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ISONIAZID IN THE TREATMENT OF PULMONARY TUBERCULOSIS

SECOND REPORT TO THE MEDICAL RESEARCH COUNCIL BY THEIR TUBERCULOSIS CHEMOTHERAPY TRIALS COMMITTEE*

In February, 1952, the Medical Research Council appointed their Tuberculosis Chemotherapy Trials Committee to plan a clinical trial of isonicotinic acid hydrazide (isoniazid) in pulmonary tuberculosis. Selected hospitals were invited to co-operate, and the first patient started treatment on March 29, 1952. The trial is still continuing and has expanded steadily. The number of participating hospitals now stands at 52, and more than 1,100 patients are undergoing, or have undergone, prescribed courses of treatment and observation.

The trial was designed so that monthly progress reports on each patient could be collected, and the accumulated information reviewed, from week to week. This continual review of results in a large number of patients has not only facilitated early publication of reports, but also enabled the Committee to stop the allocation of some treatments and to introduce others during the course of the trial.

The first report of the Committee was published on October 4, 1952 (Medical Research Council, 1952). It compared the value of isoniazid with that of streptomycin + P.A.S. in the treatment of pulmonary tuberculosis, in a series of 331 patients after three months' observation and treatment. The report suggested that over this period isoniazid lay within the same range of efficacy as streptomycin + P.A.S. It demonstrated, however, a frequent and rapid development of bacterial resistance to the drug and showed that this was a serious problem, since it affected the response to treatment.

The present report studies the effects of streptomycin combined with isoniazid ; it compares this treatment with those investigated in the first report—namely, streptomycin + P.A.S. and isoniazid alone. The progress of a total of 364 patients who were treated for three months is now presented. They were divided at random on entry to the trial into three series receiving one or another of the three treatments.

The list of the 40 hospitals which have contributed cases for this analysis, and the names of the co-operating clinicians, bacteriologists, and pathologists, are given at the end of the report. The bacteriologists and pathologists formed a laboratory subcommittee under the chairmanship of Professor R. Cruickshank. The trial was co-ordinated by Drs. Marc Daniels and Wallace Fox, of the Council's Tuberculosis Research Unit; Dr. Fox and Dr. Ian Sutherland (of the Council's Statistical Research Unit) analysed the present results and prepared the report. *X*-ray assessments were made by Dr. L. G. Blair. The isoniazid used throughout the trial has been supplied as "nydrazid" by E. R. Squibb and Sons.

*Members of the Committee: Sir Geoffrey Marshall (chairman), Professor J. W. Crofton, Professor R. Cruickshank, Dr. Marc Daniels, Dr. J. E. Geddes, Professor F. R. G. Heaf, Professor A. Bradford Hill, Dr. J. V. Hurford, Dr. D. A. Mitchison, Dr. W. D. M. Paton, Dr. J. G. Scadding, Dr. Norman Smith, Dr. P. D'Arcy Hart (secretary).

I. PLAN AND CONDUCT OF THE TRIAL

The plan and conduct of the trial have already been described in the first report and some points are dealt with more fully there.

1. General

When a patient has been accepted for the trial, treatment is allocated by the Tuberculosis Research Unit from confidentially held prearranged lists based upon random sampling numbers.

After admission to the trial and a preliminary week of observation, all patients are kept under observation for six months. During the first three months the prescribed treatment is followed for every case. During the second three months Group 3 cases (see later description of groups) remain on the same treatment. For other cases the clinician is free to undertake any treatment he wishes.

At the end of the first, second, and third month of treatment, clinical progress reports for each patient on standard forms are sent to the Tuberculosis Research Unit. At six months the clinicians send a final progress report and a full case summary.

The information is scrutinized as soon as it is received, and the most important items from the clinical progress reports are entered on special cards. Information for each patient is thus accumulated, and with these cards regular analyses of results are carried out. Laboratory data are kept separately by the bacteriologists and pathologists, and are called in as required (see Section III of this report).

2. Type of Case

Before acceptance into the trial, basic requirements for all cases were laid down as follows :—At the start of treatment : (1) Tubercle bacilli must have been demonstrated: there must be either a positive direct smear from a sputum specimen taken within the previous two weeks, or a positive culture derived from a specimen taken not more than two months previously. (2) The tubercle bacilli must not, so far as is known, be streptomycin-resistant or P.A.S.-resistant. (3) The patient must not have had more than 15 g. streptomycin and/or 300 g. P.A.S. within the previous three months, and not more than 3 g. isoniazid at any time (this last requirement was added soon after the start of the trial). (4) The patient must not be undergoing pneumoperitoneum, nor have any form of collapse therapy for the lung requiring treatment. (For fuller criteria see the first report.)

Twelve cases (3%) did not conform entirely to the bacteriological requirements, but are nevertheless included in the clinical analysis. In none of these patients was the diagnosis in doubt, and for most of them it had been established bacteriologically either before or after starting treatment, though not within the stipulated period. These cases have, however, been excluded from the bacteriological analysis (see Section III).

Cases satisfying the above requirements were admitted to the trial in one of three main disease groups: (1) acute rapidly progressive pulmonary tuberculosis believed to be of recent origin; (2) other forms of pulmonary tuberculosis considered suitable for chemotherapy; (3) chronic forms of pulmonary tuberculosis expected to make only a limited response to streptomycin + P.A.S.

Under these three headings eight subgroups were defined as follows: (1A) Bilateral lesions; age 15–30. (The definition of this subgroup corresponds to that of cases admitted to the earlier chemotherapy trials, 1946–52.) (1B) Bilateral lesions; other ages. (1C) Predominantly unilateral lesions; all ages. (2A) Chronic cases with a recent exudative lesion. (2B) Primary tuberculosis with manifest recent lesions diagnosed not more than six months previously. (2C) Other forms. (3A) Patients who have previously had, in all, not more than 15 g. streptomycin and/or 300 g. P.A.S. and/or 3 g. isoniazid. (3B) Other patients who have had some chemotherapy, but not more than 15 g. streptomycin and/or 300 g. P.A.S. within the previous three months, and/or 3 g. isoniazid. It was realized that there would be some overlap between Groups 2 and 3, as well as between the subgroups of Group 2.

3. Intake of Cases

Group 1 cases are selected by a central panel of clinicians; cases in Groups 2 and 3 are, in the main, selected by the clinicians in the co-operating hospitals from the patients already under their care.

4. Treatment

The dosage of each drug used was as follows:—*Streptomycin* (not dihydrostreptomycin): 1 g. daily, in one intramuscular injection. (Children under 15: 15 mg. per kg. of body weight daily, up to a maximum of 1 g.) *P.A.S.:* 20 g. of the sodium salt daily, in four doses, by mouth. (Children under 15: 1 g. per 3 kg. of body weight daily, up to a maximum of 20 g.) *Isoniazid:* 200 mg. daily, in two doses of 100 mg. given 12-hourly, by mouth. (Children under 15: 3 mg. per kg. of body weight daily, up to a maximum of 200 mg.)

5. Evolution of the Trial

The large number of cases and the continual analysis of the results have enabled the Tuberculosis Chemotherapy Trials Committee to introduce new treatments and to stop allocating other treatments during the course of the trial, and so to study fresh problems in the application of isoniazid as they arose. The trial has thus proceeded in several stages. The time-table has been complicated by the fact that for several reasons the new treatments have not been introduced at the same time in each of the disease subgroups of the trial. Subgroup 1A and Group 3 have followed patterns different from those of the other groups. Fig. 1 illustrates this complex time-table, and the following paragraphs should be read in conjunction with this figure.

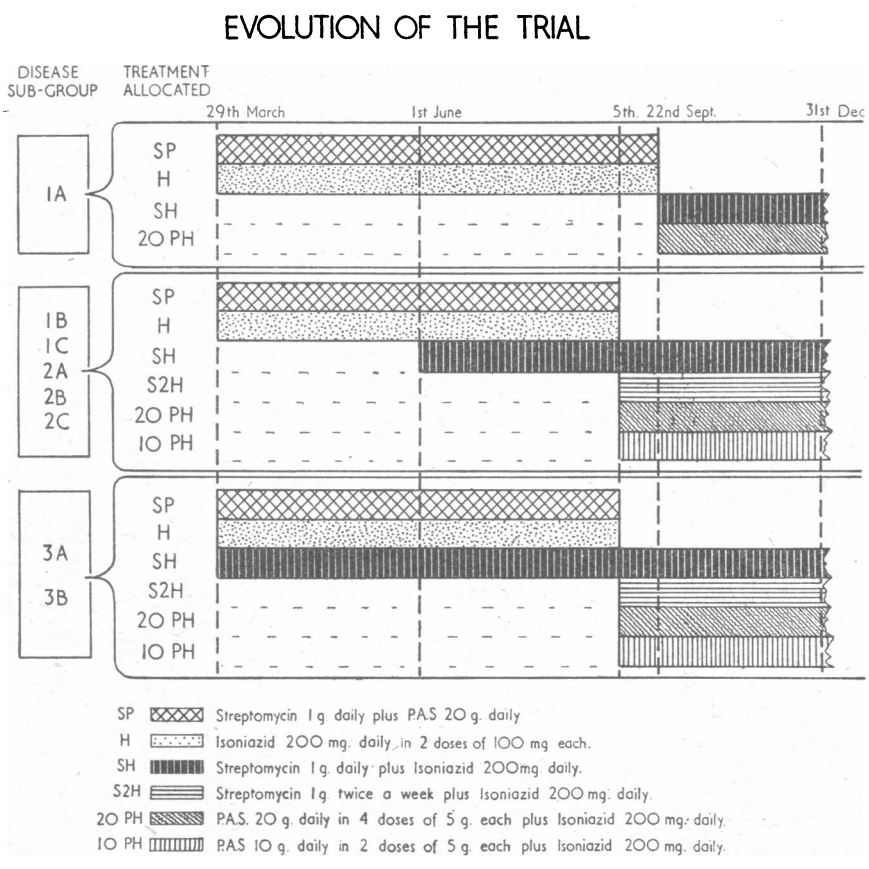

FIG. 1.—The treatments allocated in each disease subgroup from the start of the trial to the present time, showing the period of allocation of each treatment.

When the trial began on March 29, 1952, the first problem was to decide whether isoniazid was an effective drug when compared with the best chemotherapy known at that time—namely, streptomycin + P.A.S. Accordingly, two treatments—streptomycin + P.A.S. (SP) and isoniazid (H)—were allocated concurrently, and at random, to cases in all disease groups.

In view of the development of bacterial resistance to other antituberculosis drugs when given alone, it was decided from the outset to study also the results of combining isoniazid with another effective drug. A third treatment, streptomycin + isoniazid (SH), was therefore introduced at the start of the trial in Group 3, in which the cases (by definition) were expected to make only a limited response to streptomycin + P.A.S. In this way fundamental bacteriological information would become available as soon as possible.

As the trial proceeded there was growing evidence concerning the frequent development of bacterial resistance to isoniazid when given alone. The Committee therefore decided to introduce the SH treatment throughout the trial (except in subgroup 1A) from June 1, while continuing a concurrent allocation of cases to SP and H. Although the three treatments were allocated at random as

before, it was arranged, without the knowledge of the clinicians, that rather more patients should be admitted to the SH series than to either of the other two, because of its potential importance.

The cases in subgroup 1A (acute rapidly progressive tuberculosis of recent origin, bilateral and between the ages of 15 and 30) were of special importance since they corresponded by definition to those in all the previous Medical Research Council tuberculosis chemotherapy trials. The aim of the Committee was to have a sufficiently large number of cases in this subgroup to enable a clear-cut comparison to be made between isoniazid alone and each of the treatments allocated in the earlier trials. For this reason the two treatments SP and H were allocated in this subgroup from the start of the trial until September 22, by which date 99 cases had been admitted, and the Committee had decided from the bacteriological information then available that it was unjustifiable to continue to allocate isoniazid alone. From this date onwards, two other treatments were adopted for subgroup 1A—namely, SH and 20 PH (20 g. P.A.S. daily + isoniazid 200 mg. daily). (See Fig. 1.)

By the beginning of September, 1952, the numbers of patients who were on the SP and H treatments in other subgroups were adequate; also, the bacteriological analysis for the first report, although incomplete, suggested that isoniazid resistance was a serious problem affecting clinical progress. From September 5 onwards, therefore, the allocation of cases to SP and H was stopped throughout the trial (except, as stated above, in subgroup 1A). As it was essential to concentrate upon combined therapy with a view to the prevention of drug resistance, three new treatments were introduced in addition to SH (streptomycin 1 g. daily+ isoniazid 200 mg. daily)—namely, S2H (streptomycin 1 g. twice weekly + isoniazid 200 mg. daily), 20 PH (20 g. P.A.S. daily + isoniazid 200 mg. daily), and 10 PH (10 g. P.A.S. daily + isoniazid 200 mg. daily). The trial of these four treatments is still proceeding.

The first isoniazid report (Medical Research Council, 1952) compared the progress after three months' treatment of all the SP and H cases admitted to the trial before June 1, 1952. (During this period 38 Group 3 cases were allocated to the SH treatment; but, because this number of very chronic cases was considered to be inadequate for the assessment of clinical results, no comparison was then made with the Group 3 cases allocated concurrently to SP and H.)

The clinical section of the present report analyses the progress after three months' treatment of all the 364 cases which were admitted concurrently to the three treatments SP, H, and SH—that is, all the Group 3 cases allocated between March 29 and September 5, and all cases in the other disease groups (except subgroup 1A) allocated from June 1 until September 5 (see Fig. 1). The progress of the SH patients is compared with that of the SP and also of the H patients. Direct comparison between the SP and the H patients (numbering more than 500 since the start of the trial) is not made here, but will be the subject of a further report.

The bacteriological section of the present report analyses the tests for tubercle bacilli in the sputum and the development of drug resistance for the same group of 364 cases.

6. Total Number of Patients in the Present Analysis

Table I sets out the number of cases according to treatment, and shows that, of the 364 cases, 102 have been treated with streptomycin + P.A.S., 120 with isoniazid, and 142 with streptomycin + isoniazid. (Of the Group 3 cases, 29 SP and 40 H were included in the first report but appear again in the present analysis, since they were admitted concurrently with 38 SH patients. Subgroup 1A does not appear in the present analysis, since the SH treatment was not allocated concurrently with the SP and H treatments in this subgroup. Consequently, whereas Group 1 of the first report included cases in all three subgroups, Group 1 of the present report includes cases in 1B and 1C only.)

II. CLINICAL PROGRESS

1. Exclusions

Before detailing the clinical exclusions it should be pointed out that Table I and the clinical analysis include approximately 20 patients who were found to have had streptomycin- or P.A.S.-resistant organisms at the start of treatment, although this was not known when they entered the trial. Because their response to treatment may have been affected by this, it would have been desirable to exclude these cases from the clinical analysis. This has not been done because a few P.A.S. sensitivity tests are still pending. A subsidiary analysis has shown no evidence that the conclusions drawn below are in any way affected by the retention of these cases for the time being.

The totals in Table I do not include 39 cases which were admitted concurrently with the 364 but subsequently excluded for the following reasons :

(i) The 7 cases in Group 2B were excluded (3 SP, 2 H, and 2 SH). This group was too small and too different from the others to justify its retention.

(ii) Five cases were excluded before treatment was started:
1 patient died before admission to hospital (SH);
2 patients refused admission to hospital (1 SP, 1 H);
1 patient refused treatment (SP);
1 patient, although admitted, did not start treatment as no positive sputum could be obtained (H).

TABLE I.—*Number of Cases Treated Concurrently with SP, H, and SH*

		Treatment			All Cases
		Streptomycin Plus P.A.S.	Isoniazid	Streptomycin Plus Isoniazid	
Group 1: Acute rapidly progressive pulmonary tuberculosis of recent origin	1B. Bilateral; under 15 years and 31 or more	4	7	10	21
	1C. Unilateral; all ages	21	19	27	67
	Total	25	26	37	88
Group 2: Other forms of pulmonary tuberculosis suitable for chemotherapy	2A. Chronic with recent spread	14	13	24	51
	2C. Other forms (excluding primary disease)	24	31	32	87
	Total	38	44	56	138
Group 3: Chronic forms of pulmonary tuberculosis expected to make only a limited response to chemotherapy	3A. Very little previous chemotherapy	12	15	14	41
	3B. Some previous chemotherapy, but not recently	27	35	35	97
	Total	39	50	49	138
All cases		102	120	142	364

(iii) Twenty-seven cases were excluded after treatment had begun:

1 patient was found to have had four months' chemotherapy up to within a month of entering the trial (H);
1 patient was found to have a carcinoma of the bronchus, proved on biopsy (H);
3 patients were given the wrong treatment in error (2 SP, 1 SH), 2 having SP+H for one month, the third having SP+H for two months;
6 patients discharged themselves against medical advice (1 in the first month, 3 in the second, and 2 in the third) (4 SP, 1 SH, 1 H);
11 patients had severe toxic reactions attributed to streptomycin (6 SH, 5 SP);
2 patients had severe toxic reactions attributed to P.A.S. (2 SP);
1 patient was found to be pregnant and this was considered by the clinician in charge a contraindication to streptomycin (SH);
2 changes of treatment were necessary in the first month —namely, in 1 H case which showed gross spread radiologically and in which streptomycin was added because the patient was considered at risk of death in the absence of this treatment (the radiographic appearances remained unaltered in the next two months), and in another H case which deteriorated clinically but not radiographically and in which streptomycin+P.A.S. was added after four weeks.

It will be seen that there were 13 exclusions because of drug intolerance—11 to streptomycin (5 SP and 6 SH) and 2 to P.A.S. Although many patients intolerant to streptomycin or P.A.S. can be desensitized, these exclusions for drug intolerance must be considered a defect of therapy with streptomycin or with P.A.S. when compared with isoniazid, for in no case was there any interference with the prescribed regime of isoniazid due to toxicity, whether the isoniazid was taken alone or in combination. Against these 13 exclusions there is one exclusion representing a definite failure of isoniazid therapy, and one in which clinical deterioration was reported.

One patient whose treatment was changed from H to SH at the end of the second month has been included throughout as an H patient.

2. Toxicity

Toxicity of Streptomycin and of P.A.S.—Apart from the 13 cases referred to in the previous paragraph, in which treatment had to be stopped, there were some slighter toxic reactions to streptomycin in patients on the SP and SH treatments and to P.A.S. in patients on the SP treatment. These reactions were sometimes troublesome and worrying, but did not interfere unduly or more than temporarily with the prescribed regime of chemotherapy. Nevertheless, toxic reactions to streptomycin must be accepted as a defect of the combination streptomycin + isoniazid as of the combination streptomycin + P.A.S.

Toxicity of Isoniazid.—There have been no reports of serious toxicity from isoniazid in any of the trial patients, with the dosage used, over a period of three months, and there is nothing further to add, at this stage, to the information presented in the previous report.

3. Condition on Admission

Table II shows the condition of patients before the start of treatment as reflected by their general condition (assessment by the clinician in charge), temperature, sedimentation rate (Westergren 200 mm. reading at one hour), and the extent of cavitation on *x*-ray film (as estimated by an independent radiological assessor, unaware of the treatment of any case). It can be seen that, judging by the factors listed, the SP, H, and SH cases, both in Group 1 and in Group 3, have a reasonably similar distribution of severe and less severe illness. In Group 2, however, the SP patients appear to have been on the average rather more ill than the SH and H patients. For the totals of all groups the three treatment series are comparable.

4. Results at the End of Three Months

In the following sections, after a general note on the low mortality, a comparison is made between the progress of the patients on streptomycin + isoniazid (SH) and that of patients on streptomycin + P.A.S. (SP). This is followed by a comparison of the progress of patients on streptomycin + isoniazid (SH) and the progress on isoniazid (H) alone.

Mortality.—There were four deaths among the 364 cases (1.1%) during the three months of treatment; two in 102 SP patients, one in 120 H patients, one in 142 SH patients. One SP patient (in Group 3A), who died 14 days after the start of treatment, suffered clinically from chronic bronchitis and emphysema, and cannot be regarded as having died from tuberculosis; the H patient (in Group 2C) died from

TABLE II.—*Condition on Admission of SP, H, and SH Cases*

	Treatment	Total	General Condition			Average Evening Temperature in Pre-treatment Week*				Sedimentation Rate (Westergren 200 mm. Reading at 1 Hour)				Extent of Cavitation†			
			Good	Fair	Poor	Afebrile	Under 99°F.	99–99·9° F.	100° F. or more	0–10	11–20	21–50	51 or more	Nil	1-plus	2-plus	3-plus
		No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %
Group 1: Acute rapidly progressive pulmonary tuberculosis of recent origin	SP	25 100	3 12	11 44	11 44	6 24	7 28	7 28	5 20	2 8	0 0	8 32	15 60	3 12	11 44	8 32	3 12
	H	26 100	6 23	10 38	10 38	8 31	8 31	9 35	1 4	1 4	1 4	10 38	14 54	7 27	7 27	5 19	7 27
	SH	37 100	4 11	20 54	13 35	5 14	13 35	13 35	6 16	0 0	5 14	18 49	14 38	5 14	16 43	14 38	2 5
Group 2: Other forms of pulmonary tuberculosis suitable for chemotherapy	SP	38 100	7 18	17 45	14 37	10 26	14 37	6 16	8 21	3 8	7 18	13 34	15 39	10 26	9 24	9 24	10 26
	H	44 100	16 36	17 39	11 25	24 55	11 25	6 14	3 7	7 16	10 23	17 39	10 23	17 39	11 25	13 30	3 7
	SH	56 100	18 32	31 55	7 12	24 43	19 34	9 16	4 7	8 14	12 21	24 43	12 21	19 34	17 30	16 29	4 7
Group 3: Chronic forms of pulmonary tuberculosis expected to make only a limited response to chemotherapy	SP	39 100	13 33	14 36	12 31	21 54	15 38	3 8	0 0	6 15	10 26	14 36	9 23	6 15	6 15	17 44	10 26
	H	50 100	10 20	26 52	14 28	28 56	17 34	3 6	2 4	3 6	13 26	21 42	13 26	5 10	6 12	19 38	20 40
	SH	49 100	16 33	19 39	14 29	24 49	13 27	9 18	3 6	11 22	4 8	21 43	13 27	5 10	8 16	16 33	20 41
All cases	SP	102 100	23 23	42 41	37 36	37 36	36 35	16 16	13 13	11 11	17 17	35 34	39 38	19 19	26 25	34 33	23 23
	H	120 100	32 27	53 44	35 29	60 50	36 30	18 15	6 5	11 9	24 20	48 40	37 31	29 24	24 20	37 31	30 25
	SH	142 100	38 27	70 49	34 24	53 37	45 32	31 22	13 9	19 13	21 15	63 44	39 27	29 20	41 29	46 32	26 18

* A patient was considered afebrile if *every* evening temperature in the pre-treatment week of observation was below 99° F. (37·2° C.).
† Assessment on a single film taken before treatment started. Tomograms were not taken into account.

congestive cardiac failure the day after starting treatment. These two cases do not represent a failure of treatment, in contrast to the other two patients—one on SP, the other on SH (from Groups 3A and 3B)—who died of their tuberculous disease 32 days and 22 days respectively after the start of treatment; both were very ill on admission to the trial.

5. The Comparison between SH (Streptomycin + Isoniazid) and SP (Streptomycin + P.A.S.)

General Condition.—Change in the clinical condition was assessed by the physician in charge of the patient. It represents an overall impression of the patient's progress, being based on the clinical observations, the patient's appearance, and his feeling of well-being (or lack of it). Table III shows that on each treatment a considerable percentage of patients improved—87% of 142 SH patients and 75% of 102 SP patients. This difference just attains statistical significance at the 5% level, due mainly to the experience in Group 3. In this group of very chronic cases, 51% of 39 SP patients showed 1-plus (moderate) improvement, and none had 2-plus (considerable) improvement; in the 49 SH patients the corresponding figures are 49% and 22%. In Group 1, the acute rapidly progressive disease, all the 25 SP patients and 36 of the 37 SH patients improved clinically.

Weight Changes.—The weight changes for the three-months period are set out in Table IV, and here the SH patients have benefited strikingly compared with the SP patients. The difference in the average weight gains for the totals (6.1 lb. and 13.0 lb.—2.8 and 5.9 kg.), and also that for each disease group, is statistically highly significant. Of the 136 SH patients, 82% gained 7 lb. (3.2 kg.) or more and 42% gained 1 stone (6.3 kg.) or more. The corresponding figures for the 97 SP patients are 45% and 13%. It is noteworthy that the acute (Group 1) cases on both treatments have fared better than the less acute cases, and that in this group, too, the SH patients have benefited more than the SP patients. Of 36 SH patients 61% have gained 1 stone or more, compared with 32% of 25 SP patients. Of

TABLE III.—*General Condition at the End of the Third Month Compared with General Condition on Admission*

	Treatment	Total	Improvement		No Change	Deterioration		Death
			2-plus	1-plus		1-minus	2-minus	
		No. %	No. %	No. %	No. %	No. %	No. %	No. %
Group 1: Acute rapidly progressive pulmonary tuberculosis of recent origin	SP	25 100	12 48	13 52	0 0	0 0	0 0	0 0
	H	26 100	13 50	10 38	3 12	0 0	0 0	0 0
	SH	37 101	18 49	18 49	1 3	0 0	0 0	0 0
Group 2: Other forms of pulmonary tuberculosis suitable for chemotherapy	SP	38 101	12 32	19 50	6 16	0 0	1 3	0 0
	H	44 99	12 27	27 61	3 7	1* 2	0 0	1 2
	SH	56 99	21 37	31 55	4 7	0 0	0 0	0 0
Group 3: Chronic forms of pulmonary tuberculosis expected to make only a limited response to chemotherapy	SP	39 100	0 0	20 51	16 41	1 3	0 0	2 5
	H	50 100	7 14	25 50	15 30	2 4	1 2	0 0
	SH	49 100	11 22	24 49	13 27	0 0	0 0	1 2
All cases	SP	102 101	24 24	52 51	22 22	1 1	1 1	2 2
	H	120 101	32 27	62 52	21 18	3* 2	1 1	1 1
	SH	142 100	50 35	73 51	18 13	0 0	0 0	1 1*

* One patient changed treatment from H to SH at the end of two months, and is included here.

TABLE IV.—*Weight Changes in the First Three Months.*

	Treatment	Total Weighed	Weight Gain				No Change	Weight Loss		Average Gain in Weight per Patient (lb.)
			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. %	
Group 1: Acute rapidly progressive pulmonary tuberculosis of recent origin	SP	25 100	2 8	6 24	11 44	3 12	1 4	2 8	0 0	10·2
	H	26 101	9 35	8 31	6 23	2 8	1 4	0 0	0 0	17·3
	SH	36 101	14 39	8 22	11 31	2 6	0 0	1 3	0 0	16·6
Group 2: Other forms of pulmonary tuberculosis suitable for chemotherapy	SP	36 100	1 3	3 8	11 31	9 25	3 8	7 19	2 6	4·9
	H	43 100	10 23	17 40	11 26	4 9	0 0	0 0	1‡ 2	15·6
	SH	54 101	9 17	14 26	23 43	6 11	1 2	1 2	0 0	13·1
Group 3: Chronic forms of pulmonary tuberculosis expected to make only a limited response to chemotherapy	SP	36 102	1 3	0 0	9 25	20 56	2 6	2 6	2 6	4·6
	H	50 100	0 0	12 24	17 34	16 32	1 2	3 6	1† 2	8·1
	SH	46 100	4 9	8 17	21 46	11 24	0 0	1 2	1* 2	10·2
All cases	SP	97* 99	4 4	9 9	31 32	32 33	6 6	11 11	4 4	6·1
	H	119* 101	19 16	37 31	34 29	22 18	2 2	3 3	2†‡ 2	12·8
	SH	136* 100	27 20	30 22	55 40	19 14	1 1	3 2	1 1	13·0

* For three other SP patients and five SH patients the weight changes are not available. Also two SP patients, one H patient, and one SH patient had died.
† One patient included here lost 11½ lb. in two months, was too ill to be weighed at three months, and died the following day.
‡ One patient changed treatment from H to SH at the end of two months, and is included here.

the total of 61 acute cases on SP or SH, only 4 (7%) have failed to gain some weight.

Temperature.—In the present analysis a patient was considered to be initially afebrile if the evening temperature was below 99° F. (37.2° C.) on *every day* of the week of preliminary observation. The same definition applied to the last week of the third month of treatment. Table V sets out the number of patients who were febrile in the pre-treatment week, but afebrile at three months. The patients are grouped according to the initial level of pyrexia. In a total of 88 febrile SH patients, 82% were afebrile at three months, compared with 76% of 63 SP patients. There is also little difference between the three disease groups; the figures for Group 1, the acute cases, were 81% of 32 SH patients and 84% of 19 SP patients. In none of these comparisons is there a statistically significant difference.

Of 53 SH patients who were afebrile in the pre-treatment week (not shown in the table) 6, or 11%, had a low-grade pyrexia at three months (an occasional evening temperature above 99° F.). The corresponding figures for the SP patients were 4 out of 37, also 11%.

Sedimentation Rate.—Table VI sets out the number of patients with an initially elevated blood sedimentation rate (B.S.R., Westergren) which was lowered after three months' treatment. Of 101 SH patients with an initial B.S.R. of 21 or more, 45% fell to normal (10 or less) in three months; the corresponding figure for 73 SP patients was only 21%. This difference is statistically highly significant. When the initial B.S.R. was 51 or more the rates were normal at three months in 18% of 39 SH patients, and in only 5% of 38 SP patients. The B.S.R. rose from an initially normal level in 4 of 19 SH cases and 3 of 10 SP cases (not shown in the table).

Radiographic Changes in First Three Months.—Table VII sets out the radiographic changes at the end of three months' treatment. The assessments were made by an independent reading of full-plate chest *x*-ray films by a radiologist unaware of the treatment in any case. (Since the radiographic reading was intended as a comparative measure of *x*-ray change and not as an absolute assessment, it was considered that the readings of a single radiologist could be fairly accepted for assessing the relative merits of

TABLE V.—*Number of Cases Febrile in the Pre-treatment Week who were Afebrile at the End of the Third Month*

	Treatment	Average Evening Temperature in the Pre-treatment Week						All Cases Febrile in the Pre-treatment Week	
		Under 99° F.		99° F.–99·9° F.		100° F. or More			
		Total	No. Afebrile at Three Months	Total	No. Afebrile at Three Months	Total	No. Afebrile at Three Months	Total	Afebrile at Three Months
									No. %
Group 1: Acute rapidly progressive pulmonary tuberculosis of recent origin	SP	7	5	7	7	5	4	19	16 *84*
	H	8	7	9	5	1	1	18	13 *72*
	SH	13	12	13	12	6	2	32	26 *81*
Group 2: Other forms of pulmonary tuberculosis suitable for chemotherapy	SP	14	12	6	4	8	3	28	19 *68*
	H	11	9	5	4	3	3	19	16 *84*
	SH	19	16	9	6	4	2	32	24 *75*
Group 3: Chronic forms of pulmonary tuberculosis expected to make only a limited response to chemotherapy	SP	14	11	2	2	0	0	16	13 *81*
	H	17	10	3	1	2	0	22	11 *50*
	SH	13	12	8	8	3	2	24	22 *92*
			No. %		No. %		No. %		
All cases	SP	35	28 *80*	15	13 *87*	13	7 *54*	63*	48 *76*
	H	36	26 *72*	17	10 *59*	6	4 *67*	59*	40 *68*
	SH	45	40 *89*	30	26 *87*	13	6 *46*	88*	72 *82*

* Two SP patients, one H patient, and one SH patient who died are excluded from this table.

TABLE VI.—*Number of Cases with a Raised Sedimentation Rate in the Pre-treatment Week whose Sedimentation Rate was Normal at the End of the Third Month*

	Treatment	Sedimentation Rate in the Pre-treatment Week						All Cases with Initial Sedimentation Rate of 21 or More	
		11–20		21–50		51 or More			
		Total	No. with B.S.R. 0–10 at 3 Months	Total	No. with B.S.R. 0–10 at 3 Months	Total	No. with B.S.R. 0–10 at 3 Months	Total	B.S.R. of 0–10 at 3 Months
									No. %
Group 1: Acute rapidly progressive pulmonary tuberculosis of recent origin	SP	0	0	8	3	15	0	23	3 *13*
	H	1	1	10	4	14	4	24	8 *33*
	SH	5	5	18	14	14	2	32	16 *50*
Group 2: Other forms of pulmonary tuberculosis suitable for chemotherapy	SP	7	4	13	8	15	2	28	10 *36*
	H	9	5	17	4	10	3	27	7 *26*
	SH	12	8	24	17	12	3	36	20 *56*
Group 3: Chronic forms of pulmonary tuberculosis expected to make only a limited response to chemotherapy	SP	10	7	14	2	8	0	22	2 *9*
	H	13	6	21	6	12	0	33	6 *18*
	SH	4	2	20	7	13	2	33	9 *27*
			No. %		No. %		No. %		
All cases	SP	17	11 *65*	35	13 *37*	38	2 *5*	73*	15 *21*
	H	23	12 *52*	48	14 *29*	36	7 *19*	84*	21 *25*
	SH	21	15 *71*	62	38 *61*	39	7 *18*	101*	45 *45*

* For two other H patients the sedimentation rates at three months are not available. Also one SP and one SH patient had died.

TABLE VII.—*Changes in Radiographic Appearances in First Three Months*

	Treatment	Total		Improvement						No Change		Deterioration						Death	
				3-plus		2-plus		1-plus				1-minus		2-minus		3-minus			
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Group 1: Acute rapidly progressive pulmonary tuberculosis of recent origin	SP	25	*100*	2	*8*	10	*40*	6	*24*	7	*28*	0	*0*	0	*0*	0	*0*	0	*0*
	H	26	*101*	2	*8*	8	*31*	8	*31*	5	*19*	1	*4*	2	*8*	0	*0*	0	*0*
	SH	37	*100*	9	*24*	12	*32*	10	*27*	5	*14*	1	*3*	0	*0*	0	*0*	0	*0*
Group 2: Other forms of pulmonary tuberculosis suitable for chemotherapy	SP	38	*101*	4	*11*	10	*26*	14	*37*	9	*24*	0	*0*	0	*0*	1	*3*	0	*0*
	H	44	*101*	3	*7*	10	*23*	17	*39*	10	*23*	2	*5*	1†	*2*	0	*0*	1	*2*
	SH	56	*100*	8	*14*	20	*36*	11	*20*	17	*30*	0	*0*	0	*0*	0	*0*	0	*0*
Group 3: Chronic forms of pulmonary tuberculosis expected to make only a limited response to chemotherapy	SP	39	*100*	1	*3*	5	*13*	13	*33*	18	*46*	0	*0*	0	*0*	0	*0*	2	*5*
	H	50	*100*	0	*0*	4	*8*	13	*26*	28	*56*	4	*8*	0	*0*	1*	*2*	0	*0*
	SH	49	*100*	1	*2*	4	*8*	16	*33*	25	*51*	2	*4*	0	*0*	0	*0*	1	*2*
All cases	SP	102	*100*	7	*7*	25	*25*	33	*32*	34	*33*	0	*0*	0	*0*	1	*1*	2	*2*
	H	120	*100*	5	*4*	22	*18*	38	*32*	43	*36*	7	*6*	3†	*2*	1*	*1*	1	*1*
	SH	142	*100*	18	*13*	36	*25*	37	*26*	47	*33*	3	*2*	0	*0*	0	*0*	1	*1*

* This patient had 2-minus deterioration at two months, was too ill to be *x*-rayed at three months, and died the following day.
† One patient included here had 2-minus deterioration at two months, changed treatment from H to SH, and still had 2-minus deterioration at 3 months.

different treatments.) In assessing improvement or deterioration three degrees were allowed—namely: 1-plus, 2-plus, and 3-plus, and 1-minus, 2-minus, and 3-minus. In total, the SH and SP groups both contain 64% who showed radiographic improvement. The improvement was more than 1-plus in 38% of SH patients and in 31% of SP patients. (In Group 1, the acute group, 2-plus or 3-plus improvement was seen in 57% of SH cases and 48% of SP cases.) In all there was radiographic deterioration in 3 patients, and one death on streptomycin + isoniazid, and one deterioration and two deaths of patients on streptomycin + P.A.S. The differences between the two treatments are not statistically significant.

Summary of the Comparison of SH and SP

In general condition the SH patients fared rather better than the SP patients, but only among the chronic cases was the difference more than very slight. It must be remembered that assessment of general condition is to a considerable extent influenced by a knowledge of all the other observations of the patient's progress, such as the B.S.R., weight changes, and temperature. The weight gains in all three disease groups were strikingly better for patients on the SH treatment than on the SP treatment. The SH combination also proved much the more effective in lowering the B.S.R. On the other hand, the two treatments had very similar effects on the temperature, and, most important, there were no significant differences in the radiographic response.

6. The Comparison between SH (Streptomycin + Isoniazid) and H (Isoniazid)

General Condition.—Comparing streptomycin + isoniazid with isoniazid alone, it was found in regard to general condition that the response of the patients to each treatment was very similar. Table III shows that 87% of the SH patients improved, compared with 78% of the H patients. Again the response of Group 1 cases is particularly satisfactory.

Weight Changes.—Table IV shows that the average gain in weight for 136 SH patients was 13.0 lb. compared with an average gain of 12.8 lb. for 119 H patients. In each of the three disease groups the two treatments show little difference. The very chronic cases (Group 3) have, however, fared less well on either treatment than the other two groups. The close similarity in weight gain of the SH and H patients indicates that the important factor in these striking increases is either the presence of isoniazid or the absence of P.A.S.

Temperature.—Of 88 pyrexial SH patients 82% became apyrexial, compared with 68% of 59 H patients (Table V). The greatest disparity is in the very chronic cases of Group 3, where the difference attains statistical significance. In the other groups it is not important.

Sedimentation Rate.—The SH treatment has proved more effective than isoniazid alone in lowering the B.S.R. (Table VI). In 101 SH patients with an initial B.S.R. of 21 or more there was a fall to normal (10 or less) in 45%. For 84 H patients the figure was only 25%, giving a statistically highly significant difference. The difference is apparent in all three disease groups.

Radiographic Changes in First Three Months.—Table VII shows that of 142 SH patients 64% improved radiographically, compared with 54% of 120 H patients. Moreover, 38% of the SH patients showed 2-plus or 3-plus improvement, compared with 22% of the H patients. This superiority of the SH treatment, which is apparent over the whole range of the *x*-ray assessment, is statistically highly significant. Taking the acute Group 1 alone, 57% of the SH patients showed 2-plus or 3-plus improvement, compared with 38% of the H patients. In total, 3 SH patients deteriorated radiographically and one died, compared with 11 deteriorations and one death on H alone. (All 3 SH deteriorations and 7 of the H deteriorations were slight.) The SH treatment has thus shown itself to be more effective radiographically than isoniazid alone.

Summary of the Comparison of SH and H

The SH treatment was more effective than H in lowering the blood sedimentation rate and also in improving the radiographic appearances, and was slightly more effective in lowering the temperature of pyrexial patients. The two treatments were very similar in their effect on the general clinical condition and on weight, both producing striking improvement.

III. BACTERIOLOGY

The Laboratory Subcommittee (chairman, Professor R. Cruickshank) has been responsible for prescribing uniform laboratory techniques and procedures for the centres. A detailed description and discussion of these procedures will be published later as part of a further report.

The first report on the trial (Medical Research Council, 1952) gave as much bacteriological information as was then available on the presence of tubercle bacilli in the sputum during treatment with streptomycin+P.A.S. and with isoniazid. An analysis of isoniazid-sensitivity tests at one, two, and three months demonstrated that isoniazid resistance developed frequently and rapidly; this resistance was shown to affect clinical progress.

The present section analyses the bacteriology of cases treated, concurrently, with streptomycin+isoniazid (SH), streptomycin+P.A.S. (SP), or isoniazid alone (H). These are the same patients as those reported on clinically in Section II. The bacterial content of the sputum of the patients is compared after one, two, and three months of treatment. The development of bacterial resistance to streptomycin is studied for the patients treated with SH and with SP, and the development of resistance to isoniazid in patients treated with SH and with H. Because of the time needed to obtain results of cultures from sputum specimens and to complete drug-sensitivity tests on those cultures, the present analysis omits results pending at two and three months for a small percentage of cases.

1. Exclusions

For the clinical section of this report, it was decided to retain in the analysis only those patients who completed three months' treatment or who died after starting treatment. The procedure adopted for this bacteriological section has been different from that for the clinical section; the results of all available complete tests at one, two, and three months have been used. Thus any complete tests from the small number of patients withdrawn from the clinical analysis have been included—provided they had been treated for at least one month.

On the other hand, 16 patients whose clinical progress is reported have been excluded entirely from the bacteriological analysis. It was laid down that all cases at the start of treatment must be bacteriologically positive for tubercle bacilli (see p. 521). For 12 cases (4 SP, 4 H, 4 SH) the records show that no tubercle bacilli had in fact been seen or isolated from pre-treatment specimens, although positive results were obtained subsequently on one or more occasions from 4 of them. All 12 have been excluded from the bacteriological tables. It should be emphasized that there was no doubt of the clinical diagnosis, and in fact for most of these cases a positive bacteriological test had been obtained, though not within the prescribed pre-treatment period.

Four other cases (2 SP, 2 SH), all from one small centre, have been excluded because the recording of the bacteriological information was manifestly unsatisfactory.

2. Bacterial Content of Sputum

Sputum collected during the pre-treatment week, and subsequently at monthly intervals, or more often, was examined by direct microscopy and by culture. Where there was no sputum, material from laryngeal swab or gastric lavage was cultured.

The procedure for taking specimens varied considerably from centre to centre. Many centres adhered simply to the minimum requirements for the trial—namely, a single specimen taken each month; in others, specimens were taken much more often. There was evidence that in some centres examinations were made more frequently for patients on some treatments than on others.

In analysing this varied material two important points had to be observed. One was to assess the results as nearly as possible *at* one, two, or three months after the start of treatment. The other was to ensure that no apparent advantage or disadvantage accrued to a particular treatment merely because numerous or few examinations had been made on those patients allocated to it.

To meet these requirements it was decided to assess the presence or absence of tubercle bacilli each month from the results of single complete examinations of specimens, one from each patient, collected on a date as near as possible to, or exactly at, one, two, and three months after the start of treatment. A test was regarded as incomplete, and was ignored, unless a culture result was available. No result was included for a given month if the date of collection of the nearest specimen examined lay more than 7 days on either side of the appropriate date. Where there was more than one complete test within this period of 15 days, that on or nearest to the appropriate date was chosen, to avoid bias. Table VIII of the present report is therefore not comparable with Table VIII of the first report, in which the "most positive" of the results obtained at any time *during* each month was recorded.

TABLE VIII.—*Presence of Tubercle Bacilli at Single Examinations made at Monthly Intervals*

	Treatment	Total Patients Examined		"Positive" Direct Examination†		"Scanty Positive" Direct Examination*†		Direct Examination Negative and Culture Positive; or Laryngeal Swab Positive		Direct Examination and Culture Negative; or Laryngeal Swab Negative	
		No.	%	No.	%	No.	%	No.	%	No.	%
At 1 month	SP	91	*99*	33	*36*	14	*15*	14	*15*	30	*33*
	H	107	*100*	37	*35*	20	*19*	26	*24*	24	*22*
	SH	131	*99*	39	*30*	23	*18*	27	*21*	42	*32*
At 2 months	SP	89	*100*	21	*24*	8	*9*	16	*18*	44	*49*
	H	110	*99*	28	*25*	20	*18*	30	*27*	32	*29*
	SH	132	*100*	17	*13*	22	*17*	27	*20*	66	*50*
At 3 months	SP	83	*100*	16	*19*	8	*10*	13	*16*	46	*55*
	H	101	*101*	30	*30*	11	*11*	23	*23*	37	*37*
	SH	117	*100*	10	*9*	11	*9*	18	*15*	78	*67*
By disease group at 3 months:											
Group 1	SP	21	*100*	3		2		4		12	*57*
	H	21	*100*	5		2		3		11	*52*
	SH	30	*100*	1		4		4		21	*70*
Group 2	SP	29	*100*	4		2		5		18	*62*
	H	35	*100*	8		6		5		16	*46*
	SH	43	*100*	2		2		8		31	*72*
Group 3	SP	33	*100*	9		4		4		16	*48*
	H	45	*100*	17		3		15		10	*22*
	SH	44	*100*	7		5		6		26	*59*

All patients were bacteriologically positive before treatment—that is, at least one pre-treatment specimen showed bacilli on direct examination or was positive on culture.

* Defined as follows: only a few clumps of acid-fast bacilli found after five minutes' search.

† Whether culture-positive or negative.

The results at one, two, and three months of the selected single examinations of the sputum for tubercle bacilli are set out in Table VIII. It will be clear from the foregoing paragraphs that, in all the bacteriological tables, each item represents a number of *patients* for each of whom a single test has been selected (by the method already stated), and not a total of all the *tests* performed on a smaller number of patients.

The recording of the pre-treatment findings was incomplete and biased, since it favoured positive results. For this reason no comparison is possible with the findings during treatment. The pre-treatment findings have, however, been used to check that the degree of positivity of the three treatment series was comparable at the start of treatment.

For the analysis of data at two and three months results have been included only for the specimens in which at least an eight-week period had elapsed since they were collected (this being the period recommended for the incubation of cultures before regarding them as negative). The results at the second and third months would otherwise have been unduly weighted by "positives," since specimens negative on direct examination and with no culture yet available would *not* have been included, while specimens directly positive, or with early positive cultures, *would* have been included.

Results

It will be seen from Table VIII that at the end of one month's treatment the results of the tests were negative both on direct examination and on culture in 33% of 91 SP cases, 22% of 107 H cases, and 32% of 131 SH cases. These differences are not statistically significant.

At the end of the second month the percentages of cases negative both on direct examination and on culture were 49% of 89 SP cases, 29% of 110 H cases, and 50% of 132 SH cases. It will be noted that the percentage had increased under each treatment from one to two months. Further, a definite superiority of the SH and SP treatments over the H treatment had appeared; the benefit to the SH and SP cases when compared with the H cases is highly significant statistically. There is no significant difference between the SH and SP series.

At three months, further increases in the percentages negative both on direct examination and on culture had occurred, the figures being 55% of 83 SP cases, 37% of 101 H cases, and 67% of 117 SH cases; there was by then a tendency for the SH cases to show a benefit over the SP cases, but the difference does not attain significance. The cases on H lagged well behind, the benefit to the SH cases being highly significant. It must again be emphasized that this table presents only findings of single tests and so is not necessarily indicative of "sputum conversion." At the other end of the scale the percentages with a positive direct examination at three months were 19% for the SP cases, 30% for the H cases, and 9% for the SH cases.

3. Sensitivity Tests

Strains isolated from specimens collected before starting treatment, and subsequently at least once a month, were tested for streptomycin sensitivity in the SP and SH patients and for isoniazid sensitivity in the H and SH patients. The technique employed for streptomycin sensitivity was similar to that in previous trials (Medical Research Council, 1948); that for isoniazid sensitivity is outlined later (p. 530).

In addition, as the importance of initial P.A.S. resistance in patients admitted to the SP treatment became apparent, it was laid down that a P.A.S.-sensitivity test should be performed on the earliest culture available (whenever possible from the pre-treatment specimen) for all patients from whom a history of one month or more of treatment with P.A.S. alone was obtained. These tests of P.A.S. sensitivity were performed in two laboratories (see Acknowledgments).

As with the recording of the sputum tests, a sensitivity test for a given month was accepted only if it was performed on a specimen collected not more than seven days before or after the appropriate date. When more than one such result was available the one referring to a specimen taken on or nearest to the appropriate date was selected.

4. Streptomycin Sensitivity

All tests in which the "resistance ratio"* is 8 or more are classed as resistant, provided the test organisms grew in 0.5 unit per ml. or more; this latter proviso has been introduced to make allowance for the occasional exceptionally low reading for the standard strain H37Rv (inhibition by 0.06 unit per ml.). Check-tests in the reference laboratory for these few test strains indicated that they were sensitive.

As already stated (p. 521), it was required that at the start of treatment the tubercle bacilli must not, so far as was known, be either streptomycin-resistant or P.A.S.-resistant, the object of this requirement being that if the case was allocated to the SP treatment the effectiveness of chemotherapy should not be hindered by pre-existent resistance to either drug, or, if allocated to the SH treatment, by pre-existent resistance to streptomycin. In fact, for many cases the drug sensitivity was not known until well after the start of treatment, when the results of pre-treatment sensitivity tests had become available. It was then found that in 9 patients (2 SP, 7 SH) the bacilli had been streptomycin-resistant initially. Of these, 7 had a history of treatment with streptomycin, alone or in combination with P.A.S., prior to the trial. The other 2 patients are of particular interest, since neither had had any previous chemotherapy and yet both had initially streptomycin-resistant organisms (ratio 8); they are referred to again in the Discussion. These 9 patients are excluded from the following analysis of the development of streptomycin resistance under the SP and SH treatments. The 7 SH patients are referred to again in the section on isoniazid sensitivity, as it was particularly important to investigate whether their bacilli developed resistance to that drug.

There were 3 other patients (2 SP, 1 SH), in whom the streptomycin-sensitivity tests were equivocal. Although the resistance ratio was 4 in two of them, and only 2 in the third, the test organism was inhibited in a concentration of 2 units per ml. in one case, and had grown in 2 units per ml. in the other two (and was not tested further). There was therefore a suggestion that the strains might be resistant. It did not seem correct to class these strains either as initially sensitive or as initially resistant, and these patients too have been excluded from the analysis. The strains from one of the two "doubtful" SP cases remained doubtfully resistant at both one and three months, with sensitivity tests still showing growth in 2 units per ml. (not tested further). Strains from the other patient were resistant (ratio 8) at one month, doubtfully resistant at two and three months, and resistant (ratio 64) at four months. Both these patients gave a previous history of having had streptomycin alone. The SH patient with a doubtfully resistant test initially had no previous history of chemotherapy and gave a definitely sensitive test at two months.

For almost all (95%) of the remaining patients it was established that the organisms were streptomycin-sensitive at the start of treatment. No information was forthcoming for the remaining 5% (7 SP, 4 SH) for technical reasons, such as failure of the primary culture (despite a positive direct test) or of the subculture to grow; for these cases it has been assumed that the organisms were sensitive to streptomycin. Of these 11 patients, 5 on SP and 2 on SH had never had any previous chemotherapy, and a third SH patient had never had streptomycin previously.

* Defined as the ratio of the lowest concentration of streptomycin completely inhibiting growth of the test strain to the corresponding figure for the standard strain (H37Rv).

Results

It is obviously very important to compare the relative effectiveness of the P.A.S. and of the isoniazid in the SP and SH treatments respectively in preventing the emergence of streptomycin resistance. Table IX presents the results of the streptomycin-sensitivity tests after one, two, and three months' treatment with SP or SH (after excluding patients known to be streptomycin-resistant at the start of treatment). The figures in the column headed "culture positive, no sensitivity result available" usually represent failure of a subculture to grow, contamination of the culture, or overheating (incubator fault). For a few of the cases at two and three months in this column, the sensitivity result was still pending at the time of analysis.

TABLE IX.—*Results of Streptomycin Sensitivity Tests in SP and SH Cases, Excluding Those Found to be Streptomycin-resistant on Entry to Trial*

	Treatment	Total Patients with Culture Examined (*a*)	Culture-negative (No Sensitivity Test Possible)	Culture-positive but No Sensitivity Result Available	Patients Culture-positive with Sensitivity Tests				Total Resistant		
					Total Results Available (*b*)	Sensitive	Moderately Resistant (Ratio 8 to 99)	Strongly Resistant (Ratio 100 or More)	No. (*c*)	(*c*) as % of (*b*)	(*c*) as % of (*a*)
At 1 month ..	SP	86	37	2	47	46	1	0	1	*2*	*1*
	SH	124	45	4	75	74	1	0	1	*1*	*1*
At 2 months ..	SP	84	49	4	31	30	1	0	1	*3*	*1*
	SH	124	68	4	52	50	1	1	2	*4*	*2*
At 3 months ..	SP	78	53	8	17	13	2	2	4	*24*	*5*
	SH	109	82	8	19	17	2	0	2	*11*	*2*
By disease group at 3 months:											
Group 1	SP	21	14	4	3	3	0	0	0		
	SH	30	23	2	5	5	0	0	0		
Group 2	SP	29	19	4	6	6	0	0	0		
	SH	41	30	3	8	7	1	0	1		
Group 3	SP	28	20	0	8	4	2	2	4		
	SH	38	29	3	6	5	1	0	1		

Table IX shows that at one month a streptomycin-resistant culture was obtained in one out of 47 culture-positive SP cases (2%), compared with one out of 75 culture-positive SH cases (1%). At two months the corresponding figures were one out of 31 culture-positive SP cases (3%), and 2 out of 52 similar SH cases (4%). At three months there were 4 resistant cultures from 17 culture-positive SP cases (24%) (2 of them moderately and 2 strongly resistant); the corresponding figure was 2 from 19 positive SH cases (11%) (both moderately resistant). When the incidence of streptomycin resistance is expressed by a percentage of the total number of patients for whom cultures were *examined* (whether culture-positive or negative—that is, (*c*) expressed as a percentage of (*a*) in Table IX)—the figures at three months are 4 out of 78 SP patients (5%) and 2 out of 109 SH patients (2%). None of these differences is statistically significant.

On the main question—namely, the prevention of streptomycin resistance by the administration of isoniazid with the streptomycin (SH)—the figures in Table IX at three months, though small, are highly suggestive. They indicate that the addition of isoniazid in a dosage of 200 mg. a day is highly effective—indeed, of the same order of effectiveness as 20 g. of sodium P.A.S. a day (or, when less was given, as large a dose of P.A.S. a day as the patient could tolerate).

Streptomycin-sensitivity tests are already available, in addition, at four months for 7 SH patients who had continued on the combination, though at a reduced dosage of streptomycin (1 g. three times a week), during the fourth month. All 7 tests showed that the cultures were sensitive. One of the patients had yielded a resistant strain at a low level (ratio 8) at three months.

5. P.A.S. Sensitivity

The figure of 4 streptomycin-resistant strains from 17 culture-positive SP patients with sensitivity tests at three months does not seem to represent the usual experience of streptomycin resistance after this period of treatment with streptomycin 1 g. daily plus P.A.S. 20 g. daily. In the present series this high figure is in part related to previous chemotherapy with P.A.S. alone. Evidence will be presented in a further report, as well as in a detailed article from one of the co-operating centres, to show that the administration of P.A.S. alone for periods of more than a month is an important factor in the development of streptomycin resistance when a course of streptomycin+P.A.S. is given subsequently. Of the above-mentioned 4 culture-positive SP patients, known to have streptomycin-sensitive strains before treatment but resistant strains at three months, 2 gave a history of prior treatment with P.A.S. alone, and both were P.A.S.-resistant at the start of treatment. By contrast, of the 13 culture-positive patients with streptomycin-sensitive organisms at three months, only one had had P.A.S. alone previously, and this patient's strain was P.A.S.-sensitive at the start of treatment.

6. Isoniazid Sensitivity

The technique was in brief as follows: a loopful of bacterial suspension from a young primary culture on egg medium was spread on each of a series of egg-medium slopes containing graded concentrations of isoniazid of 0, 0.2, 1, 5, 10, and 50 μg. per ml.; a culture of H37Rv was treated similarly in parallel. Both sets of slopes were read at two weeks and at four weeks, and each slope was recorded at each reading in one of five categories: "confluent growth," "innumerable discrete colonies," "100–20 colonies," "less than 20 colonies," "nil." The experience gained since the publication of the first report has served to confirm the satisfactory nature of the criteria of sensitivity recorded in that report, and there appears to be no reason to introduce any modification. A small number of colonies continue to be observed occasionally on isoniazid-containing medium bearing cultures of the test organism, both before and during treatment, as well as of the standard organism, even in concentrations of isoniazid of 10 μg. per ml. This occurrence justifies the earlier decision that such sparse growths should be ignored in assessing the emergence of resistance during treatment. Accordingly, in the analysis of isoniazid resistance, readings of "less than 20 colonies" are classified with "no growth." This end-point has proved very satisfactory from the point of view both of reading the tests and of interpreting the results. A culture is designated "resistant" when growth of 20 or more colonies is observed at four weeks in concentrations of 1.0 μg. isoniazid per ml., or higher, and "of doubtful resistance" in cases of such growth in a concentration of 0.2 μg. per ml., but not more. As before it was found that the development of colonies is often incomplete after two

weeks' incubation, and the results analysed in Table X are derived solely from the four-week reading.

The 7 SH patients known to have streptomycin-resistant organisms at the start of treatment have been excluded from Table X. It was suspected that the behaviour of their organisms in regard to the development of isoniazid resistance under SH treatment might well differ from that of even more impressive; whereas 33 resistant strains were isolated from a total of 93 H patients (35%), only 3 isoniazid-resistant strains were isolated from 109 SH patients (3%) (growth at 1, 5, and 50 μg. per ml. respectively). Again, the benefit to the SH treatment is highly significant.

There is therefore a striking difference between the incidence of isoniazid resistance in patients on isoniazid

TABLE X.—*Results of Isoniazid Sensitivity Tests in H and SH Cases, Excluding Those Found to be Streptomycin-resistant on Entry to Trial*

	Treatment	Total Patients with Culture Examined (*a*)	Culture-negative (No Sensitivity Test Possible)	Culture-positive but No Sensitivity Result Available	Patients Culture-positive with Sensitivity Tests							Total Resistant		
					Total Results Available (*b*)	Sensitive	Doubtful	Resistant				No. (*c*)	(*c*) as % of (*b*)	(*c*) as % of (*a*)
						No Growth at 0·2 μg. per ml.	Growth at 0·2 μg. per ml. Not at 1	Growth at 1 μg. per ml. Not at 5	Growth at 5 μg. per ml. Not at 10	Growth at 10 μg. per ml. Not at 50	Growth at 50 μg. per ml.			
At 1 month ..	H	102	27	2	73	58	7	3	0	2	3	8	*11*	*8*
	SH	124	45	3	76	67	6	3*	0	0	0	3	*4*	*2*
At 2 months ..	H	105	38	4	63	17	14	7	6†	3	16	32	*52*	*30*
	SH	124	68	2	54	46*	3	5	0	0	0	5	*9*	*4*
At 3 months ..	H	93	36	4	53	11	9	6	6†	6	15	33	*62*	*35*
	SH	109	82	4	23	18	2	1	1	0	1	3	*13*	*3*
By disease group at 3 months:														
Group 1	H	21	11	0	10	3	1	0	0	3	3	6		
	SH	30	23	1	6	6	0	0	0	0	0	0		
Group 2	H	33	15	4	14	3	3	2	1	0	5	8		
	SH	41	30	2	9	7	1	0	0	0	1	1		
Group 3	H	39	10	0	29	5	5	4	5†	3	7	19		
	SH	38	29	1	8	5	1	1	1	0	0	2		

* One result was obtained from a guinea-pig culture.
† One of these cultures showed growth at 5 μg. per ml., but was not tested at higher concentrations.

patients with initially streptomycin-sensitive organisms; it is shown below that this was so. In order that Table X should present data for comparable groups, 5 H patients whose bacilli were subsequently found to be streptomycin-resistant before treatment were also excluded, although for these patients there was no *a priori* expectation that resistance to streptomycin would influence the development of resistance to isoniazid under that drug alone. These 5 H cases are also considered separately below.

Results

Table X sets out the results of the isoniazid-sensitivity tests at one, two, and three months in H and SH cases (after excluding patients known to be streptomycin-resistant at the start of treatment). Of 80 isoniazid-sensitivity tests on positive cultures from H patients before treatment, there had been 5 "doubtful" and no "resistant" strains. Examination of 100 SH patients' cultures before treatment also yielded 5 "doubtful" and no "resistant" strains.

At one month, from 73 culture-positive H patients with sensitivity results, 8 resistant cultures (11%) (5 at a level of 10 μg. per ml. or higher) and 7 doubtfully resistant cultures (10%) were obtained; 76 similar SH patients yielded 3 instances of isoniazid resistance (4%, all resistant at the lowest level) and 6 of doubtful resistance (8%). The differences are suggestive, but not statistically significant.

At two months, resistant cultures were obtained from 32 (52%) of 63 culture-positive H patients (half of these growing at 50 μg. per ml.), and another 14 patients (22%) yielded doubtfully resistant strains. The corresponding SH results from 54 culture-positive patients were 5 resistant cultures (9%) and 3 doubtful (6%); again resistance was at a low level (growth at 1 μg. per ml. but not 5). The benefit to the SH treatment is highly significant statistically.

At three months, the proportion of resistant strains from patients on isoniazid alone had increased to 33 (62%) from 53 culture-positive patients, compared with only 3 (13%) of 23 positive SH cultures. When the incidence of isoniazid resistance is expressed as a percentage of the total number of patients for whom cultures were *examined* (whether culture-positive or negative—that is, (*c*) expressed as a percentage of (*a*) in Table X), the difference at three months is alone and in those having the combination isoniazid + streptomycin. The combination largely prevents the development of isoniazid resistance.

Turning now to the 7 SH patients in whom streptomycin-resistant strains were isolated before treatment, 4 had produced isoniazid-resistant strains at the end of three months. The other 3 were culture-negative at three months, but one was known to have had sensitive strains at two months, and another at both two months and four months. Although the numbers are very small, they suggest that this group of patients is behaving more like a group treated with isoniazid alone than a group treated with the combination streptomycin + isoniazid. In other words, patients with streptomycin-resistant organisms are not protected from the development of isoniazid resistance by the SH treatment.

Of the 5 H patients with streptomycin-resistant organisms initially, the bacilli of 1 were also isoniazid-resistant before treatment. In this case the organisms grew at 1 but not 5 μg. per ml. in the pre-treatment test. The organisms showed the same degree of resistance at one, two, and five months, but at four months growth occurred in the 5 μg. per ml. tube; the culture was negative at three months. This strain was non-pathogenic to guinea-pigs and mice, and therefore appears to be non-virulent (this case will be reported later). Of the strains from the other 4 patients, one was resistant at three months and one sensitive. The other two patients were culture-negative at three months, but had resistant organisms at four months (the culture from one had been doubtfully resistant at one month). The behaviour of these four cases is in keeping with the behaviour of the rest of the H cases.

Isoniazid-sensitivity tests are also available at four months for 8 patients who had continued on streptomycin + isoniazid, in full dosage in one, but with a reduced streptomycin dosage of 1 g. three times a week in 7. Of these 8 patients, 4 had isoniazid-sensitive organisms (including the patient on daily streptomycin), one was doubtful, and 3 were definitely resistant (growth in 5, 10, and 50 μg. per ml. respectively). The strain from one of the 3 resistant cases was known to have been resistant at two months. There were no sensitivity tests available on the

other 2 between one month, when sensitive organisms were found, and the resistant results at four months, and they may well have developed resistance before the fourth month. Clearly this experience beyond three months' treatment with streptomycin + isoniazid indicates the need for a most careful evaluation in the light of further results when they become available.

When the data are complete it will be important to determine whether, when the bacilli of patients on streptomycin + isoniazid become resistant to one of the drugs, they become resistant to the other as well. The results of streptomycin- and isoniazid-sensitivity tests at three months in SH cases given in Tables IX and X have been derived from 23 patients. Results of isoniazid-sensitivity tests were available for all 23, whereas the results of streptomycin-sensitivity tests were available for only 19. No conclusions can be drawn from this limited information, but the findings were as follows :

		Streptomycin Sensitivity at 3 Months		
		Resistant	Sensitive	Test Pending
Isoniazid sensitivity at 3 months	Resistant	1	1	1
	Doubtful	1	0	1
	Sensitive	0	16	2

IV. DISCUSSION

In the design of the present trial there were two main departures from the plan of the earlier Medical Research Council trials of chemotherapy in pulmonary tuberculosis. One was the decision to increase the range and scale by including several different types of case, and by enlisting the co-operation of a large number of hospitals. The other arose from the realization that a rapid intake of cases would make it imperative to review the results continually if clinical material was not to be wasted, and if the best forms of treatment were to be introduced without undue delay. A system of monthly progress reports for each patient was therefore set up, and the continual analysis permitted the early publication of a report in which the effects of streptomycin + P.A.S. were compared with those of isoniazid alone (Medical Research Council, 1952).

Even before the publication of this first report it had become apparent that the effects of the combination streptomycin + isoniazid should also be studied, and this treatment was introduced from June 1, 1952, in all three disease groups of the trial, concurrently with the treatments already mentioned. As further knowledge about the effectiveness and limitations of the new drug accumulated, the trial was modified again in order to study exclusively the value of combining isoniazid with other anti-tuberculosis drugs. The trial therefore differs from earlier clinical trials because it has developed on a flexible pattern and has been modified to study fresh problems in the light of information it has itself yielded. This flexibility is one of the most valuable characteristics of the present trial, since it enables much more information to be gained from the available clinical material.

The present observations relate to 364 patients suffering from pulmonary tuberculosis and treated for three months—142 with streptomycin + isoniazid, 102 with streptomycin + P.A.S., and 120 with isoniazid alone. These three treatments were allocated concurrently and at random. The results at the end of three months are summarized in Table XI and also in Figs. 2 to 8. The analysis shows that over this limited period streptomycin + isoniazid is superior to streptomycin + P.A.S. in lowering the sedimentation rate and in increasing body weight, and rather better in improving the general condition. The two treatments have a similar effect upon pyrexia, upon the presence of tubercle bacilli in the sputum, and, most important, upon radiographic appearances. Streptomycin + isoniazid, compared with isoniazid alone over a three-month period, is found to be considerably more effective in lowering the sedimentation rate, in suppressing tubercle bacilli in the sputum (confirming the findings of Dye, Lynch, and Brees, 1953), and also in improving the radiographic appearances. It is slightly more effective in resolving pyrexia. The two treatments produce equally striking improvements in general clinical condition and in weight.

TABLE XI.—*Summary of Comparisons of Streptomycin Plus Isoniazid with Streptomycin Plus P.A.S., and with Isoniazid Alone, at the End of Three Months' Treatment*

	Streptomycin Plus Isoniazid %	Streptomycin Plus P.A.S. %	Isoniazid %
General condition:			
Improvement 2-plus	35	24	27
,, 1-plus	51	51	52
No change	13	22	18
Deterioration	0	2	3
Death	1	2	1
Weight:			
Gain 14 lb. (6·35 kg.) or more	42	13	47
,, 7–13 lb. (3·2–5·9 kg.)	40	32	29
,, less than 7 lb., or no change	15	39	20
Loss	3	15	4
Temperature:			
Afebrile at 3 months (febrile at start)	82	76	68
Sedimentation rate:			
Fall to normal from 21 or more in 3 months	45	21	25
Radiograph:			
Improvement 2-plus or 3-plus	38	31	22
,, 1-plus	26	32	32
No change	33	33	36
Deterioration	2	1	9
Sputum:			
At 3 months: Direct positive	18	29	41
Positive culture only	15	16	23
Negative	67	55	37
Isoniazid sensitivity:			
At 3 months: Sensitive	78	—	21
Doubtful	9	—	17
Resistant	13	—	62

See the text for the streptomycin-sensitivity results, and Figs. 2–8 for the numbers of patients on which these percentages are based.

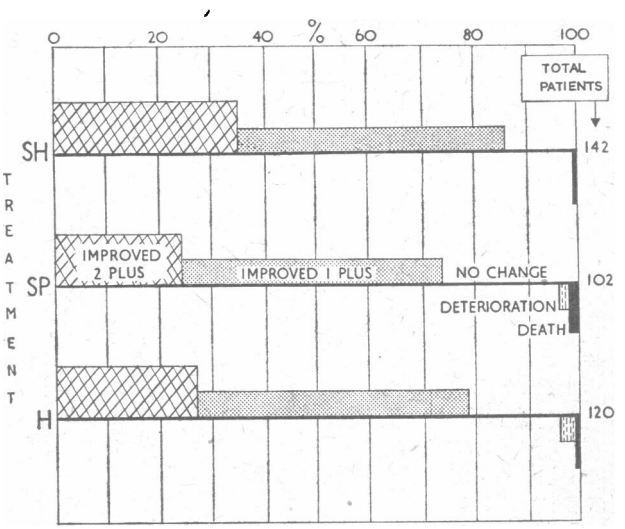

FIG. 2.—Changes in general condition in the first three months in the three treatment series. Each category of response is expressed as a percentage of the total patients.

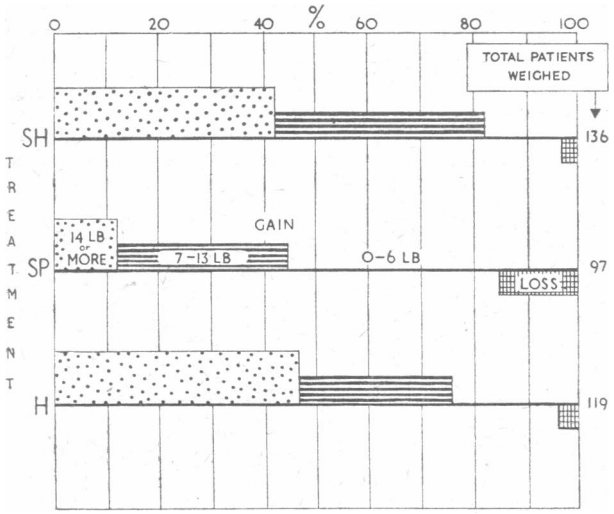

FIG. 3.—Weight changes in the first three months in the three treatment series. Each category of response is expressed as a percentage of the total patients weighed.

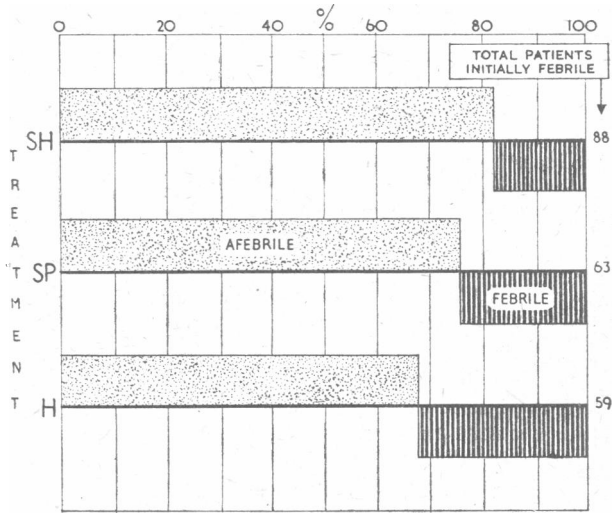

FIG. 4.—Temperature at three months in patients febrile during pre-treatment week. The response is expressed as a percentage of the total patients initially febrile.

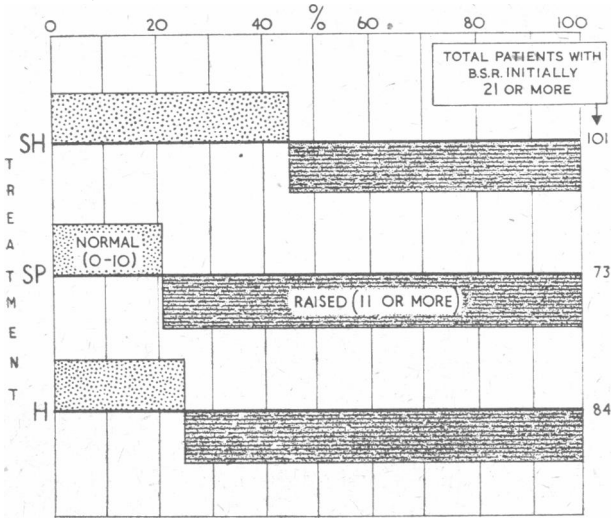

FIG. 5.—Sedimentation rate at three months in patients with a sedimentation rate of 21 or more pre-treatment. The response is expressed as a percentage of the total patients with initially raised B.S.R.

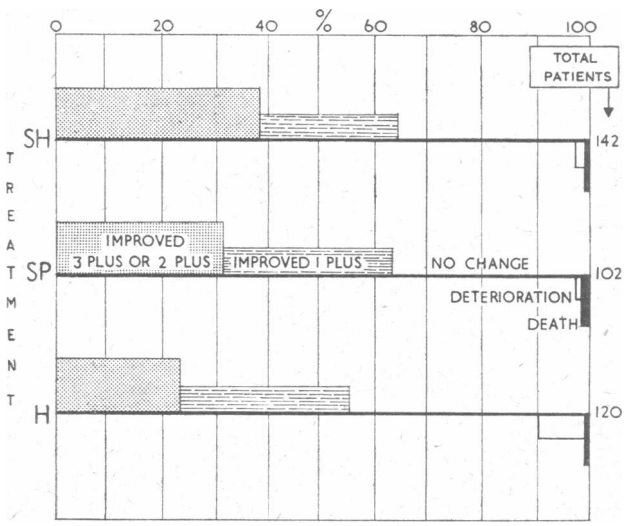

FIG. 6.—Changes in radiographic appearances in the first three months. Each category of response is expressed as a percentage of the total patients.

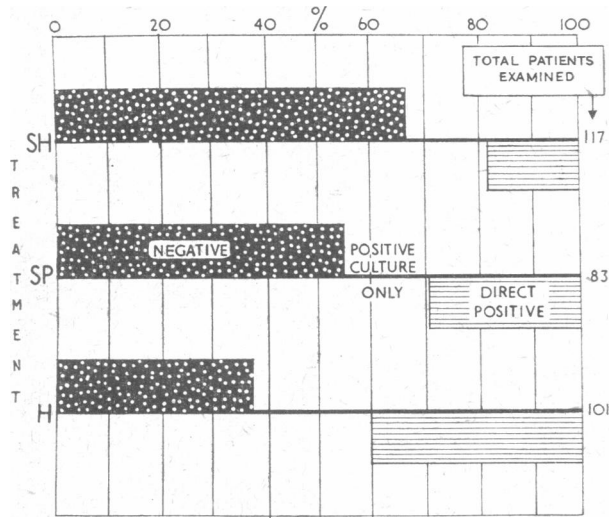

FIG. 7.—Presence of tubercle bacilli at a single examination at three months. The results are expressed as percentages of the total patients examined.

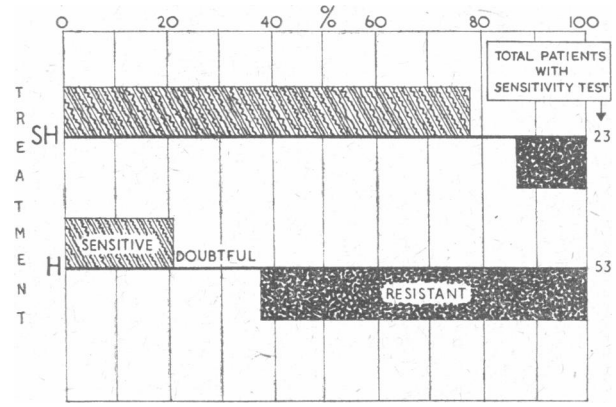

FIG. 8.—Isoniazid sensitivity in SH and H patients at three months. The results are expressed as percentages of the total patients with sensitivity tests

Although there has been virtually no toxicity from isoniazid with the dosage used, its combination with streptomycin suffers from the disadvantage of toxic reactions to the streptomycin. In the present series such reactions were severe enough to lead to withdrawal of the patient from the trial in 4% of cases (6 out of 148). On the other hand, streptomycin + isoniazid produces far fewer side-effects than streptomycin with P.A.S. in a dosage of 20 g. daily, and is also less unpleasant for the patient. Summarizing, it may be concluded that over a three-month period streptomycin 1 g. daily + isoniazid 200 mg. daily is clinically the most effective anti-tuberculosis chemotherapy yet investigated in this trial, although its superiority to streptomycin 1 g. daily + P.A.S. 20 g. daily is not great.

An important defect of the use of isoniazid by itself is the frequent and rapid emergence of bacterial resistance to the drug. In the present series of patients treated with isoniazid alone, 11% of cultures positive at one month were resistant, 52% of those at two months, and 62% of those at three months. The corresponding figures for the patients treated with streptomycin + isoniazid were only 4% isoniazid-resistant cultures at one month, 9% at two months, and 13% at three months. Moreover, when, with the combined drugs, isoniazid resistance did develop, the average level of this resistance was much lower than for patients on isoniazid alone. The administration of streptomycin 1 g. daily with isoniazid 200 mg. daily therefore lessens considerably the proportion of cases in which isoniazid-resistant strains, particularly those of high resistance, emerge over a three-month period. The very limited information on isoniazid resistance available at four months for these patients is, however, a little disquieting. If, with larger numbers, a substantial incidence of resistant strains appears, it will be important to assess what part, if any, is played by reducing the dosage of streptomycin in the fourth month.

It must be remembered that an increasing proportion of bacteriological specimens from patients on each of the three treatments studied here was found to be negative on culture as treatment proceeded, and consequently fewer and fewer sensitivity tests could be performed. Because of this, it can be argued that the figures quoted above, expressing the resistant strains as a percentage of the positive cultures on which sensitivity tests were performed, do not give an entirely fair picture of the development of resistance; they omit the culture-negative patients, some of whom will be permanently negative. An alternative presentation of the findings is that at three months 33 resistant cultures were obtained from a total of 93 of the patients on isoniazid alone (35%), compared with only 3 from a total of 109 of the patients on streptomycin + isoniazid (3%). On the other hand, these percentages give an unduly favourable impression of the incidence of resistance at three months, partly because not all the culture-negative patients will be permanently negative, and partly because a few sensitivity tests are still pending at three months. A true measure of the incidence of isoniazid resistance at three months in patients not permanently negative probably lies somewhere between 62% and 35% for those on isoniazid alone, and between 13% and 3% for those on streptomycin + isoniazid.

Of 7 patients on streptomycin + isoniazid whose organisms were initially streptomycin-resistant, 4 yielded cultures resistant to isoniazid at three months. The behaviour of this small group of patients is more akin to that of patients on isoniazid alone than to that of patients on streptomycin + isoniazid. In other words, if a patient's organisms are streptomycin-resistant initially, the combination streptomycin + isoniazid apparently affords no protection against the risk of the development of isoniazid resistance.

For the patients treated with streptomycin + isoniazid it is also important to know whether the combined therapy prevents the emergence of bacilli resistant to streptomycin. The analysis has shown that this is so. At three months, two streptomycin-resistant strains were isolated from 19 positive cultures (11%); these two strains were obtained from a total of 109 patients (2%). The true incidence of streptomycin resistance at three months in patients not permanently negative probably lies between these two percentages. The corresponding figures for isoniazid resistance in the same patients were 13% and 3%. Thus, the combination streptomycin + isoniazid appears to be as effective for three months in preventing the development of streptomycin resistance as of isoniazid resistance. The very limited information on streptomycin sensitivity available at four months for patients on the combination is satisfactory. However, it will be appreciated that, if isoniazid resistance should prove to be a problem at four months, there is a risk that streptomycin resistance may also emerge after a delay of one or two further months if treatment with streptomycin + isoniazid is continued.

For a period of three months streptomycin + P.A.S. and streptomycin + isoniazid are of the same order of effectiveness in preventing the development of streptomycin resistance. However, evidence, which will be presented later, has emerged in the course of the trial that the administration of P.A.S. alone carries with it a serious risk that P.A.S. resistance will develop; if it does, and the patient is subsequently treated with streptomycin + P.A.S., the combination no longer provides protection against the development of bacillary resistance to streptomycin. These findings are particularly important because the use of P.A.S. alone is still regarded by many clinicians as an acceptable treatment for pulmonary tuberculosis. The conclusion of the Therapeutic Trials Committee of the Swedish National Association against Tuberculosis (1952), that P.A.S. alone "should be given in cases where a moderate effect is wanted for a rather long time," seems unwarranted in view of these bacteriological findings.

The lessons to be learnt from these apparently complicated findings concerning the development of bacterial resistance are simple, and are as follows:

(1) *None of the three drugs, isoniazid, streptomycin, or P.A.S., should be used by itself in the treatment of pulmonary tuberculosis.* Equally, no new drug should at first be used by itself, except in clinical trials carefully planned to ascertain its bacteriological qualities as well as its clinical efficacy.

(2) To give a combination of two of these drugs to a patient whose organisms are already resistant to one of the two appears to be tantamount to giving the other alone, and so is equally undesirable. *It is therefore essential, whenever possible, to test the drug sensitivity of a patient's organisms before a course of chemotherapy is started, so that any unsuitable combination of drugs may be avoided and a potentially effective combination for that patient used instead.*

(3) The procedures for the assessment of drug resistance are at present slow and not always satisfactory, and many clinicians, when confronted with an ill patient, will not wish to risk further deterioration before instituting some form of chemotherapy. *A careful scrutiny of the history of previous chemotherapy, with particular regard to any drug which has been given alone, may warn the clinician of possibly unsuitable combinations, but such information cannot be regarded as a substitute for sensitivity tests, which should always be undertaken as soon as possible.*

(4) Even in newly diagnosed cases it is no longer safe to assume that the tubercle bacilli are fully sensitive; since the start of the present trial 4 out of 279 previously untreated patients whose bacilli were tested for initial streptomycin sensitivity (1%) have been found to have organisms resistant to streptomycin; there is evidence that these cases may have been infected with resistant strains. (A full report will appear later.) With the increasing use of anti-tuberculosis drugs the present low risk of becoming infected with drug-resistant bacilli may well increase. *If, therefore, chemotherapy must be initiated for a newly diagnosed case in the absence of sensitivity results, the clinician should inquire into previous chemotherapy and the results of sensitivity tests in any known contact before deciding upon a treatment combination.*

(5) There is, in fact, a great need for simple, reliable, and speedy techniques both for the culture of tubercle bacilli and for the determination of their sensitivity to chemotherapeutic agents. In the meantime *it is recommended that every patient with pulmonary tuberculosis, if still bacteriologically positive on completing a course of chemotherapy, should have further sensitivity tests performed as a routine.* This information would then be available if more chemotherapy is required at a later date, or should one of the patient's contacts develop the disease. However, the possibility that a drug-resistant strain may be replaced by a sensitive variant after the cessation of treatment must be kept in mind.

Finally, the Committee has obtained convincing evidence that streptomycin 1 g. daily + isoniazid 100 mg. twice a day is a highly effective combination of drugs when used for a period of three months in the treatment of pulmonary tuberculosis. On none of the clinical or bacteriological criteria was the combination inferior to streptomycin 1 g. daily + P.A.S. 5 g. four times a day over this period; in two respects—namely, in lowering the sedimentation rate and in fostering weight gain—it was decidedly superior. Nevertheless, the slender evidence on bacterial resistance which is available after four months' treatment is not entirely reassuring. In view of the short period of observation it is certainly not yet possible to assess the final place of streptomycin + isoniazid in the chemotherapy of pulmonary tuberculosis. The evaluation will depend to a considerable extent upon the clinical and bacteriological findings in patients treated with this combination of drugs over a longer period of time, in comparison with streptomycin + P.A.S. and other forms of chemotherapy.

The trial is continuing, and at present two different dosages of streptomycin and two of P.A.S. are being used, each in combination with isoniazid. These investigations are indispensable in determining the most effective ways in which isoniazid should be used in the treatment of pulmonary tuberculosis.

V. SUMMARY

As part of a clinical trial of isoniazid (isonicotinic acid hydrazide) in the treatment of pulmonary tuberculosis, 364 patients from 40 hospitals were studied; 142 were treated with streptomycin (1 g. daily) + isoniazid (100 mg. twice a day), 102 with streptomycin (1 g. daily) + P.A.S. (sodium salt, 5 g. four times a day), and 120 with isoniazid (100 mg. twice a day) alone. When submitting a case the physician did not know which treatment the patient would receive, this being determined by random allocation. The present report analyses the results at the end of three months' treatment and observation.

Three main groups were observed: Group 1, acute rapidly progressive disease of recent origin (excluding, from this report, bilateral disease between the ages of 15 and 30); Group 2, other forms suitable for chemotherapy; Group 3, chronic disease considered unlikely to respond to chemotherapy.

On admission, the three treatment series had a similar distribution of patients with severe and less severe illness.

At the end of three months, the general condition of the majority of patients had improved, but in this respect the differences between the three treatment series were small. The average gains in weight during the period were 13 lb. (5.9 kg.) for those on streptomycin + isoniazid (SH), 6 lb. (2.7 kg.) for those on streptomycin + P.A.S. (SP), and 13 lb. for those on isoniazid (H) alone.

The temperature of febrile patients fell to normal in 82% of SH, 76% of SP, and 68% of H cases. In patients with a sedimentation rate of 21 or more before treatment, the rate fell to 10 or less in 45% of those on SH, compared with only 21% on SP and 25% on H.

Changes in radiographic appearances were independently assessed by a radiologist unaware of the treatment of any patient. Two-plus or 3-plus improvement was seen in 38% of SH, 31% of SP, and 23% of H cases. There was little difference, over the whole range of response, between patients on SH and SP, but the patients on these treatments responded better than those on H. There were three radiographic deteriorations and one death on SH, one deterioration and two deaths on SP, and 11 deteriorations and one death on H.

The proportions of patients bacteriologically negative, both on direct examination and on culture, at a single examination at three months, were 67% for the SH series, 55% for SP, and 37% for H.

It is concluded, *judging solely from the results at three months,* that streptomycin + isoniazid, with the dosages used, is clinically the most effective of the treatments studied, although its superiority to streptomycin 1 g. daily + P.A.S. 20 g. daily is not great. A full evaluation must await a longer period of observation.

Bacillary resistance to isoniazid was found in 62% of culture-positive H patients tested at three months, compared with only 13% for similar SH patients. Bacillary resistance to streptomycin was found in 11% of these SH patients at three months. Thus the combination streptomycin + isoniazid, with the dosages studied, is as effective for three months in preventing the development of streptomycin resistance as of isoniazid resistance. Further, for three months the SH treatment is as effective as the SP treatment in preventing the emergence of bacilli resistant to streptomycin.

Patients with organisms initially streptomycin-resistant were apparently not protected from the risk of development of isoniazid resistance by the SH treatment;

patients with organisms initially P.A.S.-resistant (who had had prior treatment with P.A.S. alone) were not protected from the risk of development of streptomycin resistance by the SP treatment. Thus none of the three drugs, isoniazid, streptomycin, or P.A.S., should be used by itself, nor should two of them be used in combination for a patient whose organisms are already resistant to one of the pair. Whenever possible, the drug sensitivity of a patient's organisms should be assessed before chemotherapy is started, to avoid an unsuitable combination of drugs; and also on its completion, in case more chemotherapy is required later.

There is a great need for simple, reliable, and speedy techniques for the culture of tubercle bacilli and for the determination of their sensitivity to chemotherapeutic agents.

The trial was designed so that it could be modified to study fresh problems in the light of information it had itself yielded; at present the effects of two different dosages of streptomycin and two of P.A.S., each in combination with isoniazid, are under investigation.

ACKNOWLEDGMENTS

The hospitals and the doctors co-operating in the phase of the trial reported here are as follows:

Hospitals.—Aberdeen City Hospital; Aintree Hospital; Bangour Hospital, West Lothian; Black Notley Hospital, Braintree; British Legion Sanatorium, Nayland; Brompton Hospital; Canadian Red Cross Memorial Hospital, Taplow; Clare Hall Hospital, Herts; Connaught Military Hospital; Cumberland Hospital, Surrey; Dumfries and Galloway Sanatorium; East Fortune Hospital, East Lothian; Edgware General Hospital; Edinburgh City Hospital; Foxhall Hospital, Ipswich; Hammersmith Hospital; Heathcote Hospital, Leamington Spa; Inverurie Hospital, Aberdeen; Kettlewell Hospital, Kent; King Edward VII Sanatorium, Midhurst; King George V Hospital, Godalming; King George's Sanatorium for Sailors, Hants; Lenham Sanatorium, Kent; Llangwyfan Hospital, Denbigh; Mount Pleasant Hospital, Middlesex; North Middlesex Hospital; R. A. F. Hospital, Wroughton; Robroyston Hospital, Glasgow; Romsley Hill Sanatorium, Worcestershire; Royal Victoria Hospital, Edinburgh; St. Albans City Hospital; St. Helen's Hospital, Ipswich; St. Helier Hospital, Surrey; St. Stephen's Hospital, London; St. Wulstan's Hospital, Worcestershire; Southfield Sanatorium, Edinburgh; Sully Hospital, Glamorganshire; West Heath Sanatorium, Birmingham; Woodend Hospital, Aberdeen; Yardley Green Hospital, Birmingham.

Physicians.—Drs. P. G. Arblaster, G. P. Bardsley, D. Bell, R. W. Biagi, W. M. Borthwick, L. E. Burkeman, J. A. Chamberlin, C. W. Clayson, R. C. Cohen, A. H. C. Couch, Wing Commander I. R. Cran, Professor J. W. Crofton, Drs. V. Davies, V. F. Dawkins, M. K. Dhole, T. A. Watkin Edwards, W. J. Ferraby, H. M. Foreman, P. Forgacs, M. A. Foulis, R. Fraser, M. A. Gallagher, J. E. Geddes, I. W. B. Grant, L. J. Grant, W. C. Harris, H. F. Harwood, M. Hemming, E. V. Hess, J. A. Hill, F. Hodgkiss, N. W. Horne, J. V. Hurford, G. Penrhyn Jones, R. Sinclair Kennedy, G. M. Lewis, G. M. Little, T. W. Lloyd, L. C. Lum, G. R. W. N. Luntz, Lieutenant-Colonel J. Mackay-Dick, Dr. G. R. McNab, Captain S. Marks, Drs. A. T. Mason, K. Murray, W. A. Murray, Hayden J. Partington, A. C. P. Ritchie, J. T. Nicol Roe, H. J. T. Ross, I. D. Ross, J. D. Ross, F. A. H. Simmonds, Flying Officer A. Simpson, Drs. J. Morrison Smith, C. J. Stewart, P. Stradling, G. J. Summers, J. Sumner, D. Teare, H. E. Thomas, O. F. Thomas, B. C. Thompson, Sir Geoffrey S. Todd, Drs. H. J. Trenchard, F. W. A. Turnbull, L. R. West, W. F Wheeler, E. H. Williams, D. van Zwanenberg, and the consultant staff of Brompton Hospital (registrar, R. N. Johnston).

Bacteriologists and Pathologists.—Drs. C. S. Anderson, D. F. Barrowcliff, G. Blowers, D. M. H. Cogman, R. T. Cooke, J. E. Craik, P. B. Crone, J. C. Dick, Professor A. W. Downie, Drs. J. M. Dunbar, W. J. Godden, T. E. W. Goodier, W. I. Gordon, J. F. Heggie, E. D. Hoare, Captain C. H. Jones, Drs. E. R. Jones, P. Kidd, M. Laidlaw, G. Laws, J. T. A. Lloyd, A. Macdonald, J. Marks, P. H. Martin, A. Messer, D. A. Mitchison, E. Nassau, J. W. Nicholas, W. H. A. Picton, Squadron Leader J. S. Porterfield, Drs. I. A. Purdie, K. Rafinski, R. W. Riddell, J. M. Robertson, B. R. Sandiford, F. E. T. Scott, A. G. Signy, T. Skeoch, J. Smith, P. J. Taylor, W. K. Taylor, A. T. Wallace, R. F. Welch, W. Whitelaw. The Laboratory Subcommittee met under the chairmanship of Professor R. Cruickshank.

Dr. E. H. Bailey, Southern Group Laboratory, supplied culture medium where desired. Dr. D. A. Mitchison's laboratory, Postgraduate Medical School of London, served as reference laboratory for drug-resistance tests. Some of the P.A.S. sensitivity tests for the Scottish centres were undertaken by Dr. A. T. Wallace.

The above cannot be a comprehensive list of all the doctors who have contributed to the results reported here, nor has it been possible to name the many laboratory technicians who have done detailed and valuable work. The Tuberculosis Chemotherapy Trials Committee expresses its thanks to all members of hospital staffs who have assisted in the investigation, particularly for their willing response to the urgent requests for information for inclusion in this report.

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M. CANIS RINGWORM AND LOSS OF SCHOOLING

BY

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Cases of ringworm of the scalp produced by the two commonest pathogens, *Microsporum canis* and *M. audouini*, continue to be grouped together as one condition from the point of view of treatment. This is unfortunate. *M. canis* ringworm differs from the *M. audouini* type in being amenable to simpler measures of treatment and in being less contagious. Further, it can be demonstrated that there is no valid reason for excluding *M. canis* cases from school. In the treatment of *M. audouini* ringworm, *x*-ray epilation is unquestionably the correct procedure, and if it is not carried out the child may continue with the complaint until puberty is reached. As the technique of epilation improves, so do the risks inherent in its use diminish.

In common with others treating ringworm of the scalp, I have experienced the following difficulties. There has been an occasional case of incomplete regrowth of hair; cases in which a marked inflammatory reaction resulted, necessitating incision of sterile abscesses (Fig. 1); and cases in which the first epilation failed to eradicate the infection. Occasionally an anaesthetic has been necessary in toddlers. After *x*-ray epilation a good regrowth of hair has taken six months in boys and up to a year in girls.

Scalp ringworm caused by *M. canis* need never be treated by *x*-ray therapy, the following measures of treatment being effective in all cases. The scalp is clipped and the hair kept short, a linen cap is worn constantly, and a simple fungicidal ointment is applied daily. The mildest fungicides are effective, and Whitfield's ointment is adequate. Far stronger fungicides and rubefacients are tried from time to time in cases of *M. audouini* ringworm, but, as yet, no completely effective application has been found. There is no justification for their use in *M. canis* ringworm.

Sharp (1951) described his treatment of 120 cases of *M. canis* ringworm of the scalp (*M. audouini* ringworm is extremely rare in Australia). He used fungicidal treatment only, and the average time taken for cure was 13 weeks. In the subsequent discussion it was apparent that many dermatologists still use *x*-ray epilation in *M. canis* cases simply because by this method it is possible to get the child back to school in about six weeks.

Distinction Between Types

M. canis and *M. audouini* ringworm cases may be distinguished with reasonable accuracy clinically but only with certainty on culture. It is essential to know which type is endemic locally. For many years a focus of *M. audouini* scalp ringworm has existed in the Blackwood area of Monmouthshire, but practically none of this type of ringworm has been encountered in Newport, 12 miles distant. Of the ringworm cases in the Blackwood area, 91 out of 94 cases have been of *M. audouini*, and in the Newport area out of 32 cases only one has been produced by *M. audouini*.

There are other factors which enable one to make a clinical diagnosis of *M. canis* ringworm. Local tissue reactions are usually more pronounced and there may be erythema, papulation, or even kerion. This distinction, however, is not entirely reliable, and, exceptionally, *M. audouini* cases produce inflammatory reactions (Fig. 2). There is usually a history of an infected puppy or kitten