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THE TREATMENT OF PULMONARY TUBERCULOSIS WITH ISONIAZID

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

In February, 1952, preliminary announcements were made in the American press concerning the effects of isonicotinic acid hydrazide (now termed isoniazid) in clinical tuberculosis. The announcements were followed by medical statements concerning the experimental and clinical evidence of this drug's action on tuberculous infection. In view of the impressive nature of the evidence, the Medical Research Council appointed a Tuberculosis Chemotherapy Trials Committee to plan trials of the new drug, and selected hospitals were invited to co-operate. In March a clinical trial in pulmonary tuberculosis was begun under the auspices of the Committee. The isoniazid used for the trial was supplied as "nydrazid" by E. R. Squibb and Sons.

At the suggestion of Professor Bradford Hill, it was decided from the outset that observations would be returned monthly from the co-operating hospitals and analyses of results made from week to week, so that important evidence could become rapidly available. The following is the first interim report to be made on the trial, which is still in progress.

The work reported here was carried out in 39 hospitals; the list of hospitals, and the names of the co-operating clinicians and pathologists, are given at the end of the report. The trial was co-ordinated by Drs. Marc Daniels and Wallace Fox, of the Council's Tuberculosis Research Unit; they are also responsible for the analysis of results and preparation of the report, with statistical advice and assistance from Professor Bradford Hill and Dr. Ian Sutherland, of the Council's Statistical Research Unit. *X*-ray assessments were made by Drs. L. G. Blair and G. Simon.

Plan and Conduct of the Trial

Thanks to experience acquired in the first controlled trials of chemotherapy in tuberculosis (Medical Research Council, 1948, 1950, 1952), it was possible to organize the present trial rapidly, though on somewhat different lines from its predecessors. It was decided that the basic principle should remain the same—namely, the comparison of results in different treatment groups to which cases had been randomly allocated, the groups being observed concurrently. It was also decided that the effectiveness of the new drug should be measured against that of the best known chemotherapy—namely, streptomycin plus P.A.S. On the other hand, certain features of the new drug called for changes from the procedures previously employed. The drug was easily manufactured, and obviously would soon become widely available; and it was easier to administer than the other known anti-tuberculosis drugs. These factors, added to the striking results reported from America, would almost certainly lead to extensive use of the drug within a short time. It was essential, therefore, that information concerning its efficacy be obtained rapidly. To this end, the results had to be constantly reviewed as they became available, and the number of cases had to be much larger than in the previous trials.

These large numbers were reached by enlisting the co-operation of many more areas and hospitals than had been concerned in the previous trials, and by including several different types of case. These are described below.

After acceptance for the trial, the determination of the treatment for each case was made by reference to prearranged lists based upon random sampling numbers (drawn up in the Statistical Research Unit for each of the subgroups mentioned later and for each hospital); for some of the large hospitals, series of sealed envelopes were prepared by the Tuberculosis Research Unit from these lists, so that the treatment allocated could be determined on the spot; for the others, and for all cases in Group 1 (described below), the treatment was indicated from lists held confidentially by the Tuberculosis Research Unit.

After admission to the trial, each patient was kept under observation for at least one week before the allotted treatment was begun; during that week all the prescribed preliminary examinations were made. Clinical observations were entered on standard record forms designed specifically for this trial. For each case, at the end of one month after the beginning of treatment, the clinician sent to the Tuberculosis Research Unit a report giving the previous history of the case, the results of examination on admission and at the end of one month, and his assessment of the patient's progress. Subsequently, he sent reports on the patient's condition at two months and at three months; later reports will be due at six months. These reports were made on forms sent to the clinicians a week before the monthly examination of a patient was due. The regularity and promptitude with which these forms have been returned have made possible a continual analysis since the end of the first month after the start of the trial. At the end of three months' treatment the chest *x*-ray films were sent to the Tuberculosis Research Unit for independent assessment. The results for the 331 patients whose treatment for the trial started before June 1, 1952, and who, therefore, by the end of August, 1952, had completed at least three months' treatment, were considered sufficiently important to warrant this interim report.

Type of Case

Basic requirements for all cases before acceptance were laid down as follows: (1) At the start of treatment the case must be bacteriologically (T.B.) positive; there must be either a positive direct smear from a sputum specimen taken within

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the previous two weeks, or a positive culture derived from a specimen taken not more than two months previously. (2) At the start of treatment 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. (4) The patient must not be undergoing pneumoperitoneum, nor have any form of collapse therapy on the side of the lesion requiring treatment, and must be unlikely to require induction of collapse therapy within the ensuing three months. (Postural rest was not considered collapse therapy for the purpose of these trials.)

A small minority of cases admitted did not conform entirely with the bacteriological requirements, but are nevertheless included in the analysis, and are referred to in the section on "Bacteriology."

Cases satisfying these requirements were admitted to the trial in one of three main 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 plus P.A.S.

Under these three headings, eight subgroups were defined as follows: (1A) Bilateral lesions; age 15–30. (This subgroup corresponds to the definition of cases admitted to the earlier chemotherapy trials.) (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. (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.

It was realized that there would be some overlap between Groups 2 and 3, as well as between the subgroups of Group 2.

Intake of Cases

Group 1.—Letters were sent, by courtesy of the regional hospital boards, to chest physicians of areas served by the co-operating hospitals; they were asked to submit to the Tuberculosis Research Unit particulars and *x*-ray films of cases that appeared to conform to the definition of acute cases in Group 1. Each case submitted was considered by a central panel of clinicians; if accepted, and if not already in one of the co-operating hospitals, arrangements were made for admission of the patient within two weeks.

Groups 2 and 3.—Cases for these groups were selected by physicians of the co-operating hospitals, without reference to the Tuberculosis Research Unit.

The first case was admitted to the trial on March 29, 1952.

Treatment

For the initial stage of the trial, now reported, the Committee decided that the main comparison should be between streptomycin plus P.A.S. (SP) on the one hand, and isoniazid alone (H) on the other. In Group 3 (chronic forms not expected to respond to chemotherapy) a third treatment was introduced—streptomycin plus isoniazid. The principal object of this was to determine the effect of this combination on bacterial sensitivity to the drug. This third treatment was introduced in all groups and subgroups at a later stage, but it is not referred to again (except in the Discussion) in this interim report, which deals essentially with the comparison between streptomycin plus P.A.S. and isoniazid.

The dosage of the drugs 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 tablets 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.)

As previously stated, the treatment of each patient started at the end of a preliminary observation week, during which all initial examinations were made; it was continued for three months. It was recommended that during this period the only treatment to be given, apart from bed-rest, should be the chemotherapy prescribed for the trial, except, of course, where other treatment was considered urgently necessary for the patient. Each patient would be observed for the trial for a total period of six months; the present interim analysis, however, is concerned only with the first three months.

Number of Patients in the Trial

Table I sets out the number of cases for which treatment started before June 1, 1952, excluding 22 cases withdrawn from the trial and the 11 cases in Group 2B (see below).

TABLE I.—*Number of Cases Whose Treatment in the Trial Started Before June 1, 1952*

		Treatment		All Cases
		Streptomycin plus P.A.S.	Isoniazid	
Group 1. Acute rapidly progressive pulmonary tuberculosis of recent origin	1A. Bilateral; ages 15–30	17	23	40
	1B. Bilateral; other ages	11	11	22
	1C. Unilateral; all ages	26	17	43
	Total ..	54	51	105
Group 2. Other forms of pulmonary tuberculosis suitable for chemotherapy	2A. Chronic, with recent spread	34	39	73
	2C. Other forms (excluding primary disease)	41	43	84
	Total ..	75	82	157
Group 3. Chronic forms of pulmonary tuberculosis unlikely to respond to chemotherapy	3A. Very little previous chemotherapy	9	11	20
	3B. Some previous chemotherapy but not recently	20	29	49
	Total ..	29	40	69
Total ..		158	173	331

There are in all 331 cases, of which 173 have been treated with isoniazid and 158 with streptomycin plus P.A.S. The total with acute progressive disease (Group 1) is 105, with 51 patients on isoniazid and 54 on streptomycin plus P.A.S.

Exclusions

As previously stated, the totals in Table I do not include the Group 2B cases, nor 22 other cases which were admitted to the trial before June 1, 1952.

There were 11 Group 2B cases (primary tuberculosis with manifest recent lesions)—six on isoniazid and five on streptomycin plus P.A.S. The reason for their exclusion from the present analysis is that their numbers are too few to be of significance as a separate group, while their inclusion in the totals would merely complicate the figures, since five were children under the age of 7.

The 22 cases excluded from the remaining groups were as follows: (*a*) Five cases (two on streptomycin plus P.A.S., three on isoniazid) were excluded after the allocation of, but prior to starting, treatment—namely: two patients died before starting treatment (one SP, one H); one refused to be admitted to sanatorium (H); one refused treatment (SP); one, when admitted to sanatorium, was found to have had streptomycin 1 g. daily for the preceding four weeks (H). (*b*) Seventeen cases (11 SP, 6 H) were excluded after treatment had begun for the following reasons:

Six Patients on Isoniazid.—Four discharged against medical advice; one found to have a carcinoma of the bronchus, proved on biopsy; one found to have had four months' previous chemotherapy up to within a month of entering the trial.

Eleven Cases on Streptomycin plus P.A.S.—Two discharged against medical advice; two refused further treatment and were discharged; four showed severe intolerance to P.A.S. (in one of these, a diabetic, the vomiting produced by P.A.S. precipitated ketosis); two showed intolerance to streptomycin; one was intolerant to both streptomycin and P.A.S.

It may clearly be argued that the cases showing severe toxic reactions, apparent only in the SP groups, should be retained in the analysis, since they were failures with this particular treatment. They were, however, few in number (7 in 165), and have, for the time being, been excluded. It must be stressed also that many patients intolerant to P.A.S. or streptomycin can be desensitized.

Two patients discharged against medical advice but who had completed two months' treatment have been excluded from Tables III to VII and Table X. One whose treatment was switched from H to SP at the end of the second month has been included throughout as an H patient.

Toxicity

Toxicity of Streptomycin and P.A.S.

Apart from the seven cases just referred to, in which treatment had to be stopped, there were a number of slighter toxic reactions in the patients given streptomycin plus P.A.S. which, although troublesome and sometimes worrying, did not interfere unduly or more than temporarily with the prescribed dosage of chemotherapy. Since the literature on this subject is already adequate, an analysis of these reactions is not presented here.

There was, on the other hand, only one patient in whom treatment with isoniazid was stopped, and he had completed two months of treatment before this was done. Details of this case are given under the heading "Toxicity of Isoniazid." It is noteworthy that interference with the prescribed isoniazid regime was made in only two cases.

Toxicity of Isoniazid

In confirmation of other reports (Elmendorf *et al.*, 1952) toxicity with isoniazid has, so far, been a very minor problem. Of the 173 patients considered in this analysis, 107 were reported to have had no toxic manifestations whatsoever throughout the three-months period of treatment.

Drowsiness was reported in 13 patients (8%): 10 in the first month alone, one in the second month alone, one in the second and third months of treatment, and one for the full three months of treatment.

The deep reflexes were increased at some time during treatment in 23 patients (13%): 12 in the first month, three in the second month, two in the third month, two in the first and second months, three in the second and third months, and one over the full three months of treatment.

Tremor of the limbs was reported in 21 cases (12%): nine in the first month, four in the second month, two in the third month, one in the first and third months, four in the second and third, and one for the whole three months.

Twitching of the legs was reported in two cases, both in the third month.

Disturbances of micturition were reported in three cases. The most striking was in a patient who had difficulty in initiating micturition for the whole of the three months, starting a few days after the commencement of the isoniazid therapy. The initiation of micturition usually took 10 minutes in this patient. Another patient had a little difficulty in initiating micturition in the second month, and one patient had increased frequency in the third month.

There were four cases of *"nervous" reaction.* One patient complained of nausea and feeling nervy, another had abdominal discomfort and a feeling of fright, one patient had dizziness for nearly two weeks, the symptoms in each of these cases being limited to the first month. In one patient isoniazid was stopped two months after the beginning of treatment because the patient was restless, irritable, had marked tremor of the hands and occasional spasmodic jerks and tics of the face and limbs, and finally had night wandering. This was the one patient, referred to above, in whom no attempt was made to resume therapy. The symptoms gradually disappeared after treatment was stopped.

Nine cases of *constipation* were reported, but in no case was it severe or of long duration. *Transient flushing of the face* was reported in three cases.

In view of published reports of *haemoptysis* in patients on isoniazid, special inquiry was made into this. Seven patients were reported as having coughed up blood—one in the first month, four in the second, and two in the third. Two of them had frank haemoptysis; it was severe in one.

Skin disorders were reported in four cases. One patient had pruritus of the legs and head in the second and third months. One patient had slight generalized desquamation of the skin in the third month, whilst another had desquamation of the hands for one week in the first month. There was one case of severe herpes zoster in the second month.

One patient, after a week of epigastric pain and vomiting, became slightly jaundiced just two months after starting treatment. The jaundice was associated with excess urobilin in the urine and rather pale stools. The patient gave a history of intolerance to fats. The possibility of toxicity was considered, and the isoniazid was stopped for two days until the diagnosis of stone in the common bile duct was established. Another patient became jaundiced at the end of the first month of treatment. The clinical and biochemical features were in keeping with a diagnosis of infective hepatitis, and as there was a small outbreak in the hospital at that time it is concluded that isoniazid can be absolved from blame.

When assessing the incidence and significance of these so-called "toxic reactions" certain features should be considered. The abnormalities reported varied very much from hospital to hospital, according to the importance attached to them by individual clinicians. Further, it is likely that, as the weeks went by and no serious toxicity was encountered, minor departures from normality, such as increased deep reflexes, were less assiduously looked for; this is the impression gained at this stage from a study of the case reports. Also, it is by no means certain that all, or even many, of the abnormalities recorded can be attributed to isoniazid, as, for example, the haemoptysis. How often the observed events were merely coincidental cannot be assessed. The clinicians have rightly, when in doubt, ascribed abnormalities to isoniazid toxicity.

Summarizing, the information can be held to show that isoniazid has shown little toxicity in the dosage used over a three-months period. Clearly, that does not rule out the possibility of toxicity from longer-term treatment, from repeat courses, or from a larger daily dosage.

Certain of the centres have undertaken routine blood and liver-function tests. The results of these will be reported later.

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. It can be seen from this table that, judging by the factors listed, the SP and H cases in each group have a similar distribution of severe and less severe illness, with the exception that, judging from general condition and sedimentation rate, in the acute group (Group 1) the SP cases were on the average rather less ill than the H cases. None of the differences is greater than would be expected by chance.

Results at the End of Three Months

Mortality

There were 4 deaths among the 331 cases (1.2%) during the three-months period of observation—one in 173 H and 3 in 158 SP patients. The H patient (in group 2A) died of congestive cardiac failure secondary to chronic cor pulmonale on the first day of treatment, and therefore cannot be regarded as a failure of isoniazid therapy. Similarly, 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 dying from tuberculosis.

There remained two SP patients (from Groups 2A and 3A) who died of their tuberculous disease 63 days and 32 days respectively after the start of treatment. Both had far advanced disease on admission to the trial. In addition, the Group 3A patient was found at post-mortem examination to have had early macroscopic amyloid disease of the liver and spleen. These two patients must be regarded as failures of the streptomycin plus P.A.S. treatment.

General Condition

The assessment of changes in the general condition was made by the clinicians in charge of the patients, and constituted an overall impression of the patient's progress based on the clinical observations, and on the patient's appearance and feeling of well-being, or lack of it. It will be seen from Table III that most of the patients in each treatment group were regarded as better in their general condition, 117 of

TABLE II.—*Condition on Admission*

		Group 1		Group 2		Group 3		All Cases	
		SP	H	SP	H	SP	H	SP	H
		No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %
Total cases		54 100	51 100	75 100	82 100	29 100	40 100	158 100	173 100
General condition	Good	8 15	4 8	22 29	20 24	10 34	8 20	40 25	32 18
	Fair	27 50	22 43	29 39	46 56	11 38	20 50	67 42	88 51
	Poor	19 35	25 49	24 32	16 20	8 28	12 30	51 32	53 31
Average evening temperature in pre-treatment week*	Afebrile	9 17	12 24	39 52	42 51	14 48	22 55	62 39	76 44
	Under 99° F.	18 33	18 35	24 32	23 28	13 45	13 33	55 35	54 31
	99–99·9° F.	11 20	9 18	6 8	10 12	2 7	3 8	19 12	22 13
	100° F.+	16 30	12 24	6 8	7 9	0 0	2 5	22 14	21 12
Sedimentation rate (Westergren 200 mm. reading at 1 hour)	0–10	5 9	2 4	11 15	9 11	4 14	3 8	20 13	14 8
	11–20	5 9	3 6	14 19	17 21	5 17	11 28	24 15	31 18
	21–50	19 35	14 27	30 40	33 40	12 41	15 38	61 39	62 36
	51+	25 46	32 63	20 27	23 28	8 28	11 28	53 34	66 38
Extent of cavitation†	Nil	4 7	10 20	18 24	13 16	2 7	4 10	24 15	27 16
	1-plus	16 30	11 22	21 28	26 32	4 14	4 10	41 26	41 24
	2-plus	29 54	24 47	26 35	31 38	15 52	14 35	70 44	69 40
	3-plus	5 9	6 12	10 13	12 15	8 28	18 45	23 15	36 21

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

Group 1—Acute rapidly progressive pulmonary tuberculosis of recent origin. *Group 2*—Other forms of pulmonary tuberculosis suitable for chemotherapy. *Group 3*—Chronic forms of pulmonary tuberculosis unlikely to respond to chemotherapy.

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	SP	54 101	16 30	35 65	2 4	1 2	0 0	0 0
	H	50* 100	26 52	19† 38	5 10	0 0	0 0	0 0
Group 2	SP	75 100	19 25	32 43	21 28	2 3	0 0	1 1
	H	82 100	22 27	48 59	9 11	2 2	0 0	1 1
Group 3	SP	29 100	0 0	15 52	12 41	0 0	0 0	2 7
	H	39* 100	6 15	19 49	11 28	2 5	1 3	0 0
All cases	SP	158 100	35 22	82 52	35 22	3 2	0 0	3 2
	H	171 101	54 32	86 50	25 15	4 2	1 1	1 1

* One patient discharged against medical advice in third month and excluded from the table. † One patient switched from isoniazid to streptomycin plus P.A.S. at the end of the second month and included in this figure.

158 SP patients (74%) and 140 of 171 H patients (82%) showing some improvement. The corresponding figures for Group 1—the acute rapidly progressive disease—are 51 out of 54 SP patients and 45 out of 50 H patients; thus only 8 of these 104 patients failed to improve clinically during the three months, and only one actually deteriorated (an SP patient). On the whole the figures suggest rather more favourable results in the group on isoniazid, but the differences are not pronounced.

Weight Changes

The weight changes of the patients are set out in Table IV, and here those on isoniazid have done strikingly better: the difference in the average amount of gain is statistically highly significant. It will be seen that 115 out of 168 H patients (68%) gained 7 lb. (3.18 kg.) or more in weight in the three-months period, compared with 62 of 152 SP patients (41%). This greater increase in weight in the isoniazid group can be further illustrated by the fact that 61 of the 168 H patients (36%) gained at least a stone (6.35 kg.), compared with only 22 out of 152 SP patients (14%) (and of these latter two were pregnant). It is most striking, too, that 22 of the 49 acute (Group 1) cases on isoniazid gained at least a stone in weight (45%), compared with 11 out of the 52 on streptomycin plus P.A.S. (21%). The mean difference was similar and significant in Group 2 also, but less and not statistically significant in the chronic cases of Group 3. (Here and elsewhere statistical significance has been taken at the 5% level. A number of the differences are significant at the 1% level.)

Temperature

For the purpose of analysis, patients were regarded as initially afebrile if their evening temperature was below 99° F. (37.2° C.) on every day in the week of preliminary observation. The same definition was applied to the last week of the third month of treatment. For each febrile patient the average evening temperature was calculated for the pre-treatment week and for the final week of treatment. Table V shows the number who, being febrile at different levels in the pre-treatment week, were afebrile at the end of three months. It will be seen that of 96 febrile SP patients 64 (67%) were afebrile at the end of three months, compared with 53 of 95 H patients (56%). In the acute group, 29 out of 45 SP patients (64%) and 26 out of 38 H patients (68%) became afebrile. In neither of these comparisons is there a statistically significant difference.

Of 62 SP patients who were afebrile in the pre-treatment week, seven were febrile at the end of the third month. The corresponding figures for the H group are 6 out of 76. In only one of these (an SP case) was there high pyrexia; the others had only occasional evening temperatures above 99° F. (37.2° C.).

Sedimentation Rate

Table VI sets out the changes in sedimentation rates. In all three groups and in both treatment series the B.S.R. tended to fall, though in few patients with an original B.S.R. of over 50 did the figure fall to normal on either form of treatment. Thus in 52 SP patients with an initial B.S.R. of more than 50 it fell to 10 or less in only five cases.

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

	Treatment	Total Weighed at 3 Months		Weight Gain								No Change		Weight Loss				Average Gain in Weight per Patient (lb.)
				21 lb.+		14–20 lb.		7–13 lb.		Less than 7 lb.				Less than 7 lb.		7–13 lb.		
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	
Group 1	SP	52	101	3	6	8	15	17	33	16	31	4	8	3	6	1	2	7·9
	H	49	100	8	16	14	29	15†	31	8	16	0	0	2§	4	2	4	12·5
Group 2	SP	73	99	4*	5	6*	8	17	23	26	36	6	8	13	18	1	1	5·4
	H	80	101	11	14	20	25	25	31	15	19	3	4	6	8	0	0	11·7
Group 3	SP	27	100	1	4	0	0	6	22	16	59	2	7	1	4	1	4	4·9
	H	39	101	0	0	8	21	14	36	13	33	0	0	3	8	1‡	3	7·5
All cases	SP	152	99	8	5	14	9	40	26	58	38	12	8	17	11	3	2	6·2
	H	168	100	19	11	42	25	54	32	36	21	3	2	11	7	3	2	11·0

* One in each group pregnant. † One patient not weighed before the end of the first month. ‡ Lost 11½ lb. in the first two months; too ill to be weighed at end of three months. § Treatment switched in one case from isoniazid to streptomycin plus P.A.S. after two months. ‖ For three other SP cases and four H cases the weights at three months are not available. Also three SP patients and one H patient had died.

Group 1—Acute rapidly progressive pulmonary tuberculosis of recent origin. *Group 2*—Other forms of pulmonary tuberculosis suitable for chemotherapy. *Group 3*—Chronic forms of pulmonary tuberculosis unlikely to respond to chemotherapy.

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

	Treatment	Average Evening Temperature in Pre-treatment Week						All Cases Febrile in Pre-treatment Week		
		Under 99° F.		99° F.–99·9° F.		100° F.+				
		Total	Number Afebrile at Three Months	Total	Number Afebrile at Three Months	Total	Number Afebrile at Three Months	Total	Afebrile at Three Months	
									No.	%
Group 1	SP	18	11	11	8	16	10	45	29	64
	H	17*†	12†	9	7	12	7	38	26	68
Group 2	SP	24	17	6	2	6	5	36	24	67
	H	23	11	10	5	7	4	40	20	50
Group 3	SP	13	10	2	1	0	0	15	11	73
	H	12*	6	3	1	2	0	17	7	41
All groups	SP	55	38	19	11	22	15	96	64	67
	H	52	29	22	13	21	11	95	53	56

* One was discharged in the third month, and the temperature record is not available. † One patient switched from isoniazid to streptomycin plus P.A.S. at the end of two months and included here.

Similarly, in 64 H patients with a B.S.R. of more than 50 it fell to normal limits in only five. Furthermore, the number of patients with a B.S.R. of more than 20 that fell to normal (10 or less in the three-months period), whether on streptomycin plus P.A.S. or isoniazid, was very limited. Thus in only 25 of 112 SP patients (22%) did the B.S.R. fall to normal in the three months, and in only 25 out of 124 H patients (20%). The B.S.R. rose from normal in 3 of 19 SP patients, and 1 of 14 H patients.

Changes in Radiological Appearance During Period of Trial

Table VII sets out the radiological changes at the end of the first three months, as assessed by an independent reading of full-plate chest *x*-ray films by two radiologists unaware of the treatment in any case. In assessing improvements or deterioration three degrees were allowed—namely, 1-plus, 2-plus, or 3-plus, and 1-minus, 2-minus, or 3-minus. Of 158 SP patients 104 (66%) showed radiological improvement, compared with 56% of 171 H patients. The improvement was more than 1-plus in 29% of SP cases and 26% of H cases; taking the acute Group 1 alone, 2-plus or 3-plus improvement was seen in 37% of SP cases and 40% of H cases. There was radiological deterioration in 10 cases and one death on isoniazid, compared with radiological deterioration in one case and three deaths on streptomycin plus P.A.S. Of the 11 patients who deteriorated radiologically the deterioration in nine was classed as 1-minus—that is, comparatively slight. Only one patient, on isoniazid, was recorded as having 3-minus deterioration: this degree of deterioration was recorded arbitrarily, because the radiograph for this patient showed 2-minus deterioration at two months, but he was too ill to be *x*-rayed at three months, and died the next day. It is interesting to note that under both treatments the proportion improving was higher in the more acutely ill patients (Group 1) than in the others: in Group 1 improvement was observed in 76% of SP cases and 70% of H cases; in Group 2 the percentages were 65% for SP cases and 56% for H cases; in Group 3 the percentages were 48% for SP and 36% for H. It will be seen that in each group the frequency of radiological improvement was less on the treatment with isoniazid, but in each group and in the totals the differences are below the level of statistical significance.

Bacteriology

Because of the time needed to obtain results of cultures from sputum specimens, and to measure drug sensitivity tests on those cultures, it is not possible in this present analysis to report on the results for all cases at the end of three months' treatment. However, the available data are of sufficient interest to warrant a preliminary analysis based on results after one and two months of treatment. Data on isoniazid sensitivity are presented also for 21 cases at the end of three months.

Bacterial Content of Sputum

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

A requirement for all cases was that at the start of treatment they must be bacteriologically (T.B.) positive. How-

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*

Group	Treatment	Sedimentation Rate in the Pre-treatment Week						All Cases with Raised Sedimentation Rate		
		11–20		21–50		51 and Over				
		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.	%
1	SP	5*	4	19	5	25	4	49	13	*27*
	H	3	2	13	5	32	3	48	10	*21*
2	SP	14	10	29	14	20*	1	63	25	*40*
	H	17	10	32	11	23	2	72	23	*32*
3	SP	5	4	12	1	7	0	24	5	*21*
	H	11	2	15	4	9	0	35	6	*17*
All cases	SP	24	18	60	20	52	5	136	43	*32*
	H	31	14	60	20	64	5	155	39	*25*

* One patient was menstruating when this reading was taken.

Group 1—Acute rapidly progressive pulmonary tuberculosis of recent origin. *Group 2*—Other forms of pulmonary tuberculosis suitable for chemotherapy. *Group 3*—Chronic forms of pulmonary tuberculosis unlikely to respond to chemotherapy.

TABLE VII.—*Changes in Radiological Appearance in First Three Months*

	Treatment	Total		Improvement						No Change		Deterioration						Deaths	
				3-plus		2-plus		1-plus				1-minus		2-minus		3-minus			
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Group 1	SP	54	*100*	5	*9*	15	*28*	21	*39*	13	*24*	0	*0*	0	*0*	0	*0*	0	*0*
	H	50*	*100*	3	*6*	17	*34*	15	*30*	12	*24*	2	*4*	1†	*2*	0	*0*	0	*0*
Group 2	SP	75	*100*	2	*3*	20	*27*	27	*36*	24	*32*	1	*1*	0	*0*	0	*0*	1	*1*
	H	82	*99*	4	*5*	17	*21*	25	*30*	33	*40*	2	*2*	0	*0*	0	*0*	1	*1*
Group 3	SP	29	*100*	0	*0*	4	*14*	10	*34*	13	*45*	0	*0*	0	*0*	0	*0*	2	*7*
	H	39*	*100*	0	*0*	4	*10*	10	*26*	20	*51*	4	*10*	0	*0*	1	*3*	0	*0*
All cases	SP	158	*101*	7	*4*	39	*25*	58	*37*	50	*32*	1	*1*	0	*0*	0	*0*	3	*2*
	H	171	*101*	7	*4*	38	*22*	50	*29*	65	*38*	8	*5*	1	*1*	1	*1*	1	*1*

* One patient discharged against medical advice in the third month and not *x*-rayed. † 2-minus deterioration at two months, then switched to streptomycin plus P.A.S., and still 2-minus deterioration at three months.

ever, from eight cases admitted to the trial, the records show that no tubercle bacilli had in fact been isolated either in the pre-treatment week or subsequently, nor was there a pre-treatment culture available. These cases, together with two who gave a negative result in the pre-treatment week but a positive result subsequently, are not shown in Table VIII, which sets out the results, in the first and second months, for the cases positive in the pre-treatment week. Where more than one examination was recorded for a case within a month, the "most positive" of the results was selected for the analysis in Table VIII—for example, a case with one specimen positive on culture only and another on direct examination was recorded as being positive on direct examination.

Analysis of the results from specimens taken in the pre-treatment week shows a similar distribution in both treatment series: 18% of SP cases and 16% of H cases were positive on culture only.

For the analysis of data of the first and second months, results have been included only for those specimens from which there had been full time for a culture, if required, to develop—that is, at least eight weeks; otherwise the results, for instance, in the second month would have been unduly weighted by positive results, since specimens negative on direct examination and with no culture yet available would not be included.

In the first month the results were negative on smear and culture in 25% of SP cases and 18% of H cases; the difference is not statistically significant. In the acute Group 1, 9 of 46 SP cases were negative (20%), and 11 of 46 H cases (24%). In Groups 2 and 3 the percentage negative was 30% and 24% respectively for the SP cases, and 17% and 12% for the H cases. If we consider also the numbers negative on smear (whether positive or negative on culture), the results show a marked improvement over the results for the pre-treatment week: the percentage smear-negative was 44% for the SP cases and 43% for the H cases, compared with the original levels of 18% and 16%.

In the second month the results so far available are as follows: 26% of 94 SP cases had become negative, both on smear and on culture, against 23% of 102 H cases; the difference is not significant. If we consider the proportion negative on direct smear (whether positive or negative on culture), the figure is 51% for the SP-treated and 46% for the H-treated.

Streptomycin Sensitivity

Strains isolated from the SP patients before admission, and subsequently at least once a month, were tested for streptomycin sensitivity. The technique employed was similar to that in the previous trials.

It was required that at the start of treatment the tubercle bacilli must not, so far as could be known, be either streptomycin-resistant or P.A.S.-resistant, the object of this requirement being that, if the case were allocated to the SP group, effectiveness of chemotherapy should not be hindered by pre-existing drug resistance. In fact, for many cases the drug sensitivity was not known at the time of starting treatment. In 117 patients for whom the streptomycin sensitivity results for pre-treatment specimens are now available, the bacilli were streptomycin-sensitive in 112 and resistant in five. Analysis of the radiological assessment of four of these five SP cases at three months (one result not yet available) shows that three showed 2-plus improvement, but the other showed deterioration (1-minus). This patient was in Group 2C; there was no other evidence of deterioration except that at the end of the third month her temperature was occasionally over 99° F. (37.2° C.), whereas she was afebrile on admission.

TABLE VIII.—*Presence of Tubercle Bacilli*

	*Total Cases	"Positive" Direct Examination	"Scanty Positive" Direct Examination†	Direct Examination Negative—Culture Positive	Direct Examination and Culture Negative
In pre-treatment week:					
Group 1 .. .. SP	52	39	6	7	—
H	49	44	1	4	—
Group 2 .. .. SP	67	47	9	11	—
H	77	52	9	16	—
Group 3 .. .. SP	25	15	2	8	—
H	33	24	3	6	—
	No. %	No. %	No. %	No. %	No. %
Total .. .. SP	144 100	101 70	17 12	26 18	— —
H	159 99	120 75	13 8	26 16	— —
During first month:					
Group 1 .. .. SP	46	21	8	8	9
H	46	15	10	10	11
Group 2 .. .. SP	63	19	12	13	19
H	71	28	10	21	12
Group 3 .. .. SP	25	11	4	4	6
H	33	18	5	6	4
	No. %	No. %	No. %	No. %	No. %
Total .. .. SP	134 100	51 38	24 18	25 19	34 25
H	150 101	61 41	25 17	37 25	27 18
During second month:					
Group 1 .. .. SP	34	7	8	13	6
H	27	4	7	8	8
Group 2 .. .. SP	44	8	13	7	16
H	52	21	9	12	10
Group 3 .. .. SP	16	6	4	4	2
H	23	9	5	4	5
	No. %	No. %	No. %	No. %	No. %
Total .. .. SP	94 101	21 22	25 27	24 26	24 26
H	102 101	34 33	21 21	24 24	23 23

* Total patients from whom specimens were examined. † Defined as follows: only a few clumps of acid-fast bacilli found after five minutes' search.

Group 1—Acute rapidly progressive pulmonary tuberculosis of recent origin. *Group 2*—Other forms of pulmonary tuberculosis suitable for chemotherapy. *Group 3*—Chronic forms of pulmonary tuberculosis unlikely to respond to chemotherapy.

Too few results of streptomycin sensitivity at one and two months were available, at the time of reporting, to warrant analysis.

Isoniazid Sensitivity

The problem of isoniazid sensitivity was one of the most important items requiring study in this investigation. Preliminary laboratory investigations had indicated that untreated cultures, of tubercle bacilli contain a higher proportion of isoniazid-resistant mutants than of streptomycin-resistant mutants (Middlebrook, 1952; Hobby and Lenert, 1952); and early emergence of resistant strains clinically had already been reported (Steenken *et al.*, 1952).

Isoniazid-sensitivity tests were performed on the pre-treatment culture, and subsequently at least once a month when cultures were positive. In view of the possible difficulties of interpreting the results of these tests, it was decided to record them in some detail. A uniform technique was agreed at the beginning of the investigation by a laboratory subcommittee under the chairmanship of Professor R. Cruickshank, and this was used throughout. A loopful of bacterial suspension from the primary culture on egg medium was spread on each of a series of egg medium slopes containing graded concentrations of isoniazid (0, 0.2, 1, and 5 μg. per ml.—later also 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 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."

On analysis of the data it was found that occasional colonies (less than 20) were so often observed on the isoniazid-containing medium, both from cultures of the test organism before and during treatment, and from the standard culture, that they should probably be ignored in assessing emergence of resistance during treatment. Accordingly, in the analysis of isoniazid resistance which follows, results recording "less than 20 colonies" are classified with "no growth."

In 147 cases (of the total 173) for which isoniazid-sensitivity results are available for pre-treatment specimens, 136 showed no growth in any of the tubes containing isoniazid, and may therefore be classed as fully sensitive. In eight cases there was growth in a concentration of 0.2 μg. per ml. but not at higher concentrations, and in five of the eight growth was not seen until the four-weeks reading. In three cases there was resistance to 1 μg. per ml. but not to 5 μg. per ml. At one centre, growth of the standard H37Rv culture was observed in the concentration of 0.2 μg. per ml. but not at higher concentrations. For these reasons cultures have been designated "resistant" when growth was observed in concentrations of 1 μg. isoniazid per ml., or higher, and of "doubtful resistance" in cases of growth in a concentration of 0.2 μg. per ml. but not more. The results after one, two, and three months are shown in Table IX.

At the end of one month, cultures from 104 isoniazid-treated cases were tested. Eighty-one were sensitive (78%), 12 doubtful (12%), and 11 resistant (11%). Of the 11 resistant strains 10 were resistant only to 1 μg. per ml.

At the end of two months, tests of cultures from 58 isoniazid-treated cases are available. Seventeen (29%) were sensitive, and 11 (19%) were of doubtful resistance (3 of the 11 had not, at the time of reporting, been read at four weeks). As many as 30 of the 58 cases—that is, 52%—were now resistant. Seven of the 30 were resistant only to 1 μg. per ml. (in four growth was not observed until the reading at four weeks); 23 were resistant to 5 μg. per ml., and in 12 cases in which the test was carried to higher concentrations 11 grew at a concentration of 50 μg. per ml.—that is, were highly resistant.

Results of isoniazid-sensitivity tests at the end of three months are available for 21 cases. Only one (5%) was sensitive, and five (24%) were of doubtful resistance (four of the five had not yet been read at four weeks). Fifteen of the 21 (71%) were now resistant, 13 of them to 5 μg. or more per ml.

It is interesting to note that, apart from the proportion of definitely resistant cases increasing in successive months, the proportion of doubtfully resistant cases also increases. It seems, therefore, that, though growth in 0.2 μg. per ml. does not definitely denote resistance, it is of some significance. Secondly, in resistant cases the degree of resistance was much higher at the end of the second and third months than at the end of the first. Thirdly, of 23 cases resistant to 5 μg. or more per ml. at two months after the start of treatment, 20 showed growth at the two-weeks reading, and of the 13 corresponding cases at three months all showed growth at the two-weeks reading.

Results Related to Isoniazid Resistance

In view of the finding that bacterial resistance to isoniazid develops rapidly in a large proportion of patients, it is important to consider whether this resistance is in any way reflected in the early clinical results. So far isoniazid resistance is known to have developed before the end of the second month in 33 patients (of whom one was discharged against medical advice in the third month). The information on resistance is available at two months for 30 of these patients, and for three at one month only. Resistance seemed to develop equally frequently in each of the three disease groups.

At the foot of Table X the radiological assessments for the 32 patients with isoniazid resistance who were observed at three months are compared with those for the remaining 139 cases on isoniazid, who were not known to have become resistant (some may, in fact, have done so). The figures show decisively that the known resistant cases had a less favourable radiological assessment at the end of the three months than the remainder. Only nine (28%) of the cases

TABLE IX.—*Results of Isoniazid Sensitivity Tests*

Group:	At One Month				At Two Months				At Three Months			
	1	2	3	Total	1	2	3	Total	1	2	3	Total
Sensitive: (No growth at 0·2 μg. per ml.)	21	41	19	81	3	11	3	17	0	0	1	1
Doubtful: (Growth at 0·2 μg. per ml. but not at 1 μg.)	7	4	1	12	4	3	4	11	1	2	2	5
Resistant:												
Growth at 1 μg. per ml. but not 5	3 (1)	3	4 (1)	10 (2)	1 (1)	3 (1)	3 (2)	7 (4)	1	0	1	2
Growth at 5 μg. but not 10	0	0	0	0	0	0	0	0	1	0	0	1
Growth at 5 μg.; not tested further	0	1	0	1	5 (1)	5 (2)	1	11 (3)	1	2	3	6
Growth at 10 μg. but not 50	0	0	0	0	0	0	1	1	0	1	0	1
Growth at 50 μg.	0	0	0	0	1	6	4	11	0	4	1	5
Total resistant	3	4	4	11	7	14	9	30	3	7	5	15
Total cases tested	31	49	24	104	14	28	16	58	4	9	8	21

The figures in parentheses are cases with resistant cultures which appeared only at the 4-weeks reading; they are included in the preceding figure in each case.

Group 1—Acute rapidly progressive pulmonary tuberculosis of recent origin. *Group 2*—Other forms of pulmonary tuberculosis suitable for chemotherapy. *Group 3*—Chronic forms of pulmonary tuberculosis unlikely to respond to chemotherapy.

TABLE X.—*Radiological Assessment at Three Months Related to Clinical Condition on Entry and Isoniazid Resistance*

Clinical Condition on Entry	Isoniazid Resistance	Total Cases	Improvement 3+	Improvement 2+	Improvement 1+	No Change	Deterioration 1−	Deterioration 2−	Deterioration 3−	Death	Percentage Improved
Extent of cavitation at entry:											
3+	Known resistant	12	0	0	1	7	3	0	1	0	8
	Other cases	23	0	1	9	10	3	0	0	0	43
2+	Known resistant	16	0	1	5	10	0	0	0	0	38
	Other cases	52	2	20	14	15	1	0	0	0	69
1+ or more	Known resistant	4	0	0	2	2	0	0	0	0	50
	Other cases	64	5	16	19	21	1	1	0	1	62
General condition at entry:											
Poor	Known resistant	14	0	0	4	8	1	0	1	0	29
	Other cases	39	2	10	10	14	3	0	0	0	56
Fair or good	Known resistant	18	0	1	4	11	2	0	0	0	28
	Other cases	100	5	27	32	32	2	1	0	1	64
Sedimentation rate at entry:											
51 and over	Known resistant	14	0	0	5	6	2	0	1	0	36
	Other cases	51	3	14	16	15	3	0	0	0	65
21–50	Known resistant	14	0	1	2	10	1	0	0	0	21
	Other cases	47	2	12	15	14	2	1	0	1	62
0–20	Known resistant	4	0	0	1	3	0	0	0	0	25
	Other cases	41	2	11	11	17	0	0	0	0	59
Average evening temperature at entry:											
100° F. and over	Known resistant	6	0	0	1	2	2	0	0	1	17
	Other cases	15	0	5	6	3	1	0	0	0	73
99° F. to 99·9° F.	Known resistant	5	0	0	2	3	0	0	0	0	40
	Other cases	17	2	6	3	4	2	0	0	0	65
Under 99° F.	Known resistant	8	0	1	2	4	1	0	0	0	38
	Other cases	44	3	10	12	15	2	1	0	1	57
Afebrile	Known resistant	13	0	0	3	10	0	0	0	0	23
	Other cases	63	2	16	21	24	0	0	0	0	62
All cases	Known resistant	32	0	1	8	19	3	0	1	0	28
	Other cases	139	7	37	42	46	5	1	0	1	62

with resistant organisms showed radiological improvement, and in eight it was only slight (1-plus); 86 (62%) of the 139 other cases improved, and in more than half the improvement was 2-plus or 3-plus. Four (12%) of the resistant cases showed radiological deterioration, compared with six deteriorations and one death among the others (5%).* It is most unlikely that these differences could be due to chance.

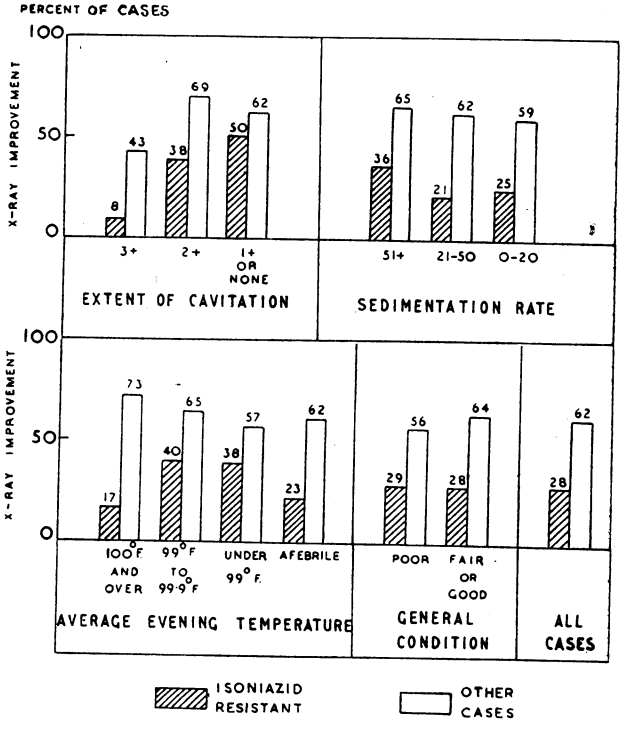
Further examination, however, shows that a high proportion of the patients in whom the bacteria became resistant were acutely ill on entry to the trial. Twenty-nine (88%) of the 33 had gross cavitation (2-plus or 3-plus), 15 (45%) had a sedimentation rate of over 50, and 14 (42%) were in poor general condition. These percentages compare with 54%, 36%, and 28% respectively among the remaining cases on isoniazid. Differences in temperature were unimportant.

These figures indicate that resistance to isoniazid developed more readily in those acutely ill on admission to the trial. The poor progress of the known resistant cases might thus be attributable to their poor clinical condition when treatment began, and not necessarily to the resistant organisms which emerged during treatment.

The point was investigated further by dividing patients whose clinical condition was similar at the outset into known resistant cases, and others, and by comparing their radiological assessments at three months. A number of such comparisons appear in Table X (and in the Diagram), the patients being grouped successively according to extent of cavitation, general condition, sedimentation rate, and temperature on entry to the trial. It appears that, in each group of patients with the same initial clinical condition, those who developed resistant strains did not fare so well as those who were not known to have become resistant. This is indicated by the percentages of patients who showed radiological improvement; these are, it will be seen, less for the known resistant cases in every comparison. (Individually the differences are greater than would be expected by chance for patients with 2-plus cavitation initially, with good or fair general condition initially, with sedimentation rates from 21 to 50 initially, and who were afebrile initially.)

*Another result received after completing the analysis shows that one of the cases "not known to be resistant" that had deteriorated had in fact developed isoniazid resistance in the second month.

Although these findings are based upon small numbers of cases, and at present incomplete information, they are very striking. Their importance is enhanced by the fact that known resistant cases have had, at this interim stage, to be compared with patients not known to be resistant. It may be expected that a proportion of the latter, as more information becomes available, will also prove to have developed bacterial resistance to isoniazid.* In the meantime their



Percentage of cases showing *x*-ray improvement after three months, related to clinical condition on entry and isoniazid resistance.

inclusion with the cases not known to be resistant may have reduced the already striking contrast between the early clinical results in patients with resistant and with sensitive organisms.

Discussion

The difficulties of clinical assessment of drugs in the treatment of tuberculosis increase with the advent of each new product. The problems were already complex at a time when no effective drug therapy was known and when a new drug could be measured against no treatment other than bed-rest; even then many errors of evaluation were made. Now it is no longer adequate to demonstrate that a new drug has some clinical value; its value relative to other known drugs must be ascertained—and ascertained with some precision. Assessment of the drug must be made either by comparing it with the most effective combination already in use, in a trial where treatment is randomly allocated as in the clinical trials of streptomycin and P.A.S. (Medical Research Council, 1948, 1950, 1952), or, if that is impossible, by observation of the new drug's effects in cases in which the most effective combination available has already failed. Clearly a new drug to-day must reach a high standard to compare with the potent action of streptomycin in combination with P.A.S.

Preliminary reports of the experimental and clinical effects of isoniazid in tuberculosis indicated that the drug was sufficiently promising to warrant large-scale clinical trial (Bernstein *et al.*, 1952; Grunberg and Schnitzer, 1952; Robitzek *et al.*, 1952). The fact that it is easily produced, and that within a short time large quantities would be generally available, made it imperative to organize the trial in such a way as to obtain a rapid answer to the main question of relative effectiveness. With the experience gained from the previous investigations it was possible to design a trial based on comparisons of treatments randomly allocated, but, in addition, to design it in such a way as to permit a continued analysis of the accumulating data. Thus any important results could be reported without delay. The trial, begun at the end of March, 1952, was extended so rapidly—38 hospitals taking part—that at the end of August, 1952, just five months later, over 300 patients had completed three months' treatment with either streptomycin plus P.A.S. or with isoniazid. Short as this period is, the results were regarded as important enough to warrant publication of the present interim report. The trial is still in progress (with over 750 cases at the time of reporting), and reports will be made later on longer-term results and on the results of combined therapy.

The present observations relate to 173 patients suffering from pulmonary tuberculosis who were treated for three months with isoniazid, and to 158 similar patients treated for the same period with streptomycin plus P.A.S. The analysis shows that in this short-term view isoniazid comes within the same range of effectiveness as streptomycin plus P.A.S. The results are summarized in Table XI. Body-weight changes are much more favourable in the patients receiving isoniazid, and in its effect on general condition clinically assessed there appears to be some advantage, though not a substantial one. On the other hand, the *x*-ray results, and the changes in temperature, in sedimentation rate, and in bacterial content of sputum, appear to be rather more favourable in the groups receiving streptomycin plus P.A.S., but the differences are not statistically significant; furthermore, in patients with acute disease of recent origin, analysis shows that these differences are smaller still or to the advantage of isoniazid (sputum conversion, temperature fall). Summarizing, except in respect of weight-gain the drug given alone does not reveal itself, at the end of three months, as any more potent than streptomycin plus P.A.S., but there is no doubt that it is remarkably effective, and an impressive addition to the list of chemotherapeutic agents in tuberculosis. Its value is enhanced by the fact that toxicity is low at the dosage used—200 mg. a day for adults—and for the period of administration, three months.

The fact that the drug is potent, that it shows a low toxicity at an effective dosage, and that it is easily administered makes it a very tempting drug to prescribe, especially for treatment outside hospital. It is therefore highly important that the question of drug resistance be fully studied. Preliminary reports (Knox *et al.*, 1952; Steenken *et al.*, 1952) have been confirmed in this trial; bacillary resistance to this drug has emerged rapidly and in a high proportion of cases. After one month some 10% were resistant; after two months 50%; after three months 70%. Furthermore, the degree of resistance was high in many cases, the proportion again increasing in succeeding months. A preliminary but detailed analysis has been made to determine if the response to treatment was affected by the development of drug resistance. Experimentally, it has been demonstrated that disease produced by isoniazid-resistant bacilli does not respond to treatment with isoniazid (Goulding *et al.*, 1952). Clinically, it is not easy to measure the effects of drug resistance, since, as found previously with streptomycin, the patients more severely ill before the start of treatment appear to run a greater risk of developing drug resistance than the others, and the more ill on the whole fare less well. However, the analysis shows clearly that, when patients of a similar pre-treatment condition are compared, those who developed drug resistance during treatment fared, as a group, less well than the others. This finding is important because of the fact that the drug has been proved clinically effective. Development of drug resistance, on the average, lessens the patient's immediate prospects of improvement; if the resistance is not reversible—and it must be emphasized that that is not known at the present stage (though reversion *in vitro* has been reported—Pansy *et al.*, 1952)—it may also affect the patient's prospects under future treatment. In addition, the widespread development of isoniazid-resistant organisms may constitute a public-health risk affecting the prospect of persons who become infected by treated patients.

These considerations, and the probability that this new drug will be even more effective clinically if development of resistance can be prevented, underline the importance of studying combinations of isoniazid with other drugs. The clinical effectiveness of isoniazid on the one hand and of streptomycin on the other may not, in combination, be additive, but if they reciprocally prevent development of drug resistance the result will certainly be a powerful combination. Here, again, the prevention of drug resistance by combination has been demonstrated in the test-tube (Pansy *et al.*, 1952; Middlebrook, 1952; Knox *et al.*, 1952), but has not yet been demonstrated clinically. The question is being fully studied in the present trial; a third

TABLE XI.—*Summary of Comparisons Between Streptomycin Plus P.A.S. and Isoniazid*

	Streptomycin plus P.A.S. %	Isoniazid %
General condition:		
Improvement 2-plus	22	32
,, 1-plus	52	50
No change	22	15
Deterioration	2	3
Death	2	1
Weight:		
Gain 14 lb. (6·35 kg.) or more	14	36
,, 7–13 lb. (3·2–5·9 kg.)	26	32
,, Less than 7 lb., or no change	46	23
Loss	13	8
Afebrile at 3 months (febrile at start)	67	56
Sedimentation rate. Fall to normal from 20+ in 3 months	22	20
Radiograph:		
Improvement 2-plus or 3-plus	29	26
,, 1-plus	37	29
No change	32	38
Deterioration	1	6
Sputum:		
Pre-treatment: Direct positive	82	84
,, Positive culture only	18	16
,, Negative	0	0
At 2 months: Direct positive	49	54
,, ,, ,, Positive culture only	26	24
,, ,, ,, Negative	26	23

treatment series, combining streptomycin and isoniazid, was introduced at an early stage and was enlarged more recently. The few results available at the time of reporting are suggestive (but can be no more than that): at the end of two months of treatment with both drugs, in 9 of 11 cases the bacilli remained sensitive to isoniazid; in one sensitivity was slightly lowered (resistance to 0.2 μg.); in one there was definite resistance. It is interesting to note that before the start of treatment the nine sensitive cases were all streptomycin-sensitive, while the other two were streptomycin-resistant. Since the expected proportion isoniazid-resistant at two months is over 50%, the findings suggest that in the nine cases the bacilli remained sensitive in all nine because of the combination with streptomycin, but that where the bacilli were already streptomycin-resistant the combination could not prevent development of isoniazid resistance. These results must await confirmation by larger numbers, and conclusive findings will be reported as early as possible. It must be emphasized also that we do not yet know if isoniazid in combination will prevent development of streptomycin resistance; if it does not, the combination obviously constitutes a risk in that the patients so treated may become streptomycin-resistant.

In conclusion, this preliminary analysis has demonstrated the relative clinical effectiveness of isoniazid in pulmonary tuberculosis over at least a short-term period, and it has confirmed the serious risk of drug resistance. It has demonstrated also that, given a trial properly designed and organized, and given the co-operation of a great many clinicians and bacteriologists, it is possible to obtain, within a period as short as five months, answers to these basic questions concerning a new drug. Many problems remain, including of course the long-term results. Until they are solved, an indiscriminate and widespread use of isoniazid, either alone or in combination, is clearly not justified. These problems are the subject of detailed investigation in the trial still in progress. Some may be resolved when further information is available on the cases in the first stage of the trial, which compares isoniazid with streptomycin plus P.A.S.; others relate to the combination of isoniazid with streptomycin given daily. In later stages of the trial various treatment series have been instituted using combinations of isoniazid daily with streptomycin twice a week, and of isoniazid together with different doses of P.A.S. The value of the drug and the risk of resistance having been demonstrated, such investigations are indispensable to determine how this new potent agent can be most effectively used.

Summary

In a clinical trial of isoniazid (isonicotinic acid hydrazide) 331 patients with various forms of pulmonary tuberculosis were studied; 173 were treated with isoniazid (200 mg. daily), 158 with streptomycin (1 g. daily) plus P.A.S. (20 g. daily). Treatment was randomly allocated in all cases, and at the time of selecting a patient the treatment which he would receive was unknown to the physician. The present interim report analyses the results at the end of three months' treatment and observation. The trial is still in progress with over 750 patients.

Three main groups were observed: Group 1, with acute rapidly progressive disease of recent origin; Group 2, with other forms suitable for chemotherapy; Group 3, with chronic disease considered unlikely to respond to chemotherapy.

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

Isoniazid showed low toxicity at the dosage used and for the period of three months.

At the end of three months there was rather more improvement in general condition in the patients on isoniazid (H) than in the other patients (SP), but the differences are not great. Average weight gains were considerably greater in the H cases (11 lb.) than in the SP cases (6 lb.).

Temperature fell to normal in 67% of febrile SP cases and in 56% of febrile H cases; in the acute Group 1, temperature fell to normal in 64% of SP cases and 68% of H cases. In cases with a sedimentation rate over 20 before treatment, it fell to 10 or less in 22% of SP cases and 20% of H cases.

The radiological changes were independently assessed. Two-plus or 3-plus improvement was seen in 29% of SP cases and 26% of H cases; in the acute group, it was seen in 37% of SP cases and 40% of H cases. Under streptomycin plus P.A.S. there was radiological deterioration in one case, and three deaths; under isoniazid, deterioration was seen in 10 cases and there was one death.

The proportion of cases becoming bacteriologically negative before the end of the second month was 26% for SP cases and 23% for H cases.

The conclusion, judging wholly from short-term results, is that isoniazid is a very effective drug in pulmonary tuberculosis, but given alone it is not more effective than streptomycin plus P.A.S.

Bacillary resistance to isoniazid was found in 11% of cases at the end of the first month, in 52% at the end of the second, and in 71% at the end of the third. Lack of progress, as assessed by radiological change, was found to be related to the emergence of drug resistance. This is therefore a most serious problem affecting the use of isoniazid. The effects of combining isoniazid with other drugs are under study.

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A.C.T.H. AND CORTISONE IN TREATMENT OF COMPLICATIONS OF LEPROSY

BY

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The chemotherapy of leprosy with sulphone is now being widely practised, with good results. The thiosemicarbazones also are being used with promising results, and other chemotherapeutic agents are under study. Leprosy treatment is becoming established on sound lines, and the outlook is very encouraging.

Certain complications of leprosy are still very difficult to treat, and, because of their nature, may be precipitated or aggravated by chemotherapy, rendering treatment of the underlying disease difficult. A further difficulty of chemotherapy, particularly with sulphones, is that occasionally a patient after a few weeks' treatment becomes intensely allergic to the drugs used, and this allergy shows itself by drug fever, dermatitis which may exfoliate, and hepatitis which may be severe and lead to liver necrosis, the whole condition sometimes being so severe as to result in death.

These complications are not fully understood, but there are certain resemblances between them and those conditions which are alleviated by A.C.T.H. and cortisone, and a trial of these hormones was therefore strongly indicated. The value of A.C.T.H. and cortisone in the treatment of hypersensitive states and drug allergy showing itself as dermatitis has been clearly demonstrated, and the hormones are obviously worth a trial in the potentially dangerous condition of allergy to sulphones.

There were, however, certain obvious dangers. Leprosy, like tuberculosis, is a disease in which troublesome symptoms may sometimes be caused by excessive tissue reaction to the bacilli and their products. This I believe to be true, though in widely varying degree, in all forms of leprosy. The action of A.C.T.H. and cortisone apparently consists largely in reducing this tissue reaction and thus alleviating symptoms so long as the action of A.C.T.H. or cortisone lasts. But it is this same tissue reaction which is needed to localize the infection and, in time, to overcome it. The question therefore arose whether A.C.T.H. and cortisone might not, while relieving symptoms, aggravate the underlying disease by reducing the tissue reaction which was keeping it in check. A good discussion of the action of cortisone and A.C.T.H. in tuberculosis appeared in a leading article in the *British Medical Journal* (1951) outlining the difficulties and dangers. It seemed probable that the use of these hormones in leprosy would be attended by the same difficulties.

It was, however, thought there were factors which favoured the use of A.C.T.H. and cortisone in the treatment of complications of leprosy, the main one being that these complications, when untreated, usually last only a week or two and then subside, although they often recur; therefore a few days' treatment, repeated later if necessary, might tide the patient over the natural period of the complication but not be sufficient to aggravate the underlying disease. Further, it was thought that by continuing chemotherapy during hormone treatment, and even perhaps increasing the dose, any tendency to aggravation of the disease by the hormones might be overcome. These hopes were not fulfilled.

Nature of the Complications

Sulphone Dermatitis, etc.

This syndrome, which includes drug fever, a generalized dermatitis which goes on to exfoliation, inflammation of mucous membranes, a general lymphadenitis, and hepatitis with jaundice which may be latent or overt, has constituted the main difficulty of mass sulphone treatment here in Nigeria, where it has been seen in about 2% of treated cases. It is not a true toxic effect of sulphones; it is caused through the patient becoming allergic to sulphones, as is indicated by the following facts. (1) It occurs between the third and ninth weeks of treatment, and if it does not occur then it will not occur at all. (2) A patient who has been taking full doses, such as 200 mg. a day, without trouble, will, when he has become allergic and has later recovered from the dermatitis syndrome, get a recurrence after a single small dose, often as low as 20 mg., of sulphone; the same patient after desensitization will tolerate full doses again without difficulty. (3) The condition is exactly the same as is seen in sulphonamide sensitization. The administration of a single tablet of any sulphonamide will cause an immediate recurrence of symptoms in a person who has recovered but not been desensitized, and a severe aggravation in a person still suffering from sulphone dermatitis. (4) Antihistamine drugs are of value in the treatment of this condition.

This condition demands early recognition, the immediate cessation of sulphone treatment, the avoidance of all sulphonamides, treatment with antihistamines, and good nursing. Even with these the patient is seriously ill and recovery takes several weeks. Without these the condition may cause death, particularly when experienced physicians are not available. So far the treatment of this condition has been along the lines indicated, and recovery has been very slow.

Acute Leprous Neuritis

A chronic neuritis is common in leprosy of all types. In the lepromatous type, with which we are almost exclusively concerned in the present study, leprous involvement of certain nerve trunks, particularly the ulnars and peroneals, is almost always present. Histopathological studies show large numbers of bacilli lying in the epineurium, perineurium, and endoneurium of the nerves, and usually there is little tissue reaction to these bacilli, and swelling of the nerve is not marked. At certain phases of the disease, and particularly in the middle or towards the end of the long chemotherapy of the disease, such nerves may suddenly become very thick, painful, and tender. The pain may be extremely severe and persistent, and without powerful analgesics the patient may be in agony for several days, or even weeks, until the inflammation spontaneously subsides. This it always does; but before this happens irreparable damage to nerve fibres often occurs, and trophic lesions and deformities follow.