven patients (1 PH, 5 HI-1 and 1 HI-2) the treatment was changed on account of toxic reactions to the chemotherapy. There was no toxicity in the H series. The PH patient had her chemotherapy changed in the third month following a hypersensitivity reaction to PAS. The HI-1 patients had their chemotherapy changed in the fifth, sixth, seventh, tenth and eleventh months, respectively, and the HI-2 patients in the sixth month, all on account of peripheral neuritis.

It was decided that patients who departed for more than six weeks from the prescribed chemotherapy on account of toxicity would be classified as having the chemotherapy changed on account of toxicity. This rule applied to one PH patient (in addition to the one referred to above) who departed from the prescribed chemotherapy for more than three months during desensitization to PAS (see page 569).

Some patients with toxic reactions did not have their chemotherapy changed. All the toxic manifestations are described in section IX.

Other departures from prescribed chemotherapy

Two PH patients had their chemotherapy modified to include streptomycin, for totals of 38 days and 17 days, respectively, the first during an attack of jaundice, the second during desensitization to PAS (see page 549). One patient received streptomycin in place of PAS with the isoniazid during hospital investigations, and five more PH patients had no supplies of chemotherapy for 41, 18, 17, 14 an seven days, respectively. Five HI-1 patients had no supplies of chemotherapy for 27, 23, nine, eight and seven days, respectively, four HI-2 patients for 10, eight, seven and seven days, respectively, and eight H patients for 28, 14, 12, 11, 10, seven, seven and seven days, respectively. These interruptions of chemotherapy were usually due to the patient's absence from Madras without a supply of medicine or admission to hospital for treatment of a non-tuberculous condition.

Presentation of the results for the patients whose chemotherapy was changed or who died

For the patients whose chemotherapy was changed there was a problem concerning the best way to present information about them after the changes had occurred. Because the *clinical findings subsequent*

to a change were not directly related to the chemotherapeutic regimen originally allocated, it was decided to exclude these subsequent findings from the tabulations. However, deterioration of the tuberculous disease under treatment was often a reason for the change of chemotherapy; if the fact that a patient had had chemotherapy changed *owing to deterioration* was not incorporated in the tabulations for the subsequent months, a fair evaluation of the progress of each treatment series could not be made. To meet this difficulty, the changes in chemotherapy were considered in two categories: those due to deterioration and those due to toxicity. The changes due to deterioration represented direct failures of the allocated chemotherapy to control the tuberculous disease; these have been included, under the heading of changes due to deterioration, in each tabulation of the clinical results subsequent to the month of change of treatment. The changes due to toxicity, on the other hand, were not necessarily associated with an unfavourable response of the tuberculous disease; these have therefore been excluded from all the tabulations after their occurrence.

The patients who died presented a similar problem, which was resolved in the same way. Those who died of tuberculosis, or in whom tuberculosis contributed to the death, have been included in the subsequent tabulations as tuberculous deaths. The patients who died of diseases other than tuberculosis do not appear in the tabulations after their death.

Weight changes

The weight changes for the 12-month period are set out in Table 6. During the first six months nearly all the patients gained weight–namely, 94% of 83 PH, 97% of 64 HI-1, 90% of 63 HI-2 and 77 % of 82 H patients, In the second six months a number of patients lost weight–namely, 46% of 80 PH, 41% of 58 HI-1, 36% of 61 HI-2 and 41% of 74 H patients. Over the full 12-month period 90% of 82 PH, 90 % of 60 HI-1, 69 % of 64 HI-2 and 69 % of 81 H patients gained weight.

Erythrocyte sedimentation rate

The distribution of the ESRs at the start of treatment, at six months and at 12 months are set out in Table 7. All four series showed a progressive increase in the number of patients with a low ESR. Thus, whereas three of 87 PH patients, three of 67 HI-1, five of 66 HI-2 and three of 86 H patients had an ESR of 20 mm or less before treatment, at

TABLE 6. WEIGHT CHANGES IN THE 12-MONTH PERIOD

Period	Treatment series	Total patients		Weight gain						No change		Weight loss				Change of chemotherapy during the period due to deterioration		Tuberculous death	
				21 lb. or more		14-20 lb.		7-13 lb.		less than 7 lb.		less than 7 lb.		7 lb. or more					
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
0-6 months *	PH	83	101	4	5	18	22	33	40	23	28	1	1	3	4	0	0	0	0	1	1
	HI-1	64	102	2	3	24	38	17	27	19	30	0	0	1	2	0	0	1	2	0	0
	HI-2	63	102	7	11	15	24	22	35	13	21	3	5	1	2	0	0	1	2	1	2
	H	82	100	5	6	8	10	26	32	24	29	0	0	11	13	1	1	4	5	3	4
6-12 months **	PH	80	100	0	0	1	1	5	6	30	38	6	8	34	42	3	4	1	1	0	0
	HI-1	58	100	0	0	1	2	3	5	22	38	4	7	22	38	2	3	4	7	0	0
	HI-2	61	100	0	0	0	0	4	7	15	25	7	11	20	33	2	3	13	21	0	0
	H	74	101	0	0	0	0	6	8	19	26	8	11	28	38	2	3	11	15	0	0
0-12 months ***	PH	82	99	6	7	19	23	36	44	13	16	1	1	5	6	0	0	1	1	1	1
	HI-1	60	100	4	7	26	43	16	27	8	13	0	0	1	2	0	0	5	8	0	0
	HI-2	64	101	7	11	14	22	12	19	11	17	3	5	2	3	0	0	14	22	1	2
	H	81	101	5	6	8	10	22	27	21	26	3	4	4	5	0	0	15	19	3	4

* Excluding four patients (one in each series) who died of non-tuberculous conditions, five patients (2 PH, 2 HI-1, 1 HI-2) who had their chemotherapy changed on account of toxicity and 14 patients (4 PH, 3 HI-1, 3 HI-2, 4 H) who were pregnant.

** Excluding one patient (PH) who died of a non-tuberculous condition, three patients (all HI-1) who had their chemotherapy changed on account of toxicity, 16 patients (4 PH, 5 HI-1, 3 HI-2, 4 H) who were pregnant and two patients (1 PH, 1 H) for whom no result was available.

*** Excluding five patients (2 PH, 1 HI-1, 1 HI-2, 1 H) who died of non-tuberculous conditions, eight patients (2 PH, 5 HI-1, 1 HI-2) who had their chemotherapy changed on account of toxicity, 13 patients (3 PH, 4 HI-1, 2 HI-2, 4 H) who were pregnant and two patients (1 PH, 1 H) for whom no result was available.

TABLE 7. DISTRIBUTIONS OF THE ERYTHROCYTE SEDIMENTATION RATE ON ADMISSION TO TREATMENT, AT 6 AND AT 12 MONTHS

ESR (mm in 1 hour)	On admission to treatment								At 6 months								At 12 months							
	PH		HI-1		HI-2		H		PH		HI-1		HI-2		H		PH		HI-1		HI-2		H	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
0-10	0	0	1	1	1	2	1	1	13	15	18	27	15	23	10	12	15	18	18	29	20	31	18	21
11-20	3	3	2	3	4	6	2	2	16	18	8	12	10	15	19	22	24	29	15	24	11	17	18	21
21-50	24	28	16	24	14	21	20	23	33	38	24	36	20	30	27	32	27	32	13	21	15	23	14	17
51-100	41	47	37	55	35	53	51	59	21	24	12	18	18	27	19	22	15	18	10	16	4	6	15	18
101 or more	19	22	11	16	12	18	12	14	3	3	4	6	1	2	3	4	1	1	2	3	0	0	1	1
Change of chemotherapy due to deterioration	—	—	—	—	—	—	—	—	0	0	1	1	1	2	4	5	1	1	5	8	14	22	15	18
Tuberculous death	—	—	—	—	—	—	—	—	1	1	0	0	1	2	3	4	1	1	0	0	1	2	3	4
Total patients *	87	100	67	99	66	100	86	99	87	99	67	100	66	101	85	101	84	100	63	101	65	101	84	100

* Excluding throughout four patients (one in each series) who died of non-tuberculous conditions in the first six months and five patients (2 PH, 2 HI-1,1 HI-2) who had their chemotherapy changed on account of toxicity in the first six months ; excluding also, at six months only, one patient (H) for whom the result was not available and, at 12 months only, one patient (PH) who died of a non-tuberculous condition, three patients (HI-1) who had their chemotherapy changed on account of toxicity and six patients (2 PH, 1 HI-1, 1 HI-2, 2 H) for whom no result was available.

six months the numbers had increased to 29 for the PH series, 26 for the HI-1, 25 for the HI-2 and 29 for the H series. At 12 months the numbers had increased further in all four series, being 39 for the PH, 33 for the HI-1, 31 for the HI-2 and 36 for the H series. Although the ESR fell in many patients, a considerable proportion in all four series retained high ESRs, even at 12 months. The ESR is, however, not a very satisfactory measure of activity of the disease in Indian patients and high rates are quite compatible with quiescent disease (Tuberculosis Chemotherapy Centre, 1959; Velu et al., 1960 [1]).

Radiographic changes

The changes in the radiographic appearances were assessed for the first six months, for the second six months and for the whole period by an independent assessor, Dr Raj Narain, who was unaware of the treatment series to which any patient had been allocated. He made three completely separate assessments. First he was shown the pretreatment and six-month radiographs, the patients being considered in a random order, and he made an assessment of the changes for the first six months. When this assessment was complete for all the patients, a similar assessment was made for the 12-month period, the assessor being shown the pretreatment and the 12-month radiographs of each patient. Finally, the radiographs at six and 12 months were viewed and the changes in the second six months were assessed. Four grades were used for the classification of improvement–namely, exceptional, considerable, moderate and slight-and three for deterioration–namely slight, moderate and considerable.

The findings are set out in Table 8. Considering the changes over the first six months, 79% of 87 PH, 73 % of 67 HI-1, 62% of 66 HI-2 and 69 % of 86 H patients showed moderate or greater improvement. The proportions of patients who showed radiographic deterioration but continued on the initially allocated chemotherapy, who deteriorated and had their chemotherapy changed during the period, or who died of tuberculosis, were 2% of the PH, 7% of the HI-1, 8 % of the HI-2 and 15 % of the H series.

Over the full 12 months, the majority of the patients showed moderate or greater improvement–namely, 85 % of the PH, 78 % of the HI-1, 71% of the HI-2 and 62% of the H series. The proportions of patients who showed radiographic deterioration,

[1] See article on page 511 of this issue.

TABLE 8

CHANGES IN RADIOGRAPHIC APPEARANCES IN THE 12-MONTH PERIOD *

Period	Treatment series	Total patients	Improvement				No change	Deterioration			Change of chemotherapy during the period due to deterioration	Tuberculous death
			exceptional	considerable	moderate	slight		slight	moderate	considerable		
		No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %
0-6 months **	PH	87 99	2 2	34 39	33 38	15 17	1 1	0 0	1 1	0 0	0 0	1 1
	HI-1	67 98	3 4	21 31	25 37	10 15	3 4	2 3	2 3	0 0	1 1	0 0
	HI-2	66 102	1 2	19 29	21 32	14 21	6 9	0 0	2 3	1 2	1 2	1 2
	H	86 98	3 3	21 24	35 41	11 13	3 3	1 1	2 2	3 3	4 5	3 3
O-12 months ***	PH	86 98	8 9	39 45	26 30	8 9	2 2	1 1	0 0	0 0	1 1	1 1
	HI-I	64 100	2 3	33 52	15 23	5 8	4 6	0 0	0 0	0 0	5 8	0 0
	HI-2	66 101	4 6	20 30	23 35	3 5	0 0	1 2	0 0	0 0	14 21	1 2
	H	86 98	3 3	21 24	29 34	8 9	1 1	4 5	2 2	0 0	15 17	3 3
6-12 months †	PH	85 100	0 0	0 0	4 5	13 15	61 72	5 6	1 1	0 0	1 1	0 0
	HI-1	63 100	0 0	0 0	3 5	14 22	38 60	3 5	1 2	0 0	4 6	0 0
	HI-2	64 101	0 0	0 0	0 0	10 16	37 58	3 5	1 2	0 0	13 20	0 0
	H	79 99	0 0	0 0	1 1	9 11	49 62	4 5	5 6	0 0	11 14	0 0

* Three separate assessments on standard radiographs,

** Excluding four patients (one in each series) who died of non-tuberculous conditions and five patients (2 PH, 2 HI-1, 1 HI-2) who had their chemotherapy changed on account of toxicity.

*** Excluding five patients (2 PH, 1 HI-1, 1 HI-2, 1 H) who died of non-tuberculous conditions and eight patients (2 PH, 5 HI-1, 1 HI-2) who had their chemotherapy changed on account of toxicity.

† Excluding one patient (PH) who died of a non-tuberculous condition and three patients (all HI-i) who had their chemotherapy changed on account of toxicity.

who deteriorated and had their chemotherapy changed during the period, or who died of tuberculosis, were 3%, 8%, 24%, and 28 %, respectively, for the four series.

In the second six months the majority of the patients in all four series–namely, 72% of the PH, 60 % of the HI-1, 58 % of the HI-2 and 62 % of the H series–showed no change radiographically. Radiographic improvement occurred in a small proportion of the patients, and was usually slight.

To summarize, the progress of the PH series throughout the 12 months was very satisfactory and the HI-1 series nearly achieved the same order of improvement. The progress of the other two series was less satisfactory.

Changes in cavitation

Table 9 presents the changes in cavitation for the 12-month period, as assessed by Dr Raj Narain. As with cavitation on admission, cavitation at 12 months was assessed on a single postero-anterior radiograph. The numbers of patients with extensive cavitation are small, but the findings indicate that the cavitation disappeared in about a quarter of them. Of the group of patients with moderate cavitation initially, the cavitation had disappeared

TABLE 9

CHANGES IN CAVITATION IN THE 12-MONTH PERIOD IN PATIENTS WITH CAVITATION ON ADMISSION TO TREATMENT, ACCORDING TO EXTENT ON ADMISSION *

Extent of cavitation on admission to treatment	Treatment series	Total patients		Disappearance of cavitation		Cavities smaller or fewer		No change		Cavities larger or more numerous		Change of chemotherapy during the period due to deterioration		Tuberculous death	
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Extensive **	PH	14	100	4	(29) ††	7	(50)	1	(7)	0	(0)	1	(7)	1	(7)
	HI-1	7	101	2	(29)	3	(43)	0	(0)	0	(0)	2	(29)	0	(0)
	HI-2	5	100	1	(20)	1	(20)	0	(0)	0	(0)	3	(60)	0	(0)
	H	8	100	0	(0)	2	(25)	1	(12)	0	(0)	3	(38)	2	(25)
Moderate ***	PH	41	100	26	63	11	27	2	5	2	5	0	0	0	0
	HI-1	31	99	16	52	11	35	2	6	0	0	2	6	0	0
	HI-2	38	100	15	39	11	29	0	0	1	3	10	26	1	3
	H	45	99	17	38	14	31	0	0	2	4	11	24	1	2
Slight †	PH	23	100	20	(87)	2	(9)	1	(4)	0	(0)	0	(0)	0	(0)
	HI-1	25	100	21	84	2	8	0	0	1	4	1	4	0	0
	HI-2	18	101	16	(89)	0	(0)	0	(0)	1	(6)	1	(6)	0	(0)
	H	25	100	21	84	2	8	0	0	1	4	1	4	0	0
Total patients with cavitation	PH	78	100	50	64	20	26	4	5	2	3	1	1	1	1
	HI-1	63	100	39	62	16	25	2	3	1	2	5	8	0	0
	HI-2	61	100	32	52	12	20	0	0	2	3	14	23	1	2
	H	78	100	38	49	18	23	1	1	3	4	15	19	3	4

* Assessment on standard radiographs on admission to treatment and at 12 months.

** Excluding three PH patients, two of whom died of non-tuberculous conditions and one who had his chemotherapy changed on account of toxicity.

*** Excluding two patients (1 HI-1, 1 H) who died of non-tuberculous conditions and five patients (4 HI-1, 1 HI-2) who had their chemotherapy changed on account of toxicity.

† Excluding one patient (HI-2) who died of a non-tuberculous condition and two patients (1 PH, 1 HI-1) who had their chemotherapy changed on account of toxicity.

†† Percentages based on fewer than 25 observations are enclosed in parentheses, as an indication of the small totals.

in 63 % of 41 PH, 52% of 31 HI-1, 39 % of 38 HI-2 and 38 % of 45 H patients; in 5 % of the PH, 6% of the HI-1, 32% of the HI-2 and 31% of the H series there were increases in cavitation, changes of chemotherapy due to deterioration, or tuberculous deaths, The progress of patients with slight cavitation was very similar in all four series, the cavitation disappearing in more than 80% of the patients. It may be concluded that there was evidence of differences between the four treatment series in patients with moderate cavitation, but little difference between them for patients with slight cavitation. The numbers of patients with extensive cavitation are too small to permit firm conclusions. Eight PH, one HI-1, five HI-2 and eight H patients had no cavitation on admission to treatment. At 12 months two of these patients (both H) had cavitation which was graded as slight.

BACTERIOLOGICAL

Smear and culture results

The results of the smear and culture examination of single collection specimens of sputum each month are set out in Table 10. The findings, being based on single monthly cultures (a usual rhythm of investigation of tuberculous patients under active treatment), are suitable for comparison with those of other studies and, in particular, with the findings of an earlier study from this Centre (Tuberculosis Chemotherapy Centre, 1959). Further investigations (to be reported elsewhere) suggest that the bacilli in specimens yielding smear-positive but culture-negative results were non-viable in all four treatment series, confirming findings already reported for patients on the PH regimen (Tuberculosis Chemotherapy Centre, 1959). Such results have therefore been regarded as bacteriologically negative. Table 10 shows that there was a rapid decline in the proportion of patients with positive cultures in all the series; by three months 78 % of 81 PH, 64% of 69 HI-1, 55 % of 64 HI-2 and 43 % of 82 H patients yielded a negative culture. At six months the proportions had increased to 88 %, 71%, 58 % and 49 %, respectively. There was comparatively little change during the rest of the period and at 12 months the proportions were 90% for the PH series, 76 % for the HI-1, 59 % for the HI-2 and 51% for the H series.

As described above (see page 540), multiple specimens were examined at monthly intervals for each patient. At three, six, nine and 12 months the average number of test results per patient ranged from 2.6 to 2.8. At each of these four monthly examinations, the numbers of patients *all* of whose cultures were negative were very similar to the numbers culture-negative on a single collection specimen. The data have not been tabulated here. However, the percentage of patients with at least one positive culture result is shown for the four treatment series each month in Fig. 1.

Fig. 2 shows, for each of the four treatment series separately, the results of the multiple-culture examinations each month for the patients who continued on the prescribed chemotherapy, together with the changes of chemotherapy due to deterioration and the deaths due to tuberculosis.

Isoniazid sensitivity

The results of the isoniazid-sensitivity tests are set out in Table 11. Each of the three series of patients treated with isoniazid alone already showed some resistant cultures at one month. Thus, 12% of the positive cultures tested from patients in the HI-1 series, 13 % in the HI-2 and 15 % in the H series were resistant. At three months the proportions of the positive cultures tested which were resistant were 9% for the PH series, 78% for the HI-1, 79 % for the HI-2 and 75 % for the H series ; at six months the corresponding proportions were 80 %, 100%, 100 % and 97 % respectively (only three of 90 strains in the four treatment series combined were sensitive). In the second six months nearly all the positive cultures were resistant, and at 12 months 52 of the 53 positive cultures from the four treatment series combined were resistant, the exception being one strain in an HI-1 patient. No patient in any of the four treatment series remained consistently bacteriologically positive with isoniazid-sensitive organisms throughout the 12 months. Thus, no isoniazid-sensitive strains were found after the third month of treatment in any of the 23 patients (4 HI-1, 5 HI-2, 14 H) who were bacteriologically positive at each of the 12 months.

In order to compare the potential public health risk in the four treatment series, as represented by excretors of isoniazid-resistant organisms, the patients who had their chemotherapy changed owing to deterioration have been added to those who continued on the allocated chemotherapy and yielded resistant strains (Table 11, last column), since all the 35 patients who deteriorated had resistant strains when their chemotherapy was changed. In this way a consolidated total of patients with resistant

TABLE 10

PRESENCE OF TUBERCLE BACILLI IN SINGLE COLLECTION SPECIMENS OF SPUTUM TAKEN FROM PATIENTS AT MONTHLY INTERVALS

Months after start of chemo-therapy	Treatment series	Total patients *	Tuberculous death	Change of chemotherapy due to deterioration	Culture positive							Culture negative **	
					smear positive, graded as :			smear negative, culture graded as :					
					3-plus	2-plus	1-plus	3-plus	2-plus	1-plus	19-1 colonies	No.	%
0	PH	90	–	–	26	25	14	1	4	7	5	8	9
	HI-1	70	–	–	28	17	19	0	2	2	2	0	0
	HI-2	68	–	–	25	22	13	0	1	2	3	2	3
	H	87	–		32	31	11	0	4	2	5	2	2
1	PH	89	0	0	1	11	23	1	5	14	12	22	25
	HI-1	68	0	0	3	13	22	0	0	10	12	8	12
	HI-2	66	0	0	0	8	21	0	0	13	10	14	21
	H	85	2	0	1	15	22	0	2	15	16	12	14
2	PH	86	0	0	0	3	17	0	1	5	14	46	53
	HI-1	66	0	0	0	2	19	0	0	4	10	31	47
	HI-2	63	0	0	1	4	14	0	0	3	9	32	51
	H	86	2	0	3	0	17	0	4	8	12	31	36
3	PH	81	1	0	0	0	8	0	0	4	5	63	78
	HI-1	69	0	0	2	6	9	0	1	2	5	44	64
	HI-2	64	0	0	2	5	13	0	2	1	6	35	55
	H	82	2	0	7	7	9	0	0	7	15	35	43
4	PH	83	1	0	0	0	3	0	0	1	6	72	87
	HI-I	66	0	0	2	4	10	0	1	3	3	43	65
	HI-2	66	1	0	3	7	7	0	0	5	3	40	61
	H	82	3	1	6	7	15	0	0	4	5	41	50
5	PH	85	1	0	0	1	0	0	0	4	4	75	88
	HI-I	66	0	1	2	3	5	0	1	1	2	51	77
	HI-2	64	1	0	3	9	6	0	1	2	2	40	62
	H	80	3	2	6	11	13	0	0	2	4	39	49

TABLE 10 (*continued*)

6	PH	85	1	0	0	1	2	0	0	2	4	75	*88*
	HI-1	66	0	1	3	2	9	0	0	2	2	47	*71*
	HI-2	64	1	1	5	6	8	0	1	1	4	37	*58*
	H	82	3	4	7	9	10	0	2	2	5	40	*49*
7	PH	81	1	1	0	0	1	0	1	1	2	74	*91*
	HI-1	64	0	1	2	4	7	0	0	4	0	46	*72*
	HI-2	62	1	5	3	3	0	0	1	0	2	37	*60*
	H	84	3	6	2	12	8	0	1	7	7	38	*45*
8	PH	83	1	1	0	0	2	0	0	1	2	76	*92*
	HI-1	62	0	1	1	5	4	0	0	4	1	46	*74*
	HI-2	65	1	6	2	9	4	0	1	1	2	39	*60*
	H	85	3	7	3	12	11	0	1	6	5	37	*44*
9	PH	83	1	1	0	0	2	0	0	1	1	77	*93*
	HI-1	61	0	2	0	4	5	0	0	3	1	46	*75*
	HI-2	64	1	9	2	4	4	0	1	0	3	40	*62*
	H	85	3	9	3	11	11	0	1	2	8	37	*44*
0	PH	85	1	1	0	1	2	0	0	1	2	77	*91*
	HI-1	63	0	2	0	6	3	0	1	0	4	47	*75*
	HI-2	62	1	10	3	3	2	0	0	1	3	39	*63*
	H	85	3	12	0	9	11	0	0	5	2	43	*51*
11	PH	81	1	1	0	0	3	0	0	2	2	72	*89*
	HI-1	63	0	4	0	0	6	0	0	3	1	49	*78*
	HI-2	61	1	12	0	4	3	0	1	0	1	39	*64*
	H	85	3	13	1	10	8	0	2	3	4	41	*48*
12	PH	82	1	1	0	1	1	0	0	1	3	74	*90*
	HI-1	62	0	5	1	3	4	0	0	1	1	47	*76*
	HI-2	64	1	14	1	1	4	1	0	1	3	38	*59*
	H	84	3	15	0	9	10	0	1	1	2	43	*51*

* Patients who died of non-tuberculous conditions are excluded after their death and patients who had their chemotherapy changed on account of toxicity are excluded after the change; tuberculous deaths and patients who had their chemotherapy changed owing to deterioration remain in the totals throughout (see pages 548 and 549).

** Even if the smear was positive (see page 553).

TABLE 11

RESULTS OF ISONIAZID-SENSITIVITY TESTS IN THE 12-MONTH PERIOD *

Months after start of chemo-therapy	Treat-ment series	Total patients ** (A)	Culture-negative (no sen-sitivity test possible)	Culture-positive but no sensitivity test result available	Patients culture-positive with sensitivity tests: total results available (B)	sensitive: no growth 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	total resistant: No. (C)	total resistant: % of B	Change of chemo-therapy due to deteri-oration (D)	Consolidated total of patients with resistant strains: No. (C+D)	Consolidated total of patients with resistant strains: % of A
1	PH	90	21	2	67	67	0	0	0	0	0	*0*	0	0	*0*
	HI-1	69	9	3	57	50	2	1	3	1	7	*12*	0	7	*10*
	HI-2	67	10	4	53	46	0	3	2***	2	7	*13*	0	7	*10*
	H	83	9	1	73	62	4	3	2	2	11	*15*	0	11	*13*
2	PH	86	38	3	45	44	1	0	0	0	1	*2*	0	1	*1*
	HI-1	66	29	0	37	24	2	7	1	3	13	*35*	0	13	*20*
	HI-2	63	26	0	37	20	5	5	5***	2	17	*46*	0	17	*27*
	H	84	26	3	55	24	7	10†	8	6	31	*56*	0	31	*37*
3	PH	86	63	1	22	20	2	0	0	0	2	*(9)* †††	0	2	*2*
	HI-1	69	41	1	27	6	1	9	5***	6	21	*78*	0	21	*30*
	HI-2	67	36	3	28	6	5	7	6	4	22	*79*	0	22	*33*
	H	84	36	0	48	12	2	18†	7	9	36	*75*	0	36	*43*
4	PH	87	77	0	10	5	1		1††	0	5	*(50)*	0	5	*6*
	HI-1	69	44	0	25	2	1	11	5	6	23	*92*	0	23	*33*
	HI-2	66	39	1	26	2	2	8	8	6	24	*92*	0	24	*36*
	H	82	43	2	36	1	5	11†	10	9	35	*97*	1	36	*44*
5	PH	86	73	1	12	3	3	4	1	1	9	*(75)*	0	9	*10*
	HI-1	68	50	1	16	0	1	9	3	3	16	*(100)*	1	17	*25*
	HI-2	66	38	1	27	4	1	6	6	10	23	*85*	0	23	*35*
	H	82	41	2	37	0	7	12	9***	9	37	*100*	2	39	*48*
6	PH	86	75	1	10	2	2	5	1	0	8	*(80)*	0	8	*9*
	HI-1	67	47	1	18	0	1	6	4	7	18	*(100)*	1	19	*28*
	HI-2	65	39	2	23	0	3	6	5	9	23	*(100)*	1	24	*37*
	H	83	39	1	38	1	8	12	11	7	38	*97*	4	42	*51*

TABLE II (continued)

	PH	85	76	0	8	1	1	5	0	1	7	(88)	1	8	9
	HI-1	66	46	0	19	1	1	7	4	6	18	(95)	1	19	29
	HI-2	64	39	0	20	0	1	6	4	9	20	(100)	5	25	39
	H	83	37	1	39	0	7	9	11	12	39	100	6	45	54
8	PH	85	79	0	5	0	0	4	1††	0	5	(100)	1	6	7
	HI-1	66	47	0	18	0	1	10	3	4	18	(100)	1	19	29
	HI-2	65	37	2	20	2	0	5	4***	9	18	(90)	6	24	37
	H	82	35	3	37	1	4	8	8	16	36	97	7	43	52
9	PH	85	77	0	7	2	0	4	1	0	5	(71)	1	6	7
	HI-1	66	49	0	15	0	1	4	5	5	15	(100)	2	17	26
	HI-2	65	40	0	16	0	1	3	4	8	16	(100)	9	25	38
	H	83	35	3	36	0	3	9	9	15	36	100	9	45	54
10	PH	85	78	1	5	0	0	3	1	1	5	(100)		6	7
	HI-1	65	47	1	15	0	1	3	6	5	15	(100)	2	17	26
	HI-2	65	41	1	13	1	0	3	2	7	12	(92)	10	22	34
	H	83	38	3	30	0	2	6	10	12	30	100	12	42	51
11	PH	84	75	1	7	0	2	2	2	1	7	(100)		8	10
	HI-1	64	47	0	13	0	1	4	3	5	13	(100)	4	17	27
	HI-2	64	42	0	10	0	0	2	6	2	10	(100)	12	22	34
	H	83	40	1	29	0	1	7	9	12	29	100	13	42	51
12	PH	84	77	0	6	0	2	3	0	1	6	(100)	1	7	8
	HI-1	64	47	0	12	1	1	3	5	2	11	(92)	5	16	25
	HI-2	65	40	0	11	0	0	2	3	6	11	(100)	14	25	38
	H	83	44	0	24	0	1	6	5	12	24	(100)	15	39	47

* All patients had strains sensitive to isoniazid before treatment.

** All the patients who died are excluded after their death and patients who had their chemotherapy changed on account of toxicity are excluded after the change; Patients who had their chemotherapy changed owing to deterioration remain in the totals throughout (see pages 548, 549, 553 and 558).

*** Includes one strain with no test result on 50 µg/ml.

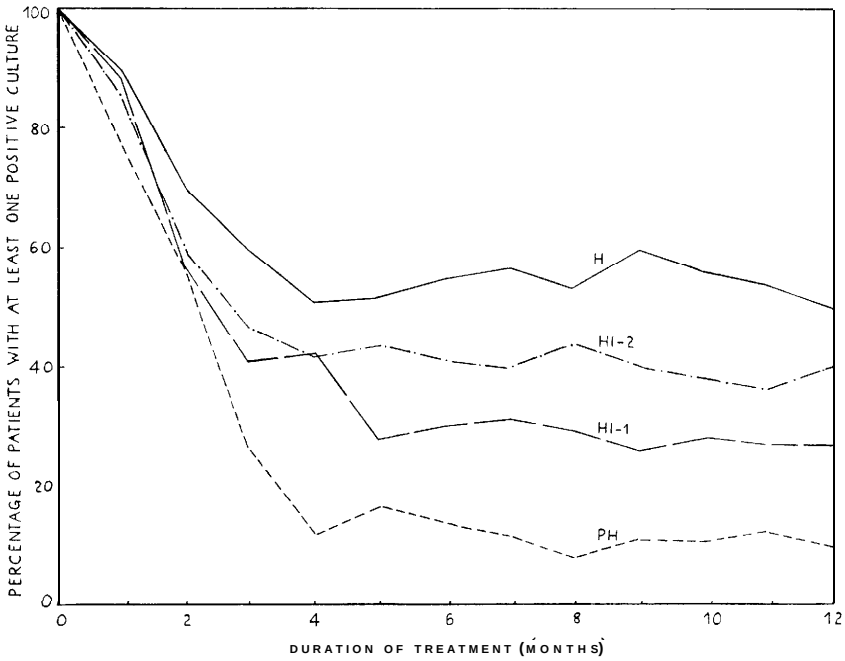
† Includes one strain with no test result on 5 µg/ml.

†† No test result on 50 µg/ml.

††† Percentages based on fewer than 25 observations are enclosed in parentheses, as an indication of the small totals.

FIG. 1

PERCENTAGE OF PATIENTS EACH MONTH WITH AT LEAST ONE POSITIVE CULTURE RESULT FROM MULTIPLE BACTERIOLOGICAL SPECIMENS (SPUTUM AND LARYNGEAL SWABS)



strains was obtained. It should be noted that (in contrast to all the other tables) the patients who died of tuberculosis have been *excluded* after their death from the totals in Table 11, since they then no longer represented a public health risk. At three months the total of patients with resistant strains represented 2 % of the PH, 30% of the HI-1, 33% of the HI-2 and 43 % of the H series. From three to 12 months there was little change in these proportions. Thus, at 12 months 8 % of the PH, 25 % of the HI-1, 38 % of the HI-2 and 47 % of the H series had resistant organisms. It may be concluded that the potential public health risk from excretors of isoniazid-resistant organisms was appreciable in the HI-1, HI-2 and H series from early in the period of treatment, and continued for the rest of the 12 months. (The possibility that these resistant organisms are of lowered infectivity will be considered in later publications relating to the attack rate of tuberculosis in the family contacts).

Response to trentmznt during the 12 months

Table 12 presents a classification of all the patients at 12 months, based primarily on the bacteriological response to treatment (see also Fig. 3). A patient's disease was classified as bacteriologically quiescent if all the cultures for at least the last three monthly examinations (that is, those at 10, 11 and 12 months) were negative. Those pstients who, following at least three months of culture negativity, yielded an isolated positive culture at one of the last three monthly examinations have been classified as bacteriologically of doubtful status. Patients whose sputum was culture-positive on at least two occasions at the examinations for the last three months were classified as bacteriologically relapsed, provided that they had previously yielded only negative results for all the cultures at three consecutive monthly examinations. Patients who never had a period of three consecutive months of bacteriological negativity were classified as bacteriologically active, as were the patients who deteriorated radiographically or

clinically, and so had their chemotherapy changed. In all, 86 % of the PH patients, 67 % of the HI-1, 56% of the HI-2 and 44% of the H patients were classified as bacteriologically quiescent at 12 months; and a further 5 % of the PH, 6 % of the HI-1 and 2 % of the HI-2 series were bacteriologically of doubtful status. There were also differences between the series in the proportions of patients who attained bacteriological quiescence between the seventh and the tenth months of treatment. Among the patients whose disease attained bacteriological quiescence, the period of persisting bacteriological negativity started between seven and 10 months in 7 % of the 74 PH, 9% of the 43 HI-1, 11% of the 37 HI-2 and 26 % of the 38 H patients with quiescent disease.

Patients with an unfavourable response were defined as those who had relapsed bacteriologically or who had active disease (including those who had their chemotherapy changed owing to deterioration) or who died of tuberculosis. The proportions with an unfavourable response were 9 % for the PH, 27 % for the HI-1, 42 % for the HI-2 and 56 % for the H series. The differences between the PH and the other three series are statistically highly significant

FIG. 2

PERCENTAGE OF PATIENTS EACH MONTH WHO WERE BACTERIOLOGICALLY NEGATIVE, BACTERIOLOGICALLY POSITIVE, WHOSE TREATMENT HAD BEEN CHANGED OWING TO DETERIORATION OR WHO DIED OF TUBERCULOSIS

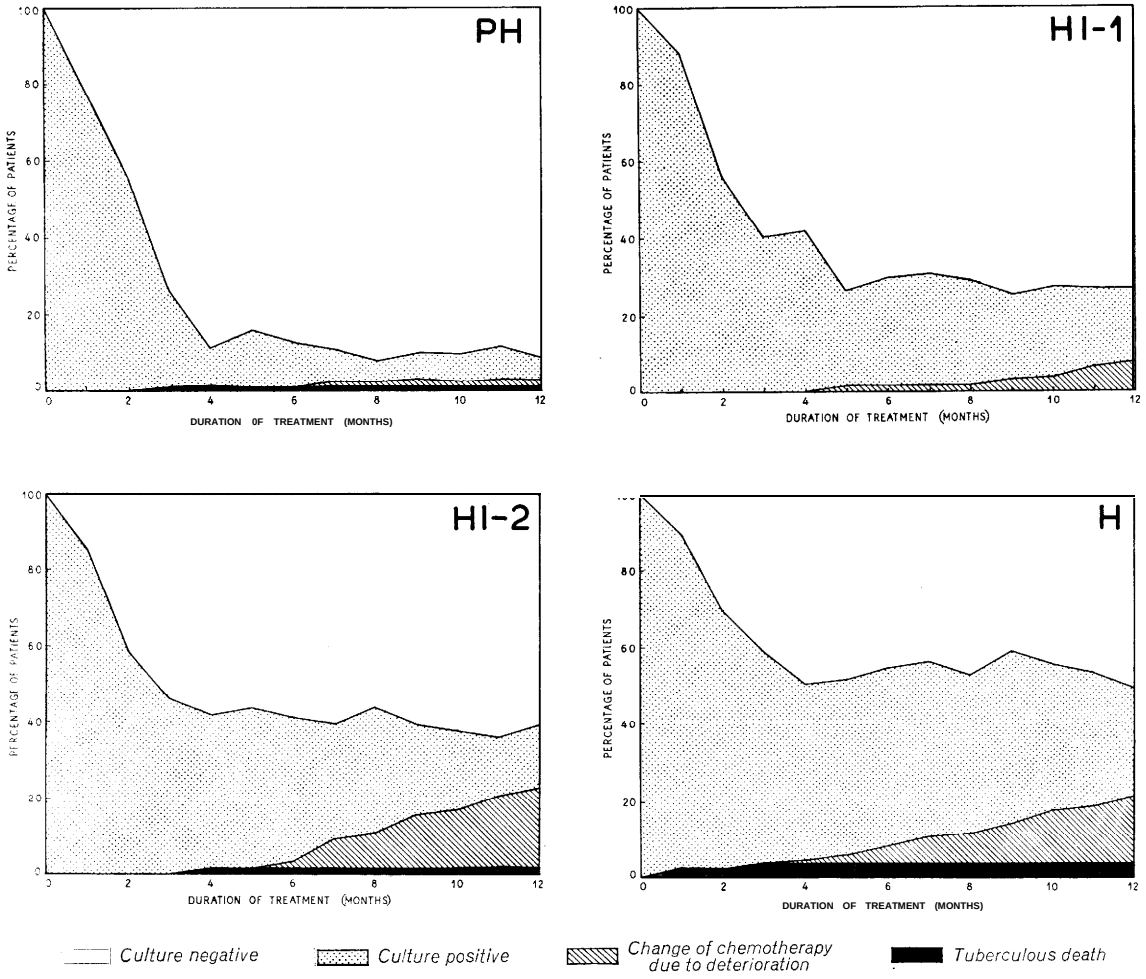
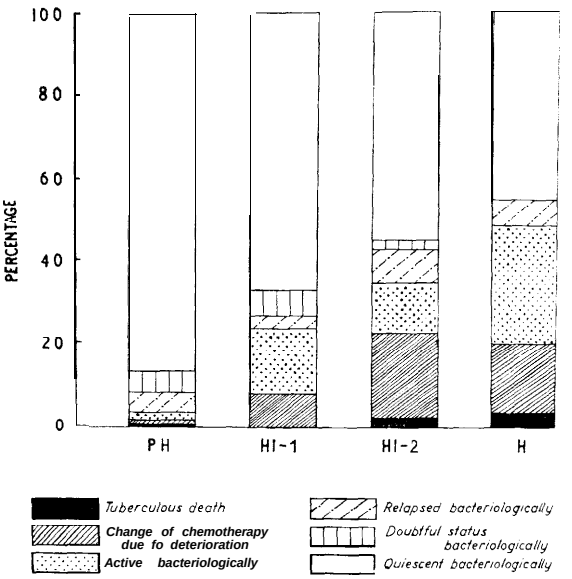


TABLE 12

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

Classification at the end of 12 months		Treatment series							
		PH		HI-1		HI-2		H	
		No.	%	No.	%	No.	%	No.	%
Patients with bacteriologically quiescent disease :	First month of persisting culture negativity								
that is, patients whose cultures were all negative for at least the last three monthly examinations-i.e., at 10, 11 and 12 months	1	11		7		5		5	
	2	14		14		11		12	
	3	22		10		10		6	
	4	17		5		5		4	
	5	1		3		1		0	
	6	4		0		1		1	
	7	2		1		2		3	
	8	1		1		1		1	
	9	0		2		0		1	
	10	2		0		1		5	
Total patients with bacteriologically quiescent disease		74	*86*	43	*67*	37	*56*	38	*44*
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 an isolated positive culture at one of the last three monthly examinations-i.e., at 10, 11 or 12 months		4	*5*	4	*6*	1	*2*	0	*0*
Patients with bacteriologically relapsed disease :									
that is, patients whose cultures were all negative at three or more consecutive monthly examinations, but who produced two or more positive cultures in the last three monthly examinations-i.e., at 10, 11 and 12 months		4	*5*	2	*3*	5	*8*	5	*6*
Patients with bacteriologically active disease :									
that is, *(a)* patients whose cultures were never all negative at three consecutive monthly examinations		2	*2*	10	*16*	8	*12*	25	*29*
or *(b)* patients who deteriorated and had their chemotherapy changed		1	*7*	5	*8*	14	*21*	15	*17*
Total patients with bacteriologically relapsed or active disease		7	*8*	17	*27*	27	*41*	*45*	*52*
Tuberculous deaths		1	1	0	0	1	*2*	3	3
Total		86	*100*	64	*103*	66	*101*	86	*99*
Patients who had their chemotherapy changed on account of toxicity		2	–	5	–	1	–	0	–
Non-tuberculous deaths		2	-	1	-	*1*	-	*1*	-
All patients		90	–	70	–	66	–	87	–

FIG. 3. CLASSIFICATION OF THE PATIENTS AT THE END OF 12 MONTHS ACCORDING TO THEIR RESPONSE TO TREATMENT



($P<0.01$). It may be concluded that the PH series fared well and that the progress of the other three series was less satisfactory, particularly that of the HI-2 and H series.

Response to treatment of the patients who had minor interruptions in their supply of medicament

Reference was made earlier (page 548) to five PH, five HI-1, four HI-2 and eight H patients who were without a supply of their medicament for periods ranging from 41 to seven days. One HI-2 and three H patients, who had been without supplies of the medicament for eight, 28, 11 and 10 days, respectively, had bacteriologically active disease at 12 months; the other 18 patients had bacteriologically quiescent disease.

VI. INFLUENCE OF THE VIRULENCE OF THE INFECTING ORGANISMS ON THE RESULTS OF TREATMENT

It has been shown (Dhayagude & Shah, 1948; Frimodt-Møller, Mathew & Barton, 1956; Mitchison et al., 1960) that, unlike sensitive strains of tubercle bacilli from previously untreated patients in Great Britain, pretreatment sensitive strains from Indian patients have a wide range of virulence in the guinea-pig. It was therefore important in the present study to measure the virulence of the patients' organisms before the start of treatment, and to investigate the response to treatment in relation to this factor. The pretreatment virulence was measured in 281 (89 %) of the 315 patients in the main analysis–namely, 82 (91%) of the PH, 63 (90 %) of the HI-1, 60 (88 %) of the HI-2 and 76 (87 %) of the H patients.

VIRULENCE OF TUBERCLE BACILLI IN THE GUINEA-PIG

The measure of virulence used was based on the rate of progression of the disease in the guinea-pig, and has been described in detail by Mitchison et al. (1960). In brief, 1 mg moist weight of a pretreatment culture of tubercle bacilli was inoculated intramuscularly into each of two guinea-pigs, one of which was killed at six weeks and the other at 12 weeks. If either died before six weeks it was counted as a 6-week animal and the remaining guinea-pig as the 12-week animal. At post-mortem examination the total extent of tuberculous disease in the spleen, liver, lungs and local glands was assessed as a score ranging from 0 to 100. The ratio of the score to the survival time in days was determined for each guinea-pig. The index of virulence employed was the mean of the ratios for the two guinea-pigs.

PRETREATMENT COMPARISON BETWEEN THE FOUR SERIES

The distributions of the index of virulence for the pretreatment strains in the four series are shown in Table 13. They were, in general, similar for the PH, HI-1 and H series, 30%, 27 % and 30 % of the patients, respectively, having organisms with high virulence (index of 0.8 or more). The HI-2 series, however, had a much smaller proportion (13 %) of strains with high virulence. The position is summarized by the average indices of virulence, which were 0.639 for the PH series, 0.584 for the HI-1, 0.498 for the HI-2 and 0.658 for the H series. The differences between the means of the four series are unexpectedly large ($P<0.05$). In view of the substantial apparent advantage to the HI-2 series in terms of initial virulence of the organisms, it was

TABLE 13

VIRULENCE IN GUINEA-PIGS OF THE STRAINS OF TUBERCLE BACILLI FROM THE PATIENTS ON ADMISSION TO TREATMENT

Index of virulence	PH		HI-1		HI-2		H	
	No.	%	No.	%	No.	%	No.	%
0.0-	6	7	2	3	7	12	3	4
0.2-	16	20	22	35	23	38	16	27
0.4-	23	28	15	24	12	20	20	26
0.6-	12	15	7	11	10	17	14	18
0.8-	11	13	9	14	2	3	9	12
1.0-	7	9	4	6	3	5	6	8
1.2-	4	5	3	5	0	0	6	8
1.4-	2	2	1	2	3	5	2	3
1.6 or more	1	1	0	0	0	0	0	0
Total patients *	82	100	63	100	60	100	76	100
Average index	0.639		0.584		0.498		0.658	

*The virulence was not determined for strains from 34 patients (8 PH, 7 HI-1, 8 HI-2, 11 H).

necessary to examine whether this reflected any other pretreatment difference and whether it had influenced the response to treatment in this series of patients.

VIRULENCE OF THE ORGANISMS IN RELATION TO OTHER CLINICAL FEATURES AT THE START OF TREATMENT

The full findings on the relationship between the virulence of the infecting organisms and the clinical condition of the patient at the start of treatment will be published separately. It is sufficient to note here that there were no important associations between pretreatment virulence and a number of the clinical aspects of the disease at the start of treatment, including the total extent of the radiographic lesion, the extent of cavitation, and the presence of tubercle bacilli in the sputum. In other words, the lower average virulence of the organisms in the patients in the HI-2 series was an independent finding. There was no evidence of an association of pretreatment virulence with other factors which might influence the progress of the patients during treatment.

PROGNOSTIC IMPORTANCE OF THE VIRULENCE OF THE ORGANISMS IN THE GUINEA-PIG

The full findings on the prognostic importance of the virulence of the strains in the guinea-pig will also be published separately. In brief, there was a tendency for patients with organisms of low virulence at the start of treatment to make more satisfactory progress than patients with organisms of high virulence. This tendency was most apparent in treatment with HI-2 and H, the least effective regimens. Even with these regimens, however, the association was not strong.

In view of this slight association, and the substantial differences in pretreatment virulence between the series, it was decided that it would be valuable to study the influence of these differences on the results of treatment, particularly in order to define more precisely the position of the HI-2 regimen in relation to the HI-1 and H regimens.

PROCEDURE FOR STUDYING THE EFFECT OF THE PRETREATMENT DIFFERENCES IN VIRULENCE

The approach used was statistical standardization of the results of treatment to allow for the pretreatment differences in virulence. The principle underlying this technique is a comparison of the progress of patients in the four treatment series who had similar indices of virulence at the start of treatment. Further details of the approach have been given in an earlier report (Tuberculosis Chemotherapy Centre 1959).

Three measures of radiographic and three of bacteriological response were standardized for differences in pretreatment virulence. The measures of radiographic response were: (1) the percentage of patients showing considerable or exceptional improvement in the period 0-6 months; (2) the corresponding percentage for the period 0-12 months; and (3) the percentage of patients with cavitation at the start of treatment in whom the cavitation had disappeared at 12 months. The measures of bacteriological response were: (1) the percentage of patients with a negative culture on a single collection specimen at six months; (2) the corresponding percentage at 12 months; and (3) the percentage of patients with bacteriologically quiescent disease (or disease of doubtful status) at the end of 12 months, according to the definition adopted in this report (see page 558) The standardized and the unstandardized percen

TABLE 14

PERCENTAGES OF PATIENTS SHOWING FAVOURABLE RADIOGRAPHIC AND BACTERIOLOGICAL RESPONSES, STANDARDIZED FOR PRETREATMENT DIFFERENCES IN VIRULENCE OF THE ORGANISMS

Radiographic response					Bacteriological response				
Nature of response	Period	Treatment series	Unstandardized percentage	Percentage standardized for pretreatment differences in virulence	Nature of response	Month	Treatment series	Unstandardized percentage	Percentage standardized for pretreatment differences in virulence
Considerable or exceptional radiographic improvement	0-6 months	PH	41	42	Negative culture on a single collection specimen	6	PH	87	87
		HI-1	34	34			HI-1	74	73
		HI-2	31	30			HI-2	54	46
		H	27	28			H	48	50
	0-12 months	PH	56	57		12	PH	89	90
		HI-1	55	56			HI-1	78	76
		HI-2	36	32			HI-2	55	49
		H	28	30			H	50	57
Disappearance of cavitation	at 12 months	PH	67	68	Bacteriologically quiescent (or doubtful) disease	12	PH	90	90
		HI-1	58	58			HI-1	75	73
		HI-2	52	49			HI-2	53	47
		H	49	49			H	43	44

tages for all six assessments are shown in Table 14. (The unstandardized percentages are based on smaller totals and differ slightly from the corresponding percentages in Tables 8, 9, 10 and 12, because pretreatment virulence data were not available for all the patients.)

Radiographic response

A comparison of the standardized and the unstandardized percentages shows that, for all practical purposes, only the results for the HI-2 series were affected by standardization for differences in pretreatment virulence; each of the percentages for this series fell slightly, so that the results became very similar to those for the H series (Table 14). The standardized percentages showing considerable or exceptional radiographic improvement in the 0-12-month period were 57 % in the PH series, 56 % in the HI-1, 32% in the HI-2 and 30% in the H series.

Bacteriological response

The effect of standardization upon the measures of bacteriological response was similar to the effect on radiographic response; there was little alteration in the percentages in the PH, HI-1 and H series, but those for the HI-2 series fell to about the level of those for the H series (Table 14). The standardized percentages of patients whose disease had attained bacteriological quiescence (or who had disease of bacteriologically doubtful status) at 12 months were 90 % in the PH series, 73 % in the HI-1, 47 % in the HI-2 and 44% in the H series. The standardized percentages for unfavourable response (for definition, see page 559) were 10 %, 27 %, 53 % and 56 %, respectively, for the four series. It may be concluded that, when allowance was made for the pretreatment differences in the virulence of the organisms, the responses of patients in the HI-2 and H series, already similar, became almost identical.

VII. PROGNOSTIC VALUE OF VARIOUS FACTORS ON ADMISSION TO TREATMENT

It is important to investigate which features of the disease at the start of treatment were associated with an unfavourable response to treatment, and this has been studied in relation to various factors– namely, the age (estimated), the ESR, the extent of cavitation, the total extent of the disease, the number of lung zones involved in disease and the bacterial content of the sputum. The findings are set out in Table 15. Unfavourable response, it will be recalled (page 559), comprises tuberculous death; bacteriologically active disease at 12 months, including change of chemotherapy due to deterioration; or bacteriologically relapsed disease at 12 months.

ESTIMATED AGE

There was no definite association between the estimated age and an unfavourable response in any of the four treatment series.

ERYTHROCYTE SEDIMENTATION RATE

In the PH series there was an association between the ESR and unfavourable response, 13 % of 60 patients with an ESR of 51 mm or more having an unfavourable response, compared with none of 26 with lower ESRs (P= 0.05). The association, although also present, was weaker in the HI-1 and H series; there was no evidence of an association in the HI-2 series.

CAVITATION

Extensive cavitation was an unfavourable prognostic sign in all four series, although this was less so in the PH than in the other three series. In the HI-1, HI-2 and H series moderate cavitation was also relatively unfavourable when compared with slight or no cavitation. Thus, 29 % of 31 HI-1, 50% of 38 HI-2 and 60% of 45 H patients with moderate cavitation had an unfavourable response, compared with 12 % of 26 HI-1, 22 % of 23 HI-2 and 39% of 33 H patients with slight or no cavitation. It is noteworthy that even for patients with slight or no cavitation the H regimen and, to a lesser extent, the HI-2 regimen were not satisfactory.

TOTAL EXTENT OF DISEASE

In all four treatment series the proportion of patients with gross or extensive disease who had an unfavourable response to treatment was higher than the corresponding proportion for the patients with less extensive disease. It will be observed that one of three HI-2 and two of five H patients with slight disease responded unfavourably. All the 12 patients with trivial disease responded satisfactorily.

NUMBER OF LUNG ZONES INVOLVED IN DISEASE

There was no association between the number of lung zones involved in disease and an unfavourable response in the PH, HI-1 and HI-2 series but there was a slight association in the H series; in all four series unfavourable responses occurred even in patients with only two lung zones involved in disease.

BACTERIAL CONTENT OF THE SPUTUM

Of the 27 PH patients with 3-plus positive smear, 19% had an unfavourable response compared with 5 % of 59 PH patients with lower gradings. The corresponding findings for the other three series were 44 % of 25 compared with 15 % of 39 for the HI-1 patients, 56% of 25 compared with 34 % of 41 for the HI-2 patients and 59% of 32 compared with 54% of 54 for the H patients. It may be concluded that in the PH, HI-1 and HI-2 series patients with a bacterial content of sputum graded as 3-plus fared less well than patients with specimens graded 2-plus, 1-plus or negative. For the H series, only the patients with a negative smear result gave evidence of a satisfactory response.

TABLE 15

UNFAVOURABLE RESPONSE TO TREATMENT ACCORDING TO VARIOUS FACTORS ON ADMISSION*

Factor on admission to treatment		PH			HI-1			HI-2			H			All series		
		total patients	unfavourable response **		total patients	unfavourable response		total patients	unfavourable response		total patients	unfavourable response		total patients	unfavourable response	
			No.	%		No.	%		No.	%		No.	%		No.	%
Estimated age (years)	12-24	30	2	*7*	15	2	*(13)***	22	9	*(41)*	20	13	*(65)*	87	26	*30*
	25-34	23	2	*(9)*	29	11	*38*	21	7	*(33)*	30	14	*47*	103	34	*33*
	35-44	14	2	*(14)*	15	4	*(27)*	15	6	*(40)*	19	11	*(58)*	63	23	*37*
	45-54	16	2	*(12)*	3	0	*(0)*	8	6	*(75)*	9	6	*(67)*	36	14	*39*
	55 or more	3	0	*(0)*	2	0	*(0)*	0	0	*(0)*	8	4	*(50)*	13	4	*(31)*
ESR (mm in 1 hour)	101 or more	19	3	*(16)*	11	5	*(45)*	12	4	*(33)*	12	10	*(83)*	54	22	*41*
	51- 100	41	5	*12*	36	9	*25*	35	16	*46*	51	27	*53*	163	57	*35*
	21-50	23	0	*(0)*	15	3	*(20)*	14	6	*(43)*	20	9	*(45)*	72	18	*25*
	O-20	3	0	*(0)*	2	0	*(0)*	5	2	*(40)*	3	2	*(67)*	13	4	*(31)*
Extent of cavitation	Extensive	14	3	*(21)*	7	5	*(71)*	5	4	*(80)*	8	8	*(100)*	34	20	*59*
	Moderate	41	3	*7*	31	9	*29*	38	19	*50*	45	27	*60*	155	58	*37*
	Slight	23	2	*(9)*	25	3	*12*	18	4	*(22)*	25	10	*40*	91	19	*21*
	Nil	8	0	*(0)*	1	0	*(0)*	5	1	*(20)*	8	3	*(38)*	22	4	*(18)*
Total extent of disease	Gross	14	2	*(14)*	5	3	*(60)*	2	1	*(50)*	8	7	*(88)*	29	13	*45*
	Extensive	16	2	*(12)*	10	4	*(40)*	13	8	*(62)*	19	12	*(63)*	58	26	*45*
	Moderate	32	2	*6*	28	3	*11*	27	12	*44*	33	18	*55*	120	35	*29*
	Limited	16	2	*(12)*	18	7	*(39)*	19	6	*(32)*	17	9	*(53)*	70	24	*34*
	Slight	3	0	*(0)*	2	0	*(0)*	3	1	*(33)*	5	2	*(40)*	13	3	*(23)*
	Trivial	5	0	*(0)*	1	0	*(0)*	2	0	*(0)*	4	0	*(0)*	12	0	*(0)*
Number of lung zones involved in disease	6	19	1	*(5)*	7	3	*(43)*	9	5	*(56)*	9	7	*(78)*	44	16	*36*
	5	20	3	*(15)*	11	2	*(18)*	15	9	*(60)*	32	21	*66*	78	35	*45*
	4	17	1	*(6)*	23	6	*(26)*	14	4	*(29)*	13	5	*(38)*	67	16	*24*
	3	14	1	*(7)*	12	3	*(25)*	13	4	*(31)*	15	9	*(60)*	54	17	*31*
	2	15	2	*(13)*	9	3	*(33)*	13	6	*(46)*	13	6	*(46)*	50	17	*34*
	1	1	0	*(0)*	2	0	*(0)*	2	0	*(0)*	4	0	*(0)*	9	0	*(0)*
Bacterial content of sputum (direct smear grade on single collection specimen)	3-plus	27	5	*19*	25	11	*44*	25	14	*56*	32	19	*59*	109	49	*45*
	2-plus	24	2	*(8)*	17	4	*(24)*	21	8	*(38)*	30	23	*77*	92	37	*40*
	1-plus	13	0	*(0)*	16	2	*(12)*	12	6	*(50)*	11	5	*(45)*	52	13	*25*
	Negative	22	1	*(5)*	6	0	*(0)*	8	0	*(0)*	13	1	*(8)*	49	2	*4*
Total patients		86	8	*9*	64	17	*27*	66	28	*4 2*	86	48	*5 6*	302	101	*33*

* Excluding the five patients who died of non-tuberculous conditions and the eight patients who had their chemotherapy changed on account of toxicity.

** That is, tuberculous death; bacteriologically active disease at 12 months, including change of chemotherapy owing to deterioration ; or bacteriologically relapsed disease at 12 months.

*** Percentages based on fewer than 25 observations are enclosed in parentheses, as an indication of the small totals.

VIII. FURTHER BACTERIOLOGICAL FINDINGS

PAS SENSITIVITY

In an earlier report (Tuberculosis Chemotherapy Centre, 1959) the results of PAS-sensitivity tests were expressed as resistance ratios–that is, as the minimal drug concentration inhibiting growth of the test strain, divided by the minimal drug concentration inhibiting growth of the standard sensitive control strain, H37Rv. " Growth " was defined as 20 or more colonies, both for the test strain and for strain H37Rv. In that report a patient was regarded as harbouring resistant organisms before treatment if

" . . . if any test yielded a resistance ratio of more than 8, or if there were two tests, one of which yielded a resistance ratio of 8 and the other 4 or more, or if three resistance ratios of 4 were obtained from among the tests on the two pretreatment cultures and the two repeat tests on those cultures ".

According to these definitions, no less than 22% of the 338 patients in the present study, who, as far as is known, had had no (or less than two weeks') previous chemotherapy, had PAS-resistant strains before the start of treatment, compared with less than 3% of the patients in the earlier study. This finding makes it evident either that a much higher proportion of patients harbouring PAS-resistant strains was admitted to the present study, or that the technique of performing the tests was different in the two studies. The former explanation is very unlikely since the proportions of patients with primarily isoniazid- or streptomycin-resistant strains were not notably different for the two studies, there being 3.8 % resistant to isoniazid and 2.3 % to streptomycin in the earlier study and 5.9% (section XII) and 3.3 % (see below), respectively, in the present study. In view of these small increases between the two studies some increase may also have occurred in the percentage of patients with PAS-resistant strains admitted to treatment in the present study, but it would seem most unlikely that a tenfold increase had taken place; there is no reason to believe that chemotherapeutic practice in Madras has recently changed to such an extent as could account for so great an increase in PAS resistance.

Evidence has been obtained (Selkon et al., 1960 [1]) that strains of tubercle bacilli from Indian and British patients differ in the pattern of their sensitivity to PAS. In essence, strains of tubercle bacilli from Indian patients, unlike those from British patients, contain, in general, a proportion of PAS-resistant organisms, which, although very small, is sufficient to yield less than 50 colonies on PAS-containing slopes in many of the tests set up in this Centre's laboratory. Consequently, if " growth " is defined as 20 or more colonies, minor variations in inoculum size can cause large changes in the apparent sensitivities to PAS of strains from Indian patients. Thus, a tendency to employ a rather larger inoculum in the present study could well have accounted for the apparent increase in primary PAS resistance. Moreover, it has been found that the occurrence of an apparently resistant strain (according to the above definitions) does not imply that further tests on the same strain, or on other strains from the same patient, will also yield resistant results. It has therefore been concluded that the definitions of resistance employed in the earlier study are not meaningful for the present study and that patients with primary PAS-resistant strains cannot be identified by these definitions.

If, on the other hand, growth is defined as 100 or more colonies, then no difference is apparent between the sensitivities of British and Indian strains (Selkon et al., 1960 [1]). In addition, according to this end-point, there is no increase in primary PAS resistance between the earlier and the present study. Two other methods of expressing the results of the PAS-sensitivity tests in the present study were therefore investigated. These are: (1) the minimal inhibitory concentration (MIC) inhibiting the growth of 20 colonies (1-plus growth); and (2) the MIC inhibiting the growth of innumerable discrete colonies, that is, approximately 100 or more colonies [2] (2-plus growth). (Resistance ratios could not be used for the 2-plus end-point in place of MICs because the concentrations of PAS used with the standard sensitive strain, H37Rv, did not always permit such ratios to be determined.)

For the pretreatment tests in the present study, the following definitions of resistance, which

[1] See article on page 599 of this issue.

[2] Whereas the 20-colony end-point was obtained by counting, the 100-colony end-point was only estimated; its possible importance was not appreciated until late in the study.

screened off a small proportion of the strains as resistant, were adopted:

	Concentration of sodium PAS (µg/ml)
Definition for 1 -plus MIC :	either, more than 16 and more than 16, on two separate specimens
	or, more than 4 and more than 64, on two separate specimens.
Definition for 2-plus MIC:	either, more than 2 and more than 2, on two separate specimens
	or, 2 and more than 4, on two separate specimens.

For strain H37Rv the 1-plus MIC was on the average 2 µg/ml and the 2-plus MIC 0.5 µg/ml sodium PAS; so that a l-plus MIC of 16 would on the average correspond to a resistance ratio of 8 and a 2-plus MIC of 2 to a resistance ratio of 4.

According to the l-plus MIC definition, 10 (3.0%) of the 338 previously untreated patients had PAS-resistant organisms (one also had a streptomycin-resistant strain) and, according to the 2-plus MIC definition, five (1.5%) of the 338 patients had PAS-resistant organisms and two also had streptomycin-resistant strains. Only two of the patients had strains which were resistant to PAS by both definitions. Of the 315 patients in the main analysis, eight (4 PH, 1 HI-1, 1 HI-2, 2 H) had resistant strains according to the 1-plus MIC definition (all four PH patients had quiescent disease at 12 months). Four patients (2 HI-1, 1 HI-2, 1 H) had resistant strains according to the 2-plus MIC definition. In the main analysis, only one patient (HI-1) had a strain which was PAS-resistant by both definitions. In view of this difficulty in identifying patients with PAS-resistant strains, it was decided not to exclude any of the patients from the main clinical analysis on the grounds of PAS resistance. The PH series may consequently have been at a minor disadvantage compared with the other three series.

The results of PAS-sensitivity tests on strains obtained during treatment from PH patients were analysed in terms of both the 1-plus MIC and 2-plus MIC end-points. Considering two definitions of resistance for each end-point (Tables 16 and 17), there was very slender evidence of an increase in the proportions of resistant strains during the later months. However, the numbers of patients with positive cultures each month during the last six months of treatment were very small, ranging only from 5 to 8. It must be concluded that the value of the PAS-sensitivity tests on Indian strains remains uncertain.

STREPTOMYCIN SENSITIVITY

Streptomycin was not included in the standard chemotherapy and streptomycin-sensitivity tests were therefore not undertaken during treatment, unless a patient had deteriorated and the chemotherapy was changed o include this antibiotic. Tests were, however, performed on the pretreatment cultures for all 341 patients, 338 of whom had had no previous chemotherapy. The great majority of patients had two sensitivity tests and a small number only one. Eleven patients yielded streptomycin-resistant strains. Interrogation on several occasions and further inquiries indicated that none of these had had previous chemotherapy likely to have been antituberculous. It is therefore probable that all 11 had been infected with streptomycin-resistant strains ; this represents a prevalence of primary streptomycin resistance of 3.3 %.

OTHER BACTERIOLOGICAL FINDINGS

The detailed findings on the pattern of emergence of isoniazid resistance in the four treatment series, changes in the catalase activity of the strains, the virulence in the guinea-pig of the strains isolated both before and during chemotherapy, and the hydrogen peroxide susceptibility of the strains will all be reported elsewhere.

TABLE 16. RESULTS OF PAS-SENSITIVITY TESTS IN PATIENTS TREATED WITH ISONIAZID PLUS PAS FOR A PERIOD OF 12 MONTHS *

(1-plus minimal inhibitory concentration end-point)

Months after start of chemotherapy	Total cultures examined **	Culture-negative (no sensitivity test possible)	Culture-positive but no sensitivity test result available	Total sensitivity test results available (A)	Minimal inhibitory concentration (MIC) in µg/ml				Total "resistant" to PAS			
					4 or less	8	16	64 or more	MIC of 8 µg/ml or more		MIC of 16 µg/ml or more	
									No.	% of A	No.	% of A
0	86	0	0	86 ***	67	14	2	3	19	*22*	5	*6*
1, 2 and 3 combined	251	118	3	130	96	24	7	3	34	*26*	10	*8*
4, 5 and 6 combined	247	214	1	32	26	1	3	2	6	*19*	5	*16*
7, 8 and 9 combined	240	220	0	20	14	2	2	2	6	*(30)* †	4	*(20)*
10, 11 and 12 combined	238	218	2	18	8	6	3	1	10	*(56)*	4	*(22)*

* All patients had strains sensitive to isoniazid on admission to treatment; the four patients who had PAS-resistant strains on admission, according to the 1-plus MIC definition (see page 567), have been excluded throughout this table.

** Patients who died are included up to the month of death and patients who had their chemotherapy changed on account of deterioration or toxicity are included up to the month of the change.

*** Based on a single sensitivity test on the first of two pretreatment cultures.

† Percentages based on fewer than 25 observations are enclosed in parentheses, as an indication of the small totals.

TABLE 17. RESULTS OF PAS-SENSITIVITY TESTS IN PATIENTS TREATED WITH ISONIAZID PLUS PAS FOR A PERIOD OF 12 MONTHS*

(2-plus minimal inhibitory concentration end-point)

Months after start of chemotherapy	Total cultures examined **	Culture-negative (no sensitivity test possible)	Culture-positive but no sensitivity test result available	Total sensitivity test results available (A)	Minimal inhibitory concentration (MIC) in µg/ml				Total "resistant" to PAS			
					2 or less	4	8	16 or more	MIC of 4 µg/ml or more		MIC of 8 µg/ml or more	
									No.	% of A	No.	% of A
0	90	0	0	90 ***	84	6	0	0	6	*7*	0	*0*
1, 2 and 3 combined	262	122	4	136	127†	8	1	0	9	*7*	1	*1*
4, 5 and 6 combined	259	225	2	32	30	0	1	1	2	*6*	2	*6*
7, 8 and 9 combined	252	232	0	20	18††	2	0	0	2	*(10)* †††	0	*(0)*
10, 11 and 12 combined	250	230	2	18	16	2	0	0	2	*(11)*	0	*(0)*

* All patients had strains sensitive to isoniazid and to PAS (according to the 2-plus MIC definition-see page 567) on admission to treatment.

** Patients who died are included up to the month of death and patients who had their chemotherapy changed on account of deterioration or toxicity are included up to the month of the change.

*** Based on a single sensitivity test on the first of two pretreatment cultures.

† Includes two strains with no test result on 2 µg/ml. †† Includes one strain with no test result on 2 µg/ml.

††† Enclosed in parentheses, as an indication of the small totals.

IX. TOXICITY AND OTHER COMPLICATIONS

TOXICITY

PAS

Three cases of hypersensitivity to PAS were encountered among the 90 PH patients, all in the second month of treatment. Two of these patients developed rashes ; one was successfully desensitized in 23 days and the other in rather more than three months. The third patient developed fever, intense itching, profuse sweating and albuminuria. These manifestations reappeared when a test dose of 0.05 g of PAS (sodium) was administered, and the chemotherapy was therefore changed to streptomycin and isoniazid. A fourth patient developed jaundice in the second month of treatment; the prescribed regimen was resumed uneventfully after 38 days, and so it was considered that the jaundice had been due to infectious hepatitis. As in the earlier study (Tuberculosis Chemotherapy Centre, 1959), gastro-intestinal side-effects were completely unimportant; it was not necessary to reduce the dosage of the medicament for any patient on account of them.

Isoniazid

Twenty patients developed definite peripheral neuritis attributed to isoniazid-namely, one (1 %) of 90 PH, 13 (19%) of 70 HI-1 and six (9%) of 68 HI-2 patients. None of the 87 H patients developed the complication. The difference between the HI-1 and HI-2 series does not attain statistical significance. These cases have been reported in detail by Devadatta et al. (1960).[1] Of the 20 cases, 18 were referred to an independent assessor (either Dr C. E. Klontz or Dr K. S. Sanjivi) who was unaware of the treatment series; the diagnosis of peripheral neuritis made by the Centre's staff was confirmed in all 18; the other two cases were diagnosed before the arrangements for an independent assessment were completed.

The symptomatology was mainly sensory and the course of the neuritis, when untreated, was characterized by slow progression in all but two of the patients. All the 20 patients had definite physical signs of peripheral neuritis. Eight of the patients developed anaesthesia of the " stocking " type (four of them also having analgesia), eight had loss of joint sense, 17 loss of vibration sense in the toes (extending to the ankles in nine cases) and six had tender calf muscles. Fifteen patients lost their ankle jerks, and in three the knee jerks were also lost. Six patients developed muscular weakness. The onset of the first symptom of peripheral neuritis occurred between the second month and the tenth month, occurring rather earlier in the HI-1 patients than in the HI-2 patients.

Serum isoniazid assays were performed for the great majority of patients by a microbiological method (Gangadharam et al., to be published) and it was found that the patients who developed peripheral neuritis had a higher mean serum level of the drug than those who did not develop this complication; the difference in the incidence of peripheral neuritis among slow and rapid inactivators attained statistical significance (Devadatta et al., 1960 [1]).

The 20 cases were managed in several different ways. The details are reported by Devadatta et al. (1960).[1] In only seven (5 HI-1, 2 HI-2) of the 20 patients was the antituberculosis chemotherapy changed because of the peripheral neuritis (although one (HI-2) of the seven patients had, in addition, a radiographic deterioration, confirmed by the independent assessor at the same time, and appears in the tables as a change of chemotherapy due to deterioration).

Mental disturbance, attributed to isoniazid, occurred in only one (HI-1) patient. This patient, who also had peripheral neuritis, exhibited signs of mental disturbance in the third month of treatment. He developed a premonition of impending death and was extremely apprehensive. The antituberculosis chemotherapy was changed, and he was also treated with pyridoxine; within three months his mental state had returned to normal.

PREGNANCY

Patients who were known to be pregnant were not admitted to the study, but two patients (1 PH, 1 H) were subsequently found to have been pregnant on admission. A further 17 patients (3 PH, 5 HI-1, 5 HI-2, 4 H) became pregnant during the course of the 12 months; of these, one (H) aborted and three (1 PH, 1 HI-1, 1 HI-2) were delivered during the 12-month period; the remaining 13 were still pregnant at 12 months. The response of pregnant

[1] See article on page 587 of this issue.

patients to antituberculosis chemotherapy will be the subject of a later report.

LEPROSY

Although patients known to have leprosy were not admitted to the study it was found in the course of the 12 months that four patients (1 PH, 1 HI-2, 2 H) were suffering from leprosy. They received sulfone therapy as out-patients in the Madras Government General Hospital. There is evidence that the anti-tuberculosis effect of sulfone is, at most, small (East African/British Medical Research Council Sulphone Investigation, 1960).

HOSPITAL AND SANATORIUM ADMISSIONS

Complicating conditions, whether tuberculous or non-tuberculous, were usually treated on an out-patient basis. If the illness was serious, or special investigation or treatment not available to out-patients was required, the patients were admitted to hospital or sanatorium. In all, 12 PH, five HI-1 eight HI-2 and 18 H patients were admitted for special investigations or treatment (a small number on two occasions and one for two medical conditions). Of these, two PH, two HI-1, five HI-2 and 12 H patients were admitted because of condition attributed directly or indirectly to pulmonary tuberculosis or to the treatment, including one HI-1 three HI-2 and nine H patients whose chemotherapy was changed because of radiographic or clinical deterioration.

The non-tuberculous conditions requiring admission consisted of five cases of smallpox (3 PH, 2 H), seven cases of acute or chronic diarrhoea (2 PH, 2 HI-1, 1 HI-2, 2 H), four obstetrical or gynaecological conditions (2 PH, 1 HI-1, 1 H) and seven miscellaneous conditions (4 PH, 2 HI-2, 1 H).

The duration of hospitalization for patients with a tuberculous deterioration was often long and seven patients (2 HI-2, 5 H) were in sanatorium for more than three of the 12 months.

X. SELF-ADMINISTRATION OF THE MEDICINE

The importance of taking the medicine regularly was emphasized to the patients, both before the start of treatment and throughout the 12 months. Two methods were used to check whether the medicine-taking was regular:

(1) Urine tests were made to detect the presence of drug in specimens obtained at routine visits of the patients to the Centre and in specimens obtained at surprise visits by the staff to the homes. For the PH patients a ferric chloride test for PAS was used (Simpson, 1956). For the patients in the HI-1, HI-2 and H series the combined naphthoquinone-mercuric chloride (combined N-M) test was performed (Short & Case, 1957; Gangadharam et al., 1958).

(2) Counts were made of the patient's stock of tablets or cachets at surprise visits to the homes.

SENSITIVITY OF THE URINE TESTS FOR PAS AND FOR ISONIAZID

It was important to compare the sensitivity of the ferric chloride test for PAS and the combined N-M test for isoniazid, in order to assess the implications of a negative finding in the urine. In the course of the routine work of the laboratory, and without the knowledge of its staff, therefore, two studies were made on volunteers from the Centre's national staff to determine the period for which the urine would remain positive after standard doses of each of four regimens (Table 18).

The first study consisted of two similar investigations undertaken at different times. In each part 13 volunteers were given a day's dosage of the PH regimen and of one of the other three regimens (selected at random), at an interval of approximately 14 days the order of administration also being determineed at random. Urine specimens were collected before the first dose and three, 14 ,18, 26 and 28 hours after the last dose. The bladder was emptied two hours before each of these post-treatment specimens was due. The results of the tests were read as part of the normal laboratory routine, The tests for PAS were positive (Table 18) on all except one of the 52 specimens obtained either at three or at 14 hours after the last dose of PH, and those for isoniazid

TABLE 18

RESULTS OF URINE TESTS FOR PAS (IN SUBJECTS GIVEN ISONIAZID PLUS PAS) AND FOR ISONIAZID (IN SUBJECTS GIVEN ISONIAZID ALONE) IN TWO STUDIES ON VOLUNTEERS

Study	Regimen	Total volunteers	Number of volunteers with positive test results: hours after taking the last dose					
			0	3	14	18	26	28
First	PH	26	2*	26	25	22	7	5*
	HI-1	8	1	6*	7*	8	7	7
	HI-2	8	0	8	8	7	4**	1**
	H	10	0*	9*	9	7	5	3
Second	HI-1	15	4*	15	14	15	11	13*
	HI-2	15	4	15	15	15	8	8
	H	15	3	15	14	13	5	7

* One specimen was not tested at this time.

** Two specimens were not tested at this time.

were positive on all except two of the 49 specimens obtained at the same intervals after the last dose of one of the isoniazid-alone regimens. At 18 hours, 22 of the 26 volunteers gave positive results for PAS and for isoniazid. At 26 and 28 hours, the results for isoniazid were more frequently positive than those for PAS, 27 (56%) of the 48 specimens tested for isoniazid being positive compared with 12 (24%) of 51 tested for PAS, the difference attaining statistical significance ($P<0.01$). The combined N-M test was therefore more sensitive. These results show that a negative result to either test means that no drug has been taken for 14 hours (and perhaps for considerably longer) and, therefore, that the equivalent of a day's supply of medicine has been missed. The same conclusions had been drawn from a similar earlier experiment in which 11 volunteers received the PH, five the HI-1, three the HI-2 and five the H regimen. The results have not been included in Table 18 since, although the readings of the tests were made in a random order, the laboratory staff knew that they were reading tests in a special comparison.

In the second study, which was also made without the knowledge of the laboratory staff, a more detailed comparison was undertaken of the persistence of isoniazid in the urine following a day's dosage of the HI-1, HI-2 and H regimens. Fifteen volunteers were given a day's dosage of each regimen in a random order, at intervals of approximately 10 days. The results are set out in the lower section of Table 18. There were 11 false positive results in the 44 specimens obtained before any isoniazid was taken-namely, four in the HI-1, four in the HI-2 and three in the H subjects; presumably, therefore, some of the positive results obtained after the isoniazid was taken may not have been due to the presence of isoniazid. These false positive results occurred in a short period when staff changes were taking place in the laboratory; both before and after this period, it was very uncommon for tests performed on specimens known to be free of isoniazid to yield false positive results.

All the specimens gave positive results at three hours and so did all but two (1 HI-1, 1 H) at 14 hours. At 18 hours, all but two specimens (both H) were positive. The proportion of positive results decreased after this time but was higher among the HI-1 than among the HI-2 or H volunteers. It may be concluded that for patients on the HI-2 and H regimens, a negative result in a morning specimen means that no medicine has been taken that morning or on the previous evening. For patients on the HI-1 regimen it indicates that no medicine has been taken on that morning and probably at no time during the previous day.

REGULARITY OF SELF-ADMINISTRATION OF THE MEDICINES

The results of tests performed on specimens of urine obtained from the patients at the routine weekly visits to the Centre are set out in Table 19. Since these specimens were obtained at every visit (except in the case of female patients who were menstruating), they permit a valid comparison of the acceptability of the four regimens. The average number of tests per patient per month was 4.0 for each of the four treatment series, and was a little higher in each series for the males than for the females. The proportion of negative test results ranged from 4.8% to 6.6% (Table 19), and was slightly higher for the females in each treatment series than for the males. The proportion of negative results was thus low in all four treatment series. Even allowing for the fact that a negative result generally means that at least two doses of the

TABLE 19

REGULARITY OF SELF-ADMINISTRATION OF DRUG (AS ASSESSED BY TESTS ON URINE SPECIMENS OBTAINED AT ROUTINE VISITS TO THE CENTRE)

	PH		HI-1		HI-2		H	
	males	females	males	females	males	females	males	females
Number of patients with test results *	56	30	35	29	48	18	53	31
Total number of test results	2722	1370	1714	1308	2209	719	2499	1194
Average number of test results per patient per month	4.1	3.7	4.1	3.9	4.1	3.9	4.0	3.9
Number of test results which were negative	118	78	73	105	111	46	161	81
Percentage of test results which were negative	*4.3*	*5.7*	*4.3*	*8.0*	*5.0*	*6.4*	*6.4*	*6.8*
	4.8		*5.9*		*5.4*		6.6	

*** Excluding two male (1 HI-2, 1 H) and three female (2 PH, 1 HI-1) patients who died of non-tuberculous conditions, four male (1 PH, 3 HI-1) and four female (1 PH, 2 HI-1, 1 HI-2) patients who had their chemotherapy changed *on* account of toxicity and *one* male (H) and one female (H) patient who died of tuberculosis within one month of the start of chemotherapy. Patients who died of tuberculosis have been included up to the month of death and patients who had their chemotherapy changed on account of deterioration have been included up to the month of the change.**

medicine have been missed, the findings suggest that the medicine was being taken with considerable regularity throughout the 12 months. However, it must be emphasized that this conclusion is based on specimens obtained at *routine* visits to the Centre, when patients knew that tests would be made. The degree of irregularity may therefore have been underestimated.

The similarity of the findings in the PH series (4.8 % of tests negative) and the H series (6.6%) is of particular interest. The PM patients had to take large white cachets each weighing more than 1.5 g and containing 1.25 g of PAS and 25 mg of isoniazid, while the H patients took smaller pink tablets each weighing 0.5 g and containing 25 mg of isoniazid, but *no PAS.* The number of cachets or tablets to be taken daily was the same for the two regimens and, in both, the medicine was given in two doses. There is no evidence that the PAS-containing cachets were any less acceptable than the isoniazid tablets, and they may even have been more acceptable. The HI-1 and HI-2 regimens were of similar acceptability; this is also of special interest since the same number of identical tablets was prescribed daily in each regimen, but as a single morning dose for the HI-1 patients and as a morning and an evening dose for the HI-2 patients.

Table 20 shows the distribution of the patients in the four treatment series, according to the percentage of negative results at the routine visits. Twenty-seven (31%) of the PH patients, 18 (28 %) of the HI-1, 25 (38 %) of the HI-2 and 22 (26 %) of the H patients never produced a negative result. A further 38 % of the PH, 25 % of the HI-1, 30 % of the HI-2 and 27% of the H patients produced negative results in less than 5 % of tests. In contrast, there were 17 patients (4 PH, 4 HI-1, 4 HI-2, 5 H) with negative results in 20% or more of the tests. Of these, two PH patients produced negative results in 48 % and 50 % of their tests, respectively, two HI-2 patients in 38 % and 49%, respectively, and one H patient in 84% of his tests. In summary, the distributions for the four treatment series were similar.

RESPONSE TO TREATMENT IN RELATION TO THE REGULARITY OF MEDICINE-TAKING

Table 20 also relates the percentage of urine tests with negative results to the frequency of unfavourable response to treatment during the 12 months, defined

TABLE 20. UNFAVOURABLE RESPONSE TO TREATMENT RELATED TO THE PROPORTION OF NEGATIVE TEST RESULTS ON URINE SPECIMENS OBTAINED AT ROUTINE VISITS TO THE CENTRE

Percentage of test results which were negative	PH			HI-1			HI-2			H		
	total patients *	unfavourable response **		total patients	unfavourable response		total patients	unfavourable response		total patients	unfavourable response	
		No.	%		No.	%		No.	%		No.	%
0	27	2	7	18	2	(11) ***	25	14	56	22	12	(55)
1-4	33	3	9	16	5	(31)	20	7	(35)	23	10	(43)
5-9	16	2	(12)	12	2	(17)	9	4	(44)	20	10	(50)
10-14	4	0	(0)	12	5	(42)	6	0	(0)	8	8	(100)
15-19	2	1	(50)	2	1	(50)	2	1	(50)	6	3	(50)
20 or more	4	0	(0)	4	2	(50)	4	2	(50)	5	3	(60)
Total	86	8	9	64	17	27	66	28	42	84	46	55

* Excluding five patients (2 PH, 1 HI-1, 1 HI-2, 1 H) who died of non-tuberculous conditions, eight patients (2 PH, 5 HI-1, 1 HI-2) who had their chemotherapy changed on account of toxicity and two patients (both H) who died of tuberculosis within one month of the start of chemotherapy. Patients who died of tuberculosis have been included up to the month of death and patients who had their chemotherapy changed on account of deterioration have been included up to the month of the change.

** That is, tuberculous death; bacteriologically active disease at 12 months, including change of chemotherapy due to deterioration; or bacteriologically relapsed disease at 12 months.

*** Percentages based on fewer than 25 observations are enclosed in parentheses, as an indication of the small totals.

as death from tuberculosis; bacteriologically active disease at 12 months, including deterioration leading to change of chemotherapy; or bacteriologically relapsed disease at 12 months.

In the PH series there was no suggestion of an association between irregularity in medicine-taking and an unfavourable response; two (7%) of the 27 patients whose urine tests were always positive had an unfavourable response, compared with six (10 %) of 59 patients who produced negative results on one or more occasions. In the HI-1 series, however, two (11%) of 18 patients who produced no negative results showed an unfavourable response, compared with 15 (33 %) of 46 whose urine specimens yielded one or more negative results ; this difference borders on statistical significance (P = 0.07). The likelihood of a genuine association in this series is increased by an analysis (not tabulated here) which showed that the patients whose urine test results were all positive were at a slight disadvantage in pretreatment clinical condition, compared with those who showed irregularities in medicine-taking.

In the HI-2 and H series, the percentages of patients showing unfavourable responses were high, even among those whose results were all positive. Thus, unfavourable responses occurred frequently with these regimens, even when they were being taken regularly.

FINDINGS AT SURPRISE VISITS TO THE PATIENT'S HOME

Information on the regularity of self-administration of the drugs from surprise visits to the home, whether obtained from urine testing or from counts of the stock of medicine, is valuable as a means of checking the co-operation of the individual patient. In the present study the information is much less suitable for analysis than that obtained from the routine urine specimens at the Centre. In the first place, the findings at surprise visits are subject to bias, since data were more likely to be obtained from ill patients resting at home than from patients who had returned to work. Moreover, on finding a negative urine result or an excessive stock of medicine, the doctors often requested the health visitors to pay more frequent surprise visits. Finally, less information was available since surprise visits to the home were paid much less frequently than the routine visits by the patient to the Centre. Because of these shortcomings no analyses of the data obtained at surprise visits are presented here.

XI. VARIOUS SOCIAL FACTORS

REST AND ACTIVITY

The general policy which was adopted was to persuade the patients to rest as much as possible in the early weeks of treatment. As their general condition improved they were allowed to increase their activity, and many were in their normal full-time occupations at the end of the year. It was difficult to estimate accurately the degree of activity, since many patients, unless actually feeling ill, would sit or potter around at home much of the day and often go for walks. The great majority of the patients, in addition, attended the Centre weekly throughout the 12 months for a supply of medicine and usually, because they could not afford the fares, had to travel on foot, some a distance of up to 5 miles (8 km) each way. Table 21 sets out the assessment of the activity at six and 12 months for the males and females separately. Considering the males first, at six months, 41 % of the PH, 46% of the HI-1, 44 % of the HI-2 and 28 % of the H patients were on part-time or full-time activity, the majority being on part-time. By 12 months the proportions had increased to 91%, 86 %, 83 % and 72 %, respectively. Considering the females, at six months, 58 % of the PH, 43 % of the HI-1, 39 % of the HI-2 and 56% of the H series had resumed at least part-time activity. At 12 months the proportions were 97 %, 79 %, 61% and 59 %, respectively. It may be concluded that the majority of patients, both male and female, had returned to at least part-time activity by the end of the period, and that many had done so by six months.

INCOME OF THE FAMILIES BEFORE TREATMENT

The total family income at the start of treatment was assessed by adding the average monthly income of the patient, in the six months immediately prior to admission to treatment, to the monthly income from any source of all the other family members, at the time of admission of the patient. Although the patients and their families were questioned carefully during treatment of the patient, as well as at the start, it will be appreciated that it remains uncertain whether all the families revealed all their sources of income.

The great majority of the family incomes-namely, 80% of those for the PH series, 77 % for the HI-1 series, 78% for the HI-2 series, and 83 % for the H series–lay between Rs 40.00 and Rs 150.00 per month ; [1] a number of families had lower, and a few had higher, total incomes. These data have not been tabulated here, because a knowledge of the total family income is of limited value unless it is related to the size and to the age- and sex-composition of the family. With this in view, therefore, each family has been expressed, as in the 1959 report, in terms of standard units; an adult male was equivalent to 1 standard unit, an adult female was taken as 0.8, and a child under the age of 15 years as 0.6 standard unit (India, Ministry of Commerce, 1949). The total income of each family was then expressed as the income per standard unit; the findings are presented in Table 22.

Considering the families of male patients first, 37 % of 57 in the PH series, 24 % of 38 in the HI-1 series, 3 1% of 49 in the HI-2 series and 25 % of 55 in the H series had an income per standard unit of less than Rs 20.00 per month ; only two families of PH patients, three of HI-1 patients, six of HI-2 patients and four of H patients had a monthly income of Rs 50.00 or more per unit. Considering the families of female patients, 67 % of 33 in the PH series, 44% of 32 in the HI-1 series, 53 % of 19 in the HI-2 series and 62% of 32 in the H series had an income per standard unit of less than Rs 20.00 per month; only three families (all of HI-1 patients) had a monthly income of Rs 50.00 or more per unit. The reported family incomes were thus rather lower, in terms of standard units, for female than for male patients.

In these families most of the income is spent on food. Chaudhuri (1959), referring to the current cost of living in India, stated that " at present price levels, a balanced diet for 1 adult costs at least Rs 1.50 a day (Rs 45.00 a month); and the minimum total requirement, including food and clothing, is about Rs 60-70 per month ".

FINANCIAL ASSISTANCE TO THE FAMILY

As explained in an earlier report (Tuberculosis Chemotherapy Centre, 1959), a fund was available to provide limited financial assistance to the families of especially needy patients. An analysis (not tabulated here) was undertaken of the financial

[1] Rs 4.80 = US$ 1.00.

TABLE 21

PHYSICAL ACTIVITY OF THE PATIENTS AT 6 AND AT 12 MONTHS

Physical activity of patient	Males *										Females **									
	6 months						12 months				6 months				12 months					
	PH		HI-1		HI-2		H		PH		HI-1		HI-2		H		PH		HI-1	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Full-time	3	5	3	8	2	4	1	2	34	61	18	51	21	44	25	46	2	6	1	3
Part-time	20	36	14	38	19	40	14	26	17	30	12	34	19	40	14	26	16	52	12	40
Slight	32	57	20	54	23	48	35	65	4	7	4	11	0	0	7	13	12	39	16	53
Resting	0	0	0	0	3	6	3	6	0	0	0	0	0	0	2	4	1	3	0	0
Change of chemotherapy due to deterioration	0	0	0	0	0	0	0	0	0	0	1	3	7	15	5	9	0	0	1	3
Tuberculous death	1	2	0	0	1	2	1	2	1	2	0	0	1	2	1	2	0	0	0	0
Total patients	56	100	37	100	48	100	54	101	56	100	35	99	48	101	54	100	31	100	30	99

Physical activity of patient	Females **									
	6 months				12 months					
	HI-2		H		PH		HI-I		HI-2	
	No.	%	No.	%	No.	%	No.	%	No.	%
Full-time	2	(11)***	5	16	22	73	12	47	11	(67)
Part-time	5	(28)	13	41	7	23	11	38	9	(0)
Slight	10	(56)	7	22	0	0	2	7	0	(0)
Resting	0	(0)	1	3	0	0	0	0	0	(0)
Change of chemotherapy due to deterioration	1	(6)	4	12	1	3	4	14	7	(39)
Tuberculous death	0	(0)	2	6	0	0	0	0	0	(0)
Total patients	18	101	32	100	30	99	29	100	18	100

Physical activity of patient	Females **		
	12 months		
	H		
	No.	%	
Full-time	11	34	
Part-time	8	25	
Slight	0	0	
Resting	1	3	
Change of chemotherapy due to deterioration	10	31	
Tuberculous death	2	6	
Total patients	32	99	

* Excluding throughout two patients (1 HI-2, 1 H) who died of non-tuberculous conditions and two patients (1 PH, 1 HI-1) who had their chemotherapy changed on account of toxicity in the first six months; excluding also, at 12 months only, two patients (both HI-I) who had their chemotherapy changed on account of toxicity in the second six months.

** Excluding throughout two patients (1 PH, 1 HI-1) who died of non-tuberculous conditions and three patients (1 PH, 1 HI-1, 1 HI-2) who had their chemotherapy changed on account of toxicity in the first six months; excluding also, at 12 months only, one patient (PH) who died of a non-tuberculous condition and one patient (HI-I) who had her chemotherapy changed on account of toxicity in the second six months.

*** Percentages based on fewer than 25 observations are enclosed in parentheses, as an indication of the small totals.

TABLE 22

TOTAL FAMILY INCOME BEFORE THE START OF TREATMENT, EXPRESSED IN TERMS OF STANDARD UNITS*

Income per standard unit (in rupees** per month)	Families of male patients in study								Families of female patients in study							
	PH series		HI-1 series		HI-2 series		H series		PH series		HI-1 series		HI-2 series		H series	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
0 -	2	4	2	5	1	2	4	7	3	9	2	6	0	(0)***	4	12
10 -	19	33	7	18	14	29	10	18	19	58	12	38	10	(53)	16	50
20 -	25	44	16	42	16	33	23	42	6	18	10	31	5	(26)	10	31
30 -	7	12	7	18	6	12	12	22	4	12	5	16	2	(11)	2	6
40 -	2	4	3	8	6	12	2	4	1	3	0	0	2	(11)	0	0
50 -	0	0	3	8	5	10	0	0	0	0	2	6	0	(0)	0	0
60 or more	2	4	0	0	1	2	4	7	0	0	1	3	0	(0)	0	0
Total families	57	101	33	99	49	100	55	100	33	100	32	100	19	101	32	99

* An adult male (15 years or over) was counted as 1 standard unit, an adult female (15 years or over) as 0.8 of a standard unit and a child below 15 as 0.6 of a standard unit.

** Rs 4.80 = US$ 1.00.

*** Percentages based on fewer than 25 observations are enclosed in parentheses, as an indication of the small totals.

assistance provided by the Centre. In the case of patients who died or had their treatment changed, only the assistance given up to the time of death or change of chemotherapy has been included. Considering the families of male patients first, 75% of 57 PH families, 63 % of 38 HI-1, 73 % of 49 HI-2 and 80% of 54 H families received financial assistance. The average monthly payment for the families receiving assistance was Rs 7.69, Rs 5.70, Rs 7.72 and Rs 8.50, respectively. Of these, 35 % of the families of patients in the PH series, 62 % in the HI-1, 25 % in the HI-2 and 16 % in the H series received assistance of less than Rs 5.00 a month, on the average. Only one family (H) received more than Rs 20.00 a month (Rs 28.21). Considering the families of female patients, 61 % of 33 PH families, 31% of 32 HI-1, 58% of 19 HI-2 and 61 % of 31 H families received financial assistance. The average monthly payment for the families receiving financial assistance was Rs 4.32, Rs 4.36, Rs 3.62 and Rs 3.73, respectively. The proportions of these families which received, on the average, less than Rs 5.00 a month were 55 %, 50 %, 55 % and 68 %, respectively in the four series. Only one family (PH) received more than Rs 15.00 a month (Rs 16.50). It may be concluded that the financial assistance was kept to a low level and that the families of male patients, as in the earlier study (Tuberculosis Chemotherapy Centre, 1959), received more financial assistance than those of female patients.

XII. PATIENTS NOT INCLUDED IN THE MAIN ANALYSIS

This section reports on the total of 26 patients (6 PH, 5 HI-1, 7 HI-2, 8 H) who were separated from the main analysis, 22 because they were excreting isoniazid-resistant organisms at the start of treatment and four for other reasons, given below.

PATIENTS WITH ISONIAZID-RESISTANT ORGANISMS AT THE START OF TREATMENT

Twenty-two patients had isoniazid-resistant organisms when treatment began. All the patients were interrogated on several occasions during the course of treatment, as their relationship of trust with the Centre's staff became more and more firmly established, to discover whether they had had previous chemotherapy and were concealing the fact. Two admitted that they had had previous chemotherapy which was believed to have included isoniazid. The duration of chemotherapy for each of these two patients was probably one month. Of the remaining 20 patients, 19 had no history of previous chemo-

therapy and the twentieth had had a week of streptomycin plus isoniazid. It is considered that these 20 patients (5.9% of the 337 patients who had had no previous chemotherapy or, in 12 cases, up to two weeks' chemotherapy and for whom pretreatment isoniazid-sensitivity test results were available) had been infected with isoniazid-resistant organisms, that is, had primary isoniazid resistance. Every effort was made to discover whether any of the 341 patients had had previous antituberculosis chemotherapy; for example, dispensary cards from other hospitals and prescriptions from private doctors were scrutinized. In addition, relatives and, where appropriate, friends, were approached.

Of the two patients who had had previous chemotherapy, one (HI-1) deteriorated radiographically and the chemotherapy was changed; the other (HI-2) had active disease at 12 months.

Detailed findings for the 20 patients with primary isoniazid resistance will be reported elsewhere, but the clinical findings are summarized here. Of the 20 patients, six were in the PH series, two in the HI-1, six in the HI-2 and six in the H series. The results of two pretreatment sensitivity tests were available for all; five PH, one HI-1 all six HI-2 and five H patients had resistant results to both tests, and the remaining three patients (PH, HI-1, H) had one resistant and one sensitive result.

Of the six PH patients, one had bacteriologically quiescent disease at one year, four who had continued on the regimen had bacteriologically active disease and one had deteriorated radiographically and the chemotherapy had been changed. Both HI-1 patients had active disease at one year. Of the HI-2 patients two had quiescent and four active disease. All the six H patients responded unfavourably; one, who was admitted to sanatorium and received streptomycin and PAS in addition to the isoniazid for 18 days, died of tuberculosis in the third month; two deteriorated radiographically and their chemotherapy was changed, two who had continued on the regimen had bacteriologically active disease at 12 months and one had relapsed bacteriologically.

Five of the six PH patients with primary isoniazid resistance had an unfavourable bacteriological response, whereas only eight of 86 PH patients with isoniazid-sensitive organisms in the main analysis had responded unfavourably; this difference is statistically highly significant ($P<0.001$). Of the 14 patients with primary isoniazid resistance in the three isoniazid-alone regimens combined, 12 had an unfavourable response compared with 93 of 216 with sensitive organisms; this difference also is statistically highly significant ($P<0.01$). It may be concluded that the patients with primary isoniazid resistance fared badly bacteriologically, whether they were treated with isoniazid alone or with isoniazid plus PAS.

PATIENTS EXCLUDED FOR OTHER REASONS

Four patients were separated from the main analysis for reasons other than isoniazid resistance at the start of treatment. One HI-1 patient absconded in the second month; at the end of the year he still had bacteriologically active disease. Another (HI-1) was, in error, advised by a staff member to take his medicine in two doses a day instead of one and did so for two months; he had disease of bacteriologically doubtful status at one year. One H patient, who had a carcinoma of the bronchus, died from this cause in the eleventh month of treatment. Finally, an H patient with isoniazid-sensitive organisms, who had had two months of previous chemotherapy, believed to be isoniazid plus streptomycin, had disease of bacteriologically doubtful status at one year.

XIII. DISCUSSION

Since the introduction of isoniazid there has been much controversy concerning the use of this drug by itself in the treatment of pulmonary tuberculosis. In a recent report on a clinical study of isoniazid alone compared with combined oral chemotherapy, carried out in East African patients in hospital (East African/British Medical Research Council Isoniazid Investigation, 1960), the reasons for undertaking that study were summarized as follows:

" 1. that a large body of medical opinion has considered that, because of simplicity of use and its low cost, isoniazid, administered by itself, is at present the best available chemotherapy for mass treatment of patients out of hospital in underdeveloped countries;

2. that this treatment is already being given either from official or from unofficial sources in many areas, and that it is urgently necessary to determine whether this is justified;

3. that remarkable clinical and radiographic improvement is known to result from treatment with isoniazid alone; and

4. that even if substantial proportions of patients remain sputum positive with isoniazid-resistant organisms following treatment with isoniazid alone, the importance of these organisms to the patients and to their contacts has not been fully elucidated, and is still the subject of controversy."

It was these reasons which also led to the study which is reported here and to a concomitant investigation of the incidence of tuberculosis in family contacts which will be reported later. The study under discussion was designed to evaluate the relative merits of three different dosages of isoniazid alone, in comparison with a standard regimen of isoniazid plus PAS, prescribed as two doses daily (PH). The three isoniazid regimens were isoniazid, in the same amount as in the PH regimen (a daily dosage, on the average, of 4.5 mg/kg body-weight), given in two doses a day (H), and isoniazid in a daily dosage, on the average, of 8.7 mg/kg, given either as one dose a day (HI-1) or as two doses a day (HI-2). The comparison of the PH and H regimens permitted an assessment of the value of PAS in the PH combination. The other two regimens contained the largest dose of isoniazid which it seemed likely could be given (in the absence of pyridoxine supplements) without an unduly high proportion of the malnourished patients under study developing peripheral neuritis. This higher dosage was studied because of the possibility that it would have greater efficacy than the lower dosage, and the two rhythms of administration were included because of the possibility that there might be differences between them either in acceptability for self-administration or in therapeutic effectiveness. The 341 patients were drawn from a poverty-stricken section of a large urban community in South India and were treated under ambulatory conditions in their own homes for a year, unless admission to sanatorium became necessary.

ASSESSMENTS OF THE RESULTS

The findings in the four treatment series for the year may be assessed in four ways-namely, in terms of two criteria of unfavourable response of the tuberculous disease, in terms of toxicity, and in terms of unfavourable response *and* toxicity.

1. Unfavourable response of the disease may be defined first as bacteriologically relapsed or bacteriologically active disease at the end of the year (see Table 12), including definite radiographic or serious clinical deterioration necessitating a change of chemotherapy during the year, or death from tuberculosis during the year. Such a response occurred in 9 % of the PH, in 27 % of the HI-1, in 42 % of the HI-2 and in 56 % of the H patients; the PH treatment thus showed a clear advantage over the other three regimens. Further, there was evidence that the apparent slight superiority of the HI-2 over the H treatment was associated with a lower average virulence in the guinea-pig of the pretreatment (isoniazid-sensitive) strains of organisms in the HI-2 patients. When statistical standardization was undertaken for pretreatment virulence, the relatively small difference between the HI-2 and H treatments in terms of unfavourable response virtually disappeared. These two treatments thus proved closely similar in their effects, and were equally unsatisfactory.

2. It is well established that many *isoniazid-resistant* strains of tubercle bacilli have a lowered virulence in the guinea-pig (Barnett et al., 1953; Middlebrook & Cohn, 1953; Peizer et al., 1953; Morse et al., 1954). A number of authorities believe that this observation applies in man also and, as a consequence, that the emergence of isoniazid-resistant strains during treatment, associated with persisting bacteriological positivity, is not necessarily a serious event, either for the patient (Deuschle et al., 1954; Middlebrook & Dressler, 1954; Oestreicher et al., 1955) or for his contacts. Unfavourable response may therefore be defined in a second way, by regarding sputum positivity as relatively unimportant and considering only definite radiographic or serious clinical deterioration leading to change of chemotherapy during the year, or tuberculous death, as an unfavourable response of the disease to treatment. When viewed in this way, 23 % of the HI-2 and 21% of the H patients showed an un favourable response; these treatments thus remained unsatisfactory. The PH and HI-1 treatments were much more satisfactory, and on this criterion the difference between them was relatively small, for 2% of the PH patients and 8 % of the HI-1 patient had an unfavourable response.

It will be possible, in due course, to assess the progress in a second year of treatment of those patients who had bacteriologically active or bacteriologically relapsed disease at the end of the first year, but had not had their chemotherapy changed owing to radiographic or clinical deterioration;

these patients amounted to 19 % of the total on the HI-1 regimen, compared with 7 % of those on the PH regimen, and nearly all of them continued on the originally prescribed regimen in the second year. If, in this period, these patients deteriorate radiographically or clinically, then the HI-1 treatment will compare less favourably with the PH treatment than it does at the end of the first year. If, on the other hand, the organisms disappear from the sputum and most of these patients attain bacteriological quiescence, the HI-1 and PH treatments will approach one another in effectiveness with, at most, a relatively minor advantage to the PH treatment.

3. The treatments may be compared in terms of major toxic manifestations. The occurrence of hypersensitivity and toxic manifestations to PAS is well known (Jones, 1954) and three (3%) of the PH patients had such complications. One further PH patient developed peripheral neuritis, an unusual complication when isoniazid is given in low dosage (Great Britain, Medical Research Council, 1952b, 1953a, 1953b, 1955; Mount et al., 1953; Tuberculosis Chemotherapy Centre, 1959), although Money (1959), in a malnourished community in East Africa, encountered an incidence of 20% when giving a dosage of 4-6 mg/kg daily. It is an increasingly frequent occurrence as the dosage is increased (United States, Public Health Service, 1954; Biehl & Nimitz, 1954). There were no cases of peripheral neuritis or other toxic manifestations among the H patients, but 19 % of the HI-1 and 9 % of the HI-2 patients developed peripheral neuritis in the course of the year; the difference between these two percentages does not attain statistical significance. The occurrence of peripheral neuritis must be considered a major disadvantage of both these treatments, and especially of the HI-1 regimen.

4. The treatments may be compared by taking into account *both* unsatisfactory response of the tuberculous disease and the toxic manifestations. When assessed in this way, the PH regimen still remains the most satisfactory, since there were few unfavourable responses (by either definition) and few cases of toxicity. The HI-1 regimen was relatively unsatisfactory by the first definition of unfavourable response, and more satisfactory by the second, but had a high level of toxicity. The HI-2 and H regimens were the least satisfactory by both definitions of unfavourable response, and toxicity was an additional disadvantage in the HI-2 regimen.

In summary, only the PH regimen emerged as a good form of chemotherapy for domiciliary treatment. The findings with this regimen in the present study are rather better than those reported in domiciliary patients in an earlier study in Madras (Tuberculosis Chemotherapy Centre, 1959). In the earlier study, 83 % of 81 patients had bacteriologically quiescent disease (or disease of bacteriologically doubtful status) at one year, compared with 91 % of 86 patients in the present study.

COMPARISON WITH OTHER STUDIES OF ISONIAZID ALONE

In the controlled investigation of patients in hospital in East Africa (East African/British Medical Research Council Isoniazid Investigation, 1960) referred to above, two of the regimens were identica1 with the PH and H regimens of the present study. In East Africa, as in India, the PH regimen was found to be satisfactory, whereas the H regimen was much less effective. A third regimen in the East African investigation was a very large dosage of isoniazid (about 20 mg/kg body-weight daily, given in two doses). It proved only slightly more effective than the H regimen in East Africa; this is in clear contrast to the findings in India, where the HI-1 regimen (about 8.7 mg/kg daily in one dose) was definitely more effective than the H regimen. This may be related to possible differences in the severity of the disease in the two studies. However, the patients on the high dosage of isoniazid in East Africa also received a large dose of pyridoxine to prevent isoniazid toxicity, and there is experimental evidence (McCune et al., 1957) that pyridoxine may interfere with the antituberculous activity of the isoniazid. It is thus uncertain precisely what effective dosage of isoniazid these patients actually received.

Phillips (1959) reported on a controlled study of minimal or moderately advanced non-cavitated disease in hospitals in the USA treated either with isoniazid alone (300 mg daily, given in three doses) or with the same dosage of isoniazid, plus PAS. At eight months the results of the two treatments were similar, so that isoniazid alone was as effective as the combination isoniazid plus PAS for the treatment of non-cavitated lesions in North America. It is of particular interest to see whether this conclusion is confirmed in the Madras patients with the less extensive lesions. The HI-2 and H treatments were found to be unsatisfactory even in patients with no cavitation or cavitation of slight extent,

with radiographic lesions whose total extent was limited or slight, or with small numbers of tubercle bacilli in the sputum on smear examination; in contrast, the PH treatment was very satisfactory under these conditions; the HI-1 regimen was less effective than the PH regimen but more effective than the HI-2 or the H regimen. The therapeutic equality of isoniazid alone and isoniazid plus PAS reported by Phillips (1959) in hospital patients in the USA therefore does not appear to extend to even the lesser grades of the more serious disease under domiciliary treatment in India in the present investigation.

PERIPHERAL NEURITIS

The clinical aspects of the peripheral neuritis have been reported in full elsewhere (Devadatta et al., 1960 [1]), but merit brief consideration here. The onset of the complication was usually insidious, the progression slow and the symptoms and signs mainly sensory. Muscular weakness was less common and, when it occurred, mild. In only two of the 20 patients did the peripheral neuritis present in a more acute fashion. There was, thus, usually adequate warning that it was developing, especially as the patients were seen weekly. Even with less frequent observation nearly all the lesions would have been detected at a relatively early stage.

The usual way of treating peripheral neuritis due to isoniazid is to change to a combination not containing that drug, and to give large doses of pyridoxine as a specific treatment. Since this vitamin is expensive it may not be practical to treat peripheral neuritis in this way in under-developed countries. If convenient and cheap ways could be found to prevent peripheral neuritis, or to treat it effectively in the early stages, then it might be possible to give even larger single doses of isoniazid alone than those in the HI-1 regimen, with the possibility of greater effectiveness in the therapy of tuberculosis. In this connexion, Turner (personal communication, 1958) has reported that oral administration of a vitamin B complex preparation which did not contain pyridoxine was effective treatment for peripheral neuritis even if the isoniazid was continued. Money (1959) has reported similar findings with yeast tablets in 13 of 16 patients. Further studies on the prevention and treatment of peripheral neuritis due to isoniazid in Indian patients are in progress.

[1] See article on page 587 of this issue.

SELF-ADMINISTRATION OF THE CHEMOTHERAPY

The problem of keeping the co-operation of tuberculous patients is well recognized in the long-term self-administration of oral chemotherapy with medicaments that contain PAS (Simpson, 1956; Dixon et al., 1957; Rigby, 1958; Wynn-Williams & Arris, 1958) and lack of co-operation is usually attributed specifically to the non-acceptability of that drug. However, no comparison has hitherto been reported of the relative acceptability of medicaments which do and do not contain PAS. It is not sufficiently widely appreciated that there is a *general* difficulty in the long-term self-administration of medicaments, and that this also applies to tuberculous patients. The difficulty has already been shown to apply to the self-administration of a single tablet of isoniazid a day and of a single tablet a day of a placebo, calcium gluconate (Velu et al., 1960 [2]). As part of the present study the acceptability for self-administration of large white cachets containing both PAS and isoniazid has now been compared with that for very much smaller tablets containing isoniazid alone, the same total number of cachets as of tablets being prescribed daily in two doses. Examinations of the urine for PAS in the PH patients, using the ferric chloride test (Simpson, 1956), and for isoniazid in the H patients, using the combined naphthoquinone-mercuric chloride test (Gangadharam et al., 1958), the latter test having been shown to be rather more sensitive. indicated that the two medicaments were of the same order of acceptability. There was, thus, no evidence either that the PAS content or the greater bulk of the cachets produced any greater irregularity in self-administration than was encountered with the smaller isoniazid tablets; the factors which may account for the difficulty of self-administration of medicaments have been discussed elsewhere (Fox, 1958). Considering the HI-1 and HI-2 regimens, which differed only in that the daily dosage of the former was prescribed as a single dose in the morning and of the latter as a morning and an evening dose, there was no evidence that either regimen was more acceptable than the other. Indeed, all four regimens in the present study appear to have been of the same order of acceptability. As in previous studies (Wynn-Williams & Arris, 1958; Tuberculosis Chemotherapy Centre, 1959; Luntz & Austin, 1960; Velu et al., 1960 [2]), there was evidence of greater irregularity in drug-taking among the females than among the males.

[2] See article on page 511 of this issue.

There was some evidence that the irregularity in self-administration in the HI-1 series was associated with unfavourable response according to the first of the two definitions referred to above; 11% of 18 patients whose urine tests were always positive, compared with 33 % of 46 whose urine tests yielded one or more negative results, had an unfavourable response. (This difference just fails to attain statistical significance.) It follows that the HI-1 regimen might be less effective in a mass campaign, where considerably more irregularity might be encountered, than in the carefully supervised patients in this study. Such a delicate balance was not found with the PH regimen and, as in an earlier study (Tuberculosis Chemotherapy Centre, 1959), there was no evidence of an association between irregularity in self-administration of the PH regimen and unfavourable response.

Thus, further evidence has been obtained that the problem of ensuring the self-administration of medicine is not confined to a particular drug, and some evidence has now been obtained that default may carry therapeutic penalties. The planning of mass campaigns against tuberculosis must pay particular attention to this aspect, especially if a chemotherapy of borderline effectiveness is to be used.

More than half the HI-2 and H patients who gave no evidence of irregularity in the self-administration of their medicine showed an unfavourable response at 12 months, so that these two regimens were still clearly unsatisfactory even when the drug was apparently being taken regularly.

DOSAGE AND RHYTHM OF ADMINISTRATION

There was very little difference between the clinical effectiveness of the HI-2 and H regimens, which is the more remarkable since the HI-2 regimen consisted of double the dosage of isoniazid given in the H regimen. Therefore, to increase the total daily dosage of isoniazid does not necessarily give greater therapeutic effectiveness; this observation is contrary to the suggestions of Kass et al. (1957) and Levy et al. (1960). On the other hand, the HI-1 treatment, in which the same daily dosage of isoniazid was given as in the HI-2 regimen, but as one instead of two doses, was the more effective of the two. Thus, in the present study the *rhythm* of administration of the isoniazid has proved more important than the total daily dosage. There is indirect evidence also that the rhythm of administration of PAS in drug combinations may possibly influence the effectiveness of the combination, for 10 g of PAS (sodium) given as two doses of 5 g a day with isoniazid prevented the emergence of *isoniazid* resistance (Great Britain, Medical Research Council, 1955), but when given in four divided doses of 2.5 g with streptomycin was less satisfactory in preventing *streptomycin* resistance (Great Britain, Medical Research Council, 1952a). On the other hand, 20 g daily given in four doses of 5 g a day with streptomycin was effective in preventing streptomycin resistance (Great Britain, Medical Research Council, 1952a). It is possible that the latter dosage was effective because the individual doses of PAS were 5 g, and not because the total daily dosage was 20 g.

The much greater effectiveness of the PH regimen than either the H or the HI-2 regimen provides information on the mechanism of action of the combination. Evidence has been reported that, in the combination isoniazid plus PAS, the action of the PAS is only in part directly on the tubercle bacilli, being in part due also to competition with isoniazid for acetylation, so that the effective serum isoniazid level is increased (Johnson & Corte, 1956; Morse et al., 1956; Mandel et al., 1956; Grosset et al., 1958). The findings of the present study suggest that the direct role of PAS on tubercle bacilli is much the more important of the two. The HI-2 regimen consisted of twice as much isoniazid as the H regimen, and yet proved no more effective. The PH regimen contained only the same low dosage of isoniazid as the H regimen, but proved very much more effective.

PRIMARY BACTERIAL RESISTANCE TO THE DRUGS

The patients and their relatives were interrogated about previous chemotherapy on several occasions, and wherever possible other inquiries were made. After excluding any patients who might possibly have had previous chemotherapy, primary drug resistance to isoniazid was found in 5.9% and to streptomycin in 3.3 % of the patients. (For reasons referred to in the present report and reported fully elsewhere by Selkon et al. (1960) [1], the prevalence of primary PAS resistance has not been defined with certainty.) The figures do not differ significantly from those in the earlier study (Tuberculosis Chemotherapy Centre, 1959), in which the prevalence of drug resistance to isoniazid in previously untreated patients was 3.8 % and to streptomycin 2.3 %.

In the present study, as in East Africa (East African/British Medical Research Council Isoniazid

[1] See article on page 599 of this issue.

Investigation, 1960) clear evidence was obtained of bacteriological disadvantage to the patients of primary isoniazid-resistant organisms, when treated with isoniazid alone. However, the present results, unlike the East African findings, indicate that the combination isoniazid plus PAS was also an unsatisfactory treatment for such patients. Of the six patients in the PH series with primary isoniazid resistance, five had an unfavourable bacteriological response, compared with eight of 86 with sensitive organisms initially, a statistically highly significant difference. It may be concluded that none of the treatments studied was effective in primary isoniazid-resistant infections.

FURTHER FINDINGS

In the course of the present study a great deal of information has been obtained for the four regimens concerning the emergence of isoniazid resistance, the catalase activity of the strains isolated before and during treatment, the susceptibility of the strains to hydrogen peroxide, and the virulence of the strains before and during treatment, as well as on the serum isoniazid levels of the patients. This material is in the process of analysis and will be the subject of a series of further publications. It is hoped that in the light of all these further data it will become possible to understand more clearly the reasons for the differences in response between the four regimens.

XIV. SUMMARY

1. A total of 341 South Indian patients with acute pulmonary tuberculosis was admitted to a comparison of treatment with four different oral chemotherapeutic regimens for a period of 12 months at home, the patients being allocated at random to the four treatment series.

2. The intake of patients began in October 1957 and ended in December 1958.

3. The regimens (and the dosages appropriate to patients weighing 100 lb. (45.4 kg)) were: (1) PH -isoniazid 200 mg plus PAS (sodium) 10 g a day, given together in the same cachet, in two equal doses; (2) HI-1–isoniazid 400 mg a day in one dose; (3) HI-2–isoniazid 400 mg a day in two equal doses; (4) H–isoniazid 200 mg a day in two equal doses. The dosage of each regimen was graded according to the patient's weight.

4. Patients on the PH and H regimens received a mean daily dosage of isoniazid of 4.6 mg/kg body-weight at the start of treatment; the HI-1 and HI-2 patients received an average of 8.7 mg/kg. The mean daily dosage of PAS in the PH regimen was 0.23 g/kg.

5. Only one patient was lost from observation in the 12-month period ; even he was re-examined at 12 months.

6. The main analysis in this report concerns 315 of the 341 patients-namely, the 90 PH, 70 HI-1, 68 HI-2, and 87 H patients who *(a)* had organisms sensitive to isoniazid on admission, *(b)* had had no previous chemotherapy (a few had had up to two weeks' chemotherapy) and *(c)* followed the allocated treatment regimen for 12 months unless it was stopped owing to death or was changed because of a deterioration or serious toxicity.

7. On admission to treatment the clinical and bacteriological condition of the patients in all four treatment series was similar, except that the patients in the PH series had more extensive disease and a smaller bacterial content of the sputum than those in the other three series, and the patients in the HI-2 series had strains of tubercle bacilli with a lower virulence in the guinea-pig than those in the other three series.

8. Over the 12 months, 90% of 82 PH, 90% of 60 HI-1, 69 % of 64 HI-2 and 69 % of 81 H patients gained weight. All four series showed a progressive increase in the numbers of patients with a low ESR. Most of the patients showed at least moderate radiographic improvement-namely, 85 % of the PH, 78 % of the HI-1, 71% of the HI-2 and 62 % of the H series. In patients with cavitation of moderate extent on admission (for which the numbers were relatively large), the cavitation had disappeared by 12 months in 63% of 41 PH, 52% of 31 HI-1, 39% of 38 HI-2, and 38% of 45 H patients.

9. At 12 months the cultures from 90% of the PH, 76 % of the HI-1, 59 % of the HI-2 and 51% of the H patients were negative. Resistance to isoniazid emerged rapidly in the three isoniazid-alone series and more slowly in the PH series. From six months onwards nearly all the positive cultures in all four series were isoniazid-resistant.

10. During the course of the year serious clinical or radiographic deterioration necessitating a change of chemotherapy occurred in 1% of the PH, 7 % of the HI-1, 21% of the HI-2 and 17% of the H series.

11. Using very stringent criteria to assess the response to treatment, 8% of the PH, 27% of the HI-1, 41 % of the HI-2 and 52 % of the H patients were classified as having bacteriologically relapsed or bacteriologically active disease at the end of 12 months (including those who had deteriorated and so had their chemotherapy changed). In addition, one PH, one HI-2 and three H patients had died of tuberculosis.

12. After statistical standardization for the pre-treatment differences in virulence, the relatively small differences in response between the HI-2 and H series practically disappeared.

13. Peripheral neuritis attributed to the isoniazid cccurred in one (1%) of the PH, 13 (19 %) of the HI-1, six (9%) of the HI-2, and none of the H patients. The clinical picture was mainly sensory, and progression was slow in 18 of the 20 patients.

14. Primary infection occurred with isoniazid-resistant organisms in 5.9 % of the patients and with streptomycin-resistant organisms in 3.3 %. The identification of patients with PAS-resistant strains before treatment was difficult.

15. Five of the six PH patients with primary isoniazid-resistant organisms had an unfavourable response (defined as bacteriologically relapsed or bacteriologically active disease at 12 months, including change of chemotherapy due to deterioration, or tuberculous death), compared with eight of 86 with isoniazid-sensitive organisms. Of the 14 patients with primary isoniazid resistance in the three isoniazid-alone regimens combined, 12 had an unfavourable response to the prescribed treatment, compared with 93 of 216 with sensitive organisms. Both these differences are statistically highly significant.

16. The self-administration of the cachets and tablets was checked by tests on the urine. There were only minor differences between the four series in the proportions of patients with negative results. There was, therefore, evidence that the large PAS-containing cachets were as acceptable for self-administration as the same number of smaller isoniazid-containing tablets, and that isoniazid alone was equally acceptable in one or in two doses a day. More irregularity in self-administration was found among female than among male patients.

17. In conclusion, this study has confirmed that the combination isoniazid plus PAS, given for 12 months, is a satisfactory domiciliary treatment for pulmonary tuberculosis in Madras City, even though the group of patients under study had poor accommodation, little rest, a poor diet, practically no nursing and were not supervised in taking their medicines. The two isoniazid-alone regimens given as two doses a day were unsatisfactory in their clinical effectiveness, whether the total daily dosage ranged (for the majority of patients) from 3.9 to 5.5 mg/kg (H) or 7.8 to 9.6 mg/kg (HI-2), and peripheral neuritis was a complication with the larger dosage. In contrast, the isoniazid-alone regimen consisting of a single daily dose of 7.8-9.6 mg/kg (HI-1) was more satisfactory in its clinical effectiveness, though peripheral neuritis was again a disadvantage. Even if there had been no peripheral neuritis with this large dose of isoniazid, however, the regimen would still have been regarded as less satisfactory than isoniazid plus PAS, on the grounds of clinical effectiveness.

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RÉSUMÉ

Une étude comparative portant sur des centaines de malades, effectuée au Centre de recherches sur la tuberculose, à Madras, Inde, avait révélé que la chimiothérapie de la tuberculose, par l'isoniazide et le PAS, donnait des résultats analogues, que le malade soit traité en sanatorium ou à domicile, et que dans ce dernier cas, les

contacts n'étaient exposés à aucun risque particulier de contagion.

Avant de généraliser le traitement à domicile, il s'agissait de préciser quels médicaments, à quelle dose et selon quelle posologie étaient les plus efficaces.

Les essais que cet article décrit, poursuivis pendant une année comportaient quatre régimes thérapeutiques: *a*) 3,9-5,5 mg/kg de poids corporel d'isoniazide+0,2-0,3 g/kg du sel sodique de l'acide *p*-aminosalicylique (PAS) en deux doses quotidiennes; *b*) 7,8-9,6 mg/kg d'isoniazide seule, en une dose quotidienne; *c*) 7,8-9,6 mg/kg d'isoniazide seule en deux doses quotidiennes; *d*) 3,9-5,5 mg/kg d'isoniazide seule, en deux doses quotidiennes.

Après avoir décrit les techniques d'administration et les réactions cliniques au traitement des divers groupes de malades, les auteurs concluent que la combinaison isoniazide+PAS durant 12 mois constitue un traitement domiciliaire satisfaisant, malgré le fait que les malades étaient mal logés, mal nourris, n'avaient que peu de repos et pratiquement pas de soins, et que personne ne s'assurait qu'ils prenaient régulièrement leurs médicaments. L'isoniazide seule, en deux doses quotidiennes, se montra insuffisante, dans les deux gammes de doses, dont les plus élevées provoquèrent en outre de la névrite périphérique. Bien que responsable aussi de cette complication aux concentrations élevées, l'isoniazide seule en une dose quotidienne se révéla plus efficace qu'administrée en deux doses.

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