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Two Controlled Studies of the Efficacy of Isoniazid Alone in Preventing Relapse in Patients with Bacteriologically Quiescent Pulmonary Tuberculosis at the End of One Year of Chemotherapy*

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An earlier report showed that, in patients with bacteriologically quiescent pulmonary tuberculosis at the end of 1 year of chemotherapy, isoniazid alone in a single daily dose of 150–200 mg, given as maintenance therapy in the second year, did not markedly prevent relapse over a 4-year period of follow-up in patients who had had residual cavitation (the "open-negative" syndrome) at 1 year, but was highly effective in patients who had not. As a result of these findings, two controlled studies, reported here, were undertaken.

The first study was undertaken in patients with bacteriologically quiescent disease and residual cavitation at 1 year, and investigated the value of isoniazid in a higher daily dose (400 mg) throughout the second year; this is known to be the optimum therapeutic dose when isoniazid is prescribed alone for 1 year in the initial treatment of the disease. The second study was carried out in patients with bacteriologically quiescent disease and no residual cavitation at 1 year, and sought to determine the value of a shorter duration (6 months) of chemotherapy in the second year with a daily dose of 300 mg of isoniazid. Neither of the two isoniazid regimens was highly satisfactory, although both appeared to have had some effect in preventing relapse during the 4-year period of follow-up.

An earlier controlled study carried out at this Centre (Evans et al., 1969) showed that, in patients with bacteriologically quiescent pulmonary tuberculosis and residual cavitation at the end of 1 year of chemotherapy, isoniazid alone in a single daily dose of 150–200 mg (approximately 4.5 mg per kg of body weight) throughout the second year did not have a marked effect in preventing bacteriological relapse over a 4-year period of follow-up. When the preliminary findings of this study became available, it was decided to investigate whether a higher dosage of isoniazid—i.e., 400 mg in a single daily dose—would be more effective. This higher dosage had been shown to be optimum therapeutically when the drug was given alone, in a single daily dose, for 1 year to previously untreated tuberculosis patients with a positive sputum, in whom the disease had been newly diagnosed (Tuberculosis Chemotherapy Centre, Madras, 1963). However, it resulted in peripheral neuropathy in approximately one-fifth of the patients (Tuberculosis Chemotherapy Centre, Madras, 1960). It was therefore decided that 6 mg of pyridoxine, which was known to be highly effective in preventing such neuropathy (Tuberculosis Chemotherapy Centre, Madras, 1963), should be incorporated into each dose of isoniazid. In a study based on random allocation to treatment, this isoniazid regimen (400 mg daily for 1 year) was compared with a placebo. The results over a 4-year period are reported in this paper.

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The earlier study (Evans et al., 1969) had also shown that, in patients with bacteriologically quiescent disease and no residual cavitation at 1 year, isoniazid alone in a single daily dose of 150–200 mg for the whole of the second year was highly effective in preventing bacteriological relapse over a 4-year period. When the preliminary findings became available, it was decided to investigate whether maintenance chemotherapy with isoniazid alone for a shorter duration (6 months) would also be highly effective if the daily dose were increased to 300 mg (without any pyridoxine supplement); the 400-mg dose was not selected as it would have required a pyridoxine supplement for the prevention of peripheral neuropathy, resulting in increased cost. A study based on random allocation was undertaken to compare this isoniazid regimen (300 mg for 6 months) with a placebo. The results over a 4-year period are reported in this paper.

PLAN AND CONDUCT OF THE TWO STUDIES

On admission to initial treatment, all the patients reported here had had newly diagnosed, previously untreated pulmonary tuberculosis with a positive sputum and isoniazid-sensitive organisms, and the great majority had had cavitary disease. In the first year they had received isoniazid either alone or in combination with streptomycin, PAS, or thioacetazone (for details, see Table 8). At 1 year, they had all had bacteriologically quiescent disease—i.e., all cultures examined at 10, 11, and 12 months (usually a total of 7–9) were negative.

Assessment of cavitation at 1 year

At 1 year, the postero-anterior radiograph and tomograms were reviewed by any two of the Centre's physicians (and, in case of disagreement, by a third), and each patient was classified as having either residual cavitation or no residual cavitation.

Treatment in the second year (the first year of follow-up)

At the end of the first year, the patients were allocated at random to treatment in the second year with isoniazid alone or a placebo. The treatment regimens were as follows:

For patients with residual cavitation:

(*a*) Isoniazid 400 mg plus pyridoxine 6 mg, in a single tablet, daily for 12 months; or

(*b*) a placebo (calcium gluconate 500 mg or lactose 500 mg), in a single tablet, daily for 12 months.

For patients with no residual cavitation:

(*a*) Isoniazid 300 mg, in a single tablet, daily for the first 6 months, and the placebo (see above), in a single tablet, daily for the next 6 months; or

(*b*) the placebo (see above), in a single tablet, daily for 12 months.

Treatment in the third and subsequent years

No antituberculosis chemotherapy was prescribed routinely for patients in either study in the third, fourth, and fifth years.

Collapse therapy and resection

No patient in either study had collapse therapy or resection.

General management during the 4-year period of follow-up

All patients were managed on an out-patient basis. During the second year, patients receiving isoniazid attended the Centre once a fortnight and those receiving the placebo attended once a month, to collect their medicaments. During the third and subsequent years, all patients attended the Centre once every 3 months for routine assessments. Throughout the period of follow-up, their homes were visited once a month by a health visitor.

The routine assessments included: (*a*) a clinical assessment at monthly intervals in the second year and at 3-monthly intervals subsequently; (*b*) a postero-anterior chest radiograph at 3-monthly intervals in the second year and at 6-monthly intervals subsequently; and (*c*) the bacteriological examination of sputum specimens as described below. In addition, for patients receiving isoniazid, the regularity of drug intake was assessed by collecting a urine specimen at every clinic attendance (i.e., once a fortnight) and examining it by the combined naphthoquinone–mercuric chloride test of Gangadharam et al. (1958).

Bacteriological investigations

The standard procedure was to obtain 14 sputum specimens from each patient in the second year, 9 in the third year, 9 in the fourth year, and 11 in the fifth year (Table 1). Extra specimens were collected if a positive culture was obtained.

The sputum specimens were examined by direct smear microscopy and by culture. If a positive culture was obtained in any month, an isoniazid sensitivity test was set up, and also a test of sensitivity to any companion drug that the patient had received during the first year. The techniques employed for

Table 1. Frequency of bacteriological examination during the 4-year period of follow-up

Year	Month	Type and No of sputum specimens [a]			Total No. of specimens for the year
		collection		supervised spot	
second	13 to 23	1	or	1	14
	24	2	and	1	
third	27, 30, and 33	1	and	1	9
	36	2	and	1	
fourth	39, 42, and 46	1	and	1	9
	48	2	and	1	
fifth	51, 54, 57, and 59 ½	1	and	1	11
	60	2	and	1	

[a] A collection specimen was one collected overnight in the home; a supervised spot specimen was one produced in the clinic after the throat of the patient had been tickled with a swab to induce coughing.

smear and culture examinations and isoniazid sensitivity tests, and the definition of isoniazid resistance, have been reported earlier (Tuberculosis Chemotherapy Centre, Madras, 1964). Identification tests (colonial morphology, catalase activity, and niacin production) were undertaken on all cultures selected for sensitivity tests, using procedures described by Thomas et al. (1961).

Definition of bacteriological relapse

A bacteriological relapse is defined as the occurrence of 2 or more positive cultures in any 6-month period—e.g., in 7 consecutive monthly examinations in the second year or in 3 consecutive 3-monthly examinations in subsequent years.

Assessment of radiographs

An independent assessor (Dr J. Frimodt-Møller), who did not know what treatment had been given, or any other particulars of any individual patient, made the following assessments, using postero-anterior chest radiographs:

(1) total extent of radiographic lesion at the start of the initial treatment and at 1 year;

(2) extent of cavitation at the start of the initial treatment; and

(3) *for patients with residual cavitation at 1 year:* [1] radiographic changes between 12 and 24 months [2] and between 24 and 60 months; and

for patients with no residual cavitation at 1 year: [1] radiographic changes between 12 and 18 months [2] and between 18 and 60 months.

In order to ensure uniformity in standards, each of the assessments was undertaken for all the patients at a single session. The procedures and classifications employed have been described in detail elsewhere (Tuberculosis Chemotherapy Centre, Madras, 1960).

RESULTS

Study of patients with residual cavitation at 1 year

Number of patients in the study. A total of 123 patients had bacteriologically quiescent disease with residual cavitation at 1 year. Of these, 59 were allocated to the placebo group for the second year and 64 to the 400-mg isoniazid regimen. However, 1 patient (placebo), while in a general hospital for cirrhosis of the liver, was given streptomycin plus isoniazid by the hospital authorities for 7 weeks in the second year. Another patient (isoniazid) was withdrawn from the study on account of psychosis induced by isoniazid (page 607). Excluding these 2 patients, there remain 58 placebo patients and 63 isoniazid patients in the analysis.

Prestudy factors. All the patients had positive cultures on admission to initial treatment; moreover, the first collection specimen of sputum was smear-positive in 91% of the 58 placebo patients and 95% of the 63 isoniazid patients, including 62% and 59%, respectively, in whom it was moderately or heavily positive. Moderate or extensive cavitation was present in 74% of the placebo patients and 59% of the isoniazid patients ($P = 0.1$), and moderate, extensive, or gross lesions (for definitions, see Tuberculosis Chemotherapy Centre, Madras, 1960) in 90% of the patients in each series.

In the first year, sputum conversion [3] had commenced within 3 months in 60% of the placebo patients and 67% of the isoniazid patients. At 1 year—i.e., at the start of the present study—40% of the placebo patients and 38% of those on isoniazid had moderate, extensive, or gross residual radiographic lesions.

[1] Assessment made by the Centre's physicians (see page 604).

[2] That is, the period for which isoniazid was prescribed for half the patients.

[3] That is, negativity of all cultures for at least 3 consecutive months.

In summary, the two series of patients were similar in all prestudy factors considered.

Frequency of culture examination. The mean number of cultures per patient was 14.3 in the placebo series and 14.2 in the isoniazid series in the second year; 8.7 and 9.1, respectively, in the third year; 8.6 and 8.4, respectively, in the fourth year, and 10.5 in each series in the fifth year. Thus, the two series were examined with high and similar frequency during the 4-year period of follow-up.

Bacteriological relapse. A bacteriological relapse occurred during the 4-year period in 9 of the 58 patients in the placebo series and in 9 of the 63 in the isoniazid series (Table 2). Of these, 1 placebo patient and 5 isoniazid patients had sputum conversion subsequently without recourse to retreatment, and remained persistently culture-negative till the end of the study. Thus, relapse requiring retreatment occurred in 8 (14%) of patients in the placebo series and in 4 (6%) in the isoniazid series, a suggestive but non-significant difference (P = 0.1).[1]

In 6 patients (4 placebo, 2 isoniazid), retreatment was necessitated by the radiographic deterioration (confirmed by an independent assessor, Dr K. S. Sanjivi) associated with the bacteriological relapse; 1 of the 2 isoniazid patients had tuberculous meningitis also. In the other 6, retreatment was given solely for bacteriological reasons. Thus, 4 patients (3 placebo, 1 isoniazid) had at least 1 positive smear and at least 5 positive cultures during the 3 months immediately preceding the start of retreatment. A fifth (placebo) had repeatedly produced positive cultures, interspersed with negative ones, during the previous year. The sixth (isoniazid) had produced a positive culture (20–100 colonies) at 2 successive monthly examinations.

Of the 8 placebo patients who needed retreatment, 5 had their relapse in the second year, 2 in the fourth year, and 1 in the fifth year (Table 2); 7 had isoniazid-sensitive cultures at the time of the relapse. Of the 4 isoniazid patients requiring retreatment, 2 showed a relapse while they were receiving isoniazid—i.e., in the second year—1 with an isoniazid-resistant culture and the other with an isoniazid-sensitive culture; the other 2 showed relapses in the fourth year, both with isoniazid-sensitive cultures.

Radiographic progress. Between the 12th and 24th months, 5 patients died without showing any evidence of bacteriologically active tuberculosis; 4 patients had a bacteriological relapse for which retreatment was started, including 3 (2 placebo, 1 isoniazid) who had an associated clear-cut radiographic deterioration. For the remaining 112 patients (52 placebo, 60 isoniazid), the radiographic changes between 12 and 24 months are set out in Table 3. It will be seen that 58% of the placebo patients and 52% of those on isoniazid showed improvement, which was slight in all but 2.

Between the 24th and 60th months, when none of the patients received any routine chemotherapy, 6 patients died without showing any evidence of bacteriologically active tuberculosis; 8 patients had a bacteriological relapse for which retreatment was started, including 3 (2 placebo, 1 isoniazid) who had an associated clear-cut radiographic deterioration. Of the remaining 43 placebo patients and 55 isoniazid patients (Table 3), 44% and 69%, respectively, showed radiographic improvement, the difference being significant (P = 0.01). However, it will be noted that the improvement was slight in all but 3 and therefore the difference observed is probably of little importance. This conclusion was supported by the finding that the proportions of patients with the various radiographic changes at 60 and at 24 months were similar in the placebo and in the isoniazid series. (These assessments were specially undertaken for all the patients, in random order, by an independent assessor—Dr K. V. Krishnaswamy.)

Deaths. Of the 49 placebo patients and 54 isoniazid patients who did not have a bacteriological relapse, 7 and 4, respectively, died during the 4-year period of follow-up. Of these, 4 died of respiratory causes—2 in the 14th and 56th months, respectively, in *status asthmaticus*; 1 in the 22nd month from non-tuberculous bronchopneumonia; and 1 in the 28th month, 10 days after a spontaneous pneumothorax. Death was due to gastrointestinal causes in two and cardiovascular causes in three. One patient died of an undiagnosed febrile condition, and one from complications of advanced leprosy.

Of the 11 patients who died, 10 had been consistently culture-negative for periods ranging from 7 to 53 months (mean: 28 months) before death. The remaining patient died of acute dysentery; he had produced 1 positive culture (1 colony) 5 months before death but this was followed by 6 negative cultures. It may be concluded, therefore, that none of the 11 deaths was due to active tuberculosis. No autopsies were performed.

[1] As the progress of the patients receiving isoniazid cannot be inferior to that of the placebo patients, P-values corresponding to 1-tail tests of significance are reported whenever progress is considered.

Table 2. Bacteriological relapse during the 4-year period of follow-up in patients with residual cavitation at 1 year

Treatment in the second year	Total No of patients (A)	Patients who had a bacteriological relapse						
		Total	Those requiring retreatment					
			No	% of (A)	Year of relapse			
					second	third	fourth	fifth
placebo	58	9	8	14	5	0	2	1
isoniazid	63	9	4	6	2	0	2	0

Isoniazid toxicity. None of the patients developed peripheral neuropathy. However, one patient—a slow inactivator of isoniazid—became disoriented and violent 6 weeks after the start of the isoniazid regimen (400 mg, plus 6 mg of pyridoxine, in a single daily dose). By means of a therapeutic test, isoniazid was found to be the cause of the psychosis and was therefore discontinued. (This patient had had no untoward symptoms in the year of initial treatment, when he had received 150–175 mg of isoniazid daily in 2 divided doses together with PAS)

Study of patients with no residual cavitation at 1 year

Number of patients in the study. A total of 246 patients had bacteriologically quiescent disease with no residual cavitation at 1 year. Of these, 119 were allocated to the placebo for the whole of the second year and 127 to 300 mg of isoniazid for 6 months followed by the placebo for 6 months. One patient was re-treated for what was thought at the time to be a bacteriological relapse; subsequently, however, it was found that he had been excreting only atypical mycobacteria. Excluding this patient, there remain 118 placebo patients and 127 isoniazid patients in the analysis.

Prestudy factors. All the patients had positive cultures on admission to initial treatment; moreover, 89% of the placebo patients and 84% of those on isoniazid had a positive smear from the first collection specimen of sputum, including 58% and 50%, respectively, in whom the smear was moderately or heavily positive. Cavitation was present in 84% of the placebo patients and in 83% of the isoniazid patients,

Table 3. Radiographic changes in patients with residual cavitation at 1 year

Radiographic change	12–24 months				24-60 months			
	placebo		isoniazid		placebo		isoniazid	
	No.	%	No	%	No	%	No	%
Improvement:		58		52		44		69
moderate	0		2		0		3	
slight	30		29		19		35	
No change	19	36	27	45	23	54	14	26
Deterioration:		6		3		2		5
slight	3		1		1		3	
moderate	0		1		0		0	
Total	52	100	60	100	43	100	55	100
Retreatment started because of radiographic deterioration	2		1		2		1	

Table 4. Bacteriological relapse during the 4-year period of follow-up in patients with no residual cavitation at 1 year

Treatment in the second year	Total No. of patients (A)	Patients who had a bacteriological relapse						
		Total	Those requiring retreatment					
			No.	% of (A)	Year of relapse			
					second	third	fourth	fifth
placebo	118	23	14	12	7	5	1	1
isoniazid	127 [a]	12	6	5	1	2	2	1

[a] One patient, whose sputum was culture-negative throughout, developed tuberculosis of the spine in the 48th month and was re-treated. Including this patient, the proportion with a relapse requiring retreatment was 6 %.

and limited, moderate, or extensive disease in 91% and 86%, respectively; no patient had gross disease. Thus, the two series were similar on admission to initial treatment.

In the first year, sputum conversion had commenced within 3 months in 69% of the placebo patients and 81% of the isoniazid patients (P=0.04). At 1 year, limited or moderate residual radiographic lesions were present in 32% and 21%, respectively (P = 0.07); no patient had an extensive lesion. (For the implications of these differences for the findings, see footnote on this page.)

Frequency of culture examination. The mean number of cultures per patient in each series was 14.2 in the second year, 8.7 in the placebo series and 8.8 in the isoniazid series in the third year; 8.6 in each series in the fourth year; and 10.2 in each series in the fifth year. Thus, the two series were examined with high and similar frequency during the 4-year period of follow-up.

Bacteriological relapse. A bacteriological relapse occurred during the 4-year period of follow-up in 23 of the 118 patients in the placebo series and in 12 of the 127 in the isoniazid series (Table 4). Of these, 9 placebo patients and 6 isoniazid patients had sputum conversion subsequently without recourse to retreatment, and all except 1 remained persistently culture-negative until the end of the study (however, 1 patient (placebo) died in *status asthmaticus*, and another (isoniazid) was discharged, both in the 48th month). The exception (isoniazid) was persistently culture-negative for 10 months subsequent to the relapse, but produced 1 positive culture (2 colonies) in the 60th month, together with 2 negative cultures. Thus, a bacteriological relapse requiring retreatment occurred in 14 (12%) in the placebo series and in 6 (5%) in the isoniazid series (1 other patient (isoniazid) developed extrapulmonary tuberculosis—see below).

Retreatment was started because of clear-cut radiographic deterioration (confirmed by the independent assessor, Dr K. S. Sanjivi) associated with the bacteriological relapse in 8 patients (6 placebo, 2 isoniazid), and solely for bacteriological reasons in 12 patients (8 placebo, 4 isoniazid). Of the latter 12 patients, 11 had at least 1 positive smear and at least 4 positive cultures during the 3 months immediately preceding the start of retreatment. The 12th (placebo) had produced 8 positive cultures during the 3-month period, including 4 with a growth of 20 or more colonies.

Of the 14 placebo patients who needed retreatment, 7 had their relapse in the second year, 5 in the third year, 1 in the fourth year, and 1 in the fifth year (Table 4); 11 patients had cultures sensitive to isoniazid at the time of their relapse. Of the 6 isoniazid patients who had a relapse of their pulmonary disease requiring retreatment, 1 relapsed in the last 6 months of the second year (while receiving the placebo), 2 in the third year, 2 in the fourth year, and 1 in the fifth year. All 6 patients had isoniazid-sensitive cultures at the time of relapse.

One other patient (isoniazid) developed tuberculosis of the spine in the 48th month and had to be re-treated (her sputum remained culture-negative throughout). In all, therefore, 14 (12%) of 118 placebo patients and 7 (6%) of 127 isoniazid patients had a relapse requiring retreatment.[1]

[1] The corresponding percentages, after statistical standardization for the differences between the 2 series in the speed of sputum conversion in the first year and the total extent of the lesion at 1 year (see above), were 11% and 6%, respectively, a suggestive but non-significant difference (P = 0.1).

Radiographic progress. Between the 12th and 18th months, 2 patients died without any evidence of bacteriologically active tuberculosis. In 2 others (both placebo), retreatment was started because of clear-cut radiographic deterioration associated with a bacteriological relapse. For the remaining 241 patients (116 placebo, 125 isoniazid), the radiographic changes between 12 and 18 months are set out in Table 5. It will be seen that 33% in each series showed improvement, which was slight in all but 1 patient.

Between the 18th and 60th months, when none of the patients received routine chemotherapy, 6 patients died without any evidence of bacteriologically active tuberculosis; 19 patients had a relapse for which retreatment was started, including 6 (4 placebo, 2 isoniazid) who had an associated clear-cut radiographic deterioration. Of the remaining 101 placebo patients and 115 isoniazid patients (Table 5), 50% and 44%, respectively, showed radiographic improvement, which was slight in all but 7 (4 placebo, 3 isoniazid).

In summary, the radiographic progress of the placebo patients and of the isoniazid patients was similar during the 4-year period of follow-up.

Deaths. Of 95 placebo patients and 114 isoniazid patients who did not have a relapse, 2 and 5, respectively, died during the 4-year period of follow-up. Of these, 3 died of gastrointestinal disorders, 1 died of cancer, 1 committed suicide, and 2 died of unknown causes. None of the deaths was attributed to active tuberculosis, as all the patients had been consistently culture-negative for periods ranging from 12 to 45 months (mean: 29 months) before death. An autopsy was not performed on any of the patients.

Isoniazid toxicity. None of the patients had a mental disturbance. However, one patient (a slow inactivator of isoniazid) developed peripheral neuropathy in the fifth month after the start of the isoniazid regimen (300 mg in a single daily dose). Pyridoxine was prescribed and the isoniazid was continued until the end of the sixth month, as scheduled. (One patient in the placebo series had symptoms suggestive of peripheral neuropathy, which were relieved by the oral administration of vitamin B complex.)

Bacterial population at the time of relapse

In the 2 controlled studies reported above, 20 patients had a bacteriological relapse followed by sputum conversion (to culture negativity) without recourse to retreatment and remained persistently culture-negative thereafter, and 32 patients had a bacteriological relapse for which retreatment was started. It is of interest to compare the bacterial populations in these 2 groups of patients at the time of relapse. Of the 20 patients who were not re-treated,

Table 5. Radiographic changes in patients with no residual cavitation at 1 year

Radiographic change	12–18 months				18–60 months			
	placebo		isoniazid		placebo		isoniazid	
	No.	%	No.	%	No.	%	No.	%
Improvement:		33		33		50		45
moderate	1		0		4		3	
slight	37		41		47		48	
No change	76	65	83	66	50	50	59	51
Deterioration		2		1		0		4
slight	1		1		0		1	
moderate	1		0		0		2	
considerable	0		0		0		2	
Total	116	100	125	100	101	100	115	100
Retreatment started because of radiographic deterioration	2		0		4		2	

80% produced only negative smears in the month of relapse and in the following 3-month period, compared with 25% of 32 patients who were re-treated—a highly significant difference ($P<0.001$). Considering next the findings of culture examination during this period, the highest growth observed was 100 colonies or less for 70% of the former and 34% of the latter ($P = 0.03$). Finally, the proportions of patients who produced at least 3 positive smears during this period were 0% and 47%, respectively ($P<0.001$), and, of those who produced at least 3 positive cultures, 10% and 75%, respectively ($P<0.001$). Thus, the patients who had sputum conversion without recourse to retreatment had considerably smaller bacterial populations at the time of relapse than those who were re-treated.

Regularity of self-administration of isoniazid

As stated earlier (page 604), a urine specimen was examined once a fortnight for patients receiving isoniazid in the second year. Table 6 sets out the distributions of patients according to the percentage of negative test results, together with the mean values. It will be seen that approximately one-third of the patients had negative results on at least half the occasions, and that the mean proportion was of the order of 40%. Table 6 shows also the influence of irregularity in drug intake on the incidence of relapse requiring retreatment. Although the numbers are small, there is suggestive evidence of an association, both in patients with residual cavitation at 1 year and in those with no residual cavitation. Considering both groups together (it will be noted that the proportions re-treated and the proportions with negative urine test results are very similar in the 2 groups), the proportions re-treated were 3%, 3%, and 11%, respectively, in patients with <20%, 20–49%, and 50% or more negative urine test results—a significant trend ($P = 0.03$). The prestudy condition in these 3 categories of patients was similar (data not tabulated here). It may be concluded, therefore, that irregularity in drug intake influenced the incidence of relapse requiring retreatment.

Prognostic significance of various prestudy factors

The influence of various prestudy factors on the occurrence of relapse requiring retreatment was studied, separately for the placebo series and for the isoniazid series.[1] Within each series, however, patients with residual cavitation at 1 year and those with no residual cavitation have been considered together, as the incidence of relapse requiring retreatment was practically the same in the 2 groups. Thus, in the placebo series, it was 14% of 58 in the former group and 12% of 118 in the latter; in the isoniazid series, the corresponding proportions were 6% of 63 and 6% of 127, respectively.

Placebo series. Considering the condition on admission to initial treatment of patients in the placebo series—i.e., those who, by random allocation, received no chemotherapy after the first year—there was clear evidence that the total extent of radiographic disease influenced the likelihood of relapse requiring retreatment (Table 7); thus, retreatment became necessary for 6% of 47 patients with trivial, slight, or limited disease, 11% of 84 patients with moderate disease, and 22% of 45 patients with extensive or gross disease—a significant trend ($P = 0.01$). The extent of cavitation, however, was of no prognostic importance. Next, there was a suggestion that the smear result of the first collection specimen was of some importance ($P = 0.1$).

Considering the speed of sputum conversion in the first year, 5% of 116 patients with an early sputum conversion—i.e., by 3 months—were re-treated, compared with 27% of 60 patients in whom sputum conversion occurred at 4 months or later—a highly significant difference ($P<0.0001$).

Finally, the total extent of the residual radiographic lesion at 1 year was of prognostic importance, the proportions requiring retreatment being 8% of 98 in patients with slight, trivial, or no disease, compared with 18% of 78 in patients with at least limited disease ($P = 0.04$).

Isoniazid series. In the 2 isoniazid series combined—i.e., among patients who received isoniazid for 6 or 12 months in the second year—none of the prestudy factors appeared to influence the likelihood of relapse requiring retreatment (Table 7).

Efficacy of isoniazid in patients having an unfavourable prestudy condition. A further point of interest that emerges from Table 7 is the clear evidence of the value of isoniazid in patients who had an unfavourable prestudy condition. For instance, in those with extensive or gross disease on admission to initial treatment, the proportion requiring retreatment was 22% of 45 in the placebo series and 5% of 43 in the isoniazid series ($P = 0.02$). The corresponding proportions were 15% of 104 and 2% of 101, respect-

[1] As only positive associations were expected, P-values corresponding to 1-tail tests of significance have been employed.

Table 6. Results of urine tests performed during isoniazid treatment in the second year

Percentage of negative urine test results	Patients with residual cavitation at 1 year			Patients with no residual cavitation at 1 year			All patients		
	total	re-treated		total	re-treated		total	re-treated	
		No.	%[a]		No	%		No.	%
Less than 20	23	1	(4)	39	1	3	62	2	3
20–49	18	0	(0)	45	2	4	63	2	3
50 or more	22	3	(14)	43	4	9	65	7	11
Total	63	4	6	127	7	6	190	11	6
Mean percentage of negative test results	36			38			37		

[a] Parentheses indicate that the percentage is based on fewer than 25 observations

Table 7. Relapse requiring retreatment, related to prestudy factors

Prestudy factors	Placebo			Isoniazid		
	total patients	re-treated		total patients	re-treated	
		No.	%		No.	%
On admission to initial treatment						
Total extent of radiographic disease:						
trivial, slight, or limited	47	3	6	68	4	6
moderate	84	9	11	79	5	6
extensive or gross	45	10	22	43	2	5
Extent of cavitation:						
nil or slight	86	10	12	103	6	6
moderate or extensive	90	12	13	87	5	6
Direct smear microscopy (result of first collection specimen):						
negative or +	72	6	8	89	9	10
++ or +++	104	16	15	101	2	2
In the first year						
Month of sputum conversion:						
1 or 2	59	3	5	80	5	6
3	57	3	5	65	4	6
4 or more	60	16	27	45	2	4
At 1 year						
Total extent of residual radiographic lesion:						
nil or trivial	48	4	8	58	3	5
slight	50	4	8	62	2	3
limited or more	78	14	18	70	6	9
All patients	176	22	12	190	11	6

Table 8. Relapse requiring retreatment, related to chemotherapeutic regimen in the first year

Regimen in the first year	Efficacy in the first year[a] (%)	No. of patients in the present study	Patients requiring retreatment during the 4-year period	
			No.	%
Isoniazid 14 mg/kg, given alone in 1 dose daily	66	56	3	7
Streptomycin 1 g or 0.75 g plus isoniazid 15 mg/kg, given together once weekly	71	25	2	
Isoniazid 200 mg plus PAS 6 g, given together in 1 dose daily for the first 6 months, followed by isoniazid 7 mg/kg, given alone in 1 dose daily for the next 6 months	67	40	3	
Isoniazid 4 mg/kg plus PAS 0.2 g/kg, given together in 2 divided doses daily	83	98	10	12
Isoniazid 7 mg/kg plus thioacetazone 3 mg/kg, given together in 1 dose daily	62	44	7	
Streptomycin 1 g or 0.75 g plus isoniazid 14 mg/kg or 15 mg/kg, given together twice weekly	93	103	8	8

[a] Assessed as the percentage of patients with bacteriologically quiescent disease at 1 year.

ively, in patients with a ++ or +++ smear result initially ($P<0.001$), and 27% of 60 and 4% of 45, respectively, in patients who had a sputum conversion at 4 months or later ($P<0.01$).

Influence of the chemotherapeutic regimen in the first year on the occurrence of relapse requiring retreatment. The patients reported in this paper had received one of six chemotherapeutic regimens in the first year. The details of these regimens and their efficacies in the first year are set out in Table 8, which also presents, for each regimen, the proportion of patients who had a relapse requiring retreatment during the 4-year period of follow-up.

The 6 regimens can be divided into 3 distinct categories—namely, those of low efficacy (the first 3), those of moderate efficacy (the fourth and the fifth), and those of high efficacy (the sixth). Analyses, not tabulated here, showed that the prestudy condition of the patients was similar for the 3 categories of regimen; furthermore, the proportions of patients who received maintenance chemotherapy with isoniazid for (*a*) 6 months or (*b*) 12 months in the second year were also similar for the 3 categories.

Of 121 patients who had received a regimen of low efficacy in the first year, 7% had a relapse requiring retreatment in the 4-year period of follow-up; the corresponding proportions were 12% of 142 for patients who had received a regimen of moderate efficacy and 8% of 103 for those who had received one of high efficacy. Thus, there was no evidence that the efficacy of the regimen, assessed as the percentage of patients with bacteriologically quiescent disease at 1 year, influenced the likelihood of relapse requiring retreatment in the subsequent 4 years.

DISCUSSION

In the 2 controlled studies reported in this paper, 53 patients had a bacteriological relapse—i.e., 2 or more positive cultures among 6 or more examined in a 6-month period. However, 20 (38%) of these patients had a sputum conversion subsequently without recourse to retreatment, and remained persistently culture-negative thereafter. Thus, a bacteriological relapse, as defined above, did not always carry an unfavourable prognosis. Consequently, the value of maintenance chemotherapy with isoniazid has been assessed mainly in terms of the reduction in the incidence of relapse requiring retreatment. (It must be emphasized that the patients in these studies were under intensive bacteriological surveillance, approximately 43 cultures per patient being examined during the 4-year period of follow-up. In situations where the frequency of bacteriological examination is lower, a finding of 2 positive cultures in a 6-month period could be of greater prognostic significance.)

As regards the patients with bacteriologically quiescent disease and residual cavitation at 1 year, a relapse requiring retreatment occurred in 14% of 58 patients who received a placebo in the second year and in 6% of 63 patients who received isoniazid in

a single daily dose of 400 mg throughout the second year; the reduction of 8% is suggestive but not significant (P = 0.1). In an earlier study at this Centre (Evans et al., 1969), the corresponding proportions were 10% of 41 for patients who received a placebo and 7% of 55 for patients who received isoniazid in a single daily dose of 150–200 mg throughout the second year, the reduction due to isoniazid being 3%. These findings indicate that 400 mg of isoniazid in the second year (in a single daily dose) is not adequate as maintenance chemotherapy, although it may be slightly better than 150–200 mg. Therefore it may be concluded that a double-drug regimen is indicated for the prevention of relapse in patients with residual cavitation at 1 year (it should be noted that none of the patients had received intensive chemotherapy with 3 or more drugs in the early stages of treatment in the first year). In this context, it is of interest that, in a group of British patients with bacteriologically quiescent disease and residual cavitation at 1 year, 28% of 50 who were allocated to no chemotherapy in the second year had to be re-treated on account of bacteriological relapse during a 3-year period of follow-up, compared with 6% of 34 who were allocated to isoniazid plus PAS for the second year (Great Britain, Medical Research Council, 1962)—a significant difference (P = 0.01).

Considering next the patients with bacteriologically quiescent disease and no residual cavitation at 1 year, a relapse requiring retreatment occurred in 12% of 118 patients who received a placebo in the second year and in 6% of 127 who received isoniazid in a single daily dose of 300 mg for the first 6 months of the second year.[1] Thus, maintenance chemotherapy for 6 months with 300 mg of isoniazid appears to have had some effect. However, it was not as effective as isoniazid for 12 months in a single daily dose of 150–200 mg; none of 103 patients who received the latter regimen in an earlier controlled study (Evans et al., 1969) had to be re-treated, compared with 12% of 107 who received a placebo in the same study (P < 0.0001).

In the patients who did not receive any maintenance chemotherapy in the second year, the cavitation status at 1 year was of little prognostic importance—a finding similar to that in an earlier study (Evans et al., 1969). However, there was clear evidence that the total extent of the lesion on admission to initial treatment and at 1 year, and the speed of sputum conversion in the first year, significantly influenced the likelihood of relapse requiring retreatment. Finally, in patients for whom there was a relatively high risk of relapse—e.g., those who had a late sputum conversion in the first year—there was convincing evidence that maintenance chemotherapy with isoniazid was valuable.

With regard to the patients who received maintenance chemotherapy with isoniazid in the second year (for 6 or 12 months), none of the prestudy factors appeared to be prognostically important. However, there was some evidence that irregularity in drug intake, as assessed by the proportion of negative urine test results, influenced the likelihood of relapse requiring retreatment. In the present study, the mean proportion of negative urine test results was of the order of 40%, suggesting that the isoniazid regimens would have been more efficacious had the patients been more regular in their drug intake. However, it will be appreciated that, in symptom-free patients with bacteriologically quiescent disease at the end of 1 year of chemotherapy, it is extremely difficult to ensure a high degree of regularity in long-term self-medication.

An earlier study undertaken at this Centre (Evans et al., 1969) demonstrated that the occurrence of a relapse in the second to fifth years was not related to the efficacy of the regimen in the first year, even when the latter varied considerably (Tuberculosis Chemotherapy Centre, Madras, 1960). The findings of the present investigation confirm this observation, the proportions of patients who had a relapse requiring retreatment being 7% of 121, 12% of 142, and 8% of 103, respectively, for regimens with low, moderate, and high efficacies in the first year. It should be noted that this conclusion concerns regimens that did not contain an initial intensive phase with three or more drugs.

In the first study reported in this paper, 64 patients were given 400 mg of isoniazid plus 6 mg or pyridoxine, in a single daily dose, for the second year. None of them developed peripheral neuropathy. However, in 1 patient a toxic psychosis due to isoniazid occurred after 6 weeks. In an earlier study (Tuberculosis Chemotherapy Centre, Madras, 1960), mental disturbance attributed to isoniazid occurred in 1 of 70 patients who received 400 mg of isoniazid (without pyridoxine) in a single daily dose for 1 year. Finally, in a study in East Africa (East African/British Medical Research Council Fourth Thiacetazone

[1] The corresponding percentages, after statistical standardization for the differences between the 2 series in the speed of sputum conversion in the first year and in the total extent of the lesion at 1 year (page 608), were 11% and 6%, respectively—a suggestive but non-significant difference (P = 0.1).

Investigation, 1966), none of 181 patients who were given 450 mg of isoniazid plus 6 mg of pyridoxine (plus 150 mg of thioacetazone) in 1 dose daily showed any sign of mental disturbance. It may be concluded, therefore, that mental disturbance is a relatively rare occurrence in patients receiving a moderately high dosage of isoniazid.

In the second study reported in this paper, a single daily dose of 300 mg of isoniazid was prescribed for 127 patients during a 6-month period in the second year. None of the patients had a mental disturbance. However, one developed peripheral neuropathy in the fifth month. When the same dosage of isoniazid was given together with 150 mg of thioacetazone in a single daily dose for 12 months (Tuberculosis Chemotherapy Centre, Madras, 1966) or for 18 months (East African/British Medical Research Council Fourth Thiacetazone Investigation, 1966), peripheral neuropathy occurred in 1 of 80 and in none of 179, respectively. No pyridoxine supplement was given to the patients in any of the above-mentioned studies. It may be concluded, therefore, that the incidence of peripheral neuropathy with 300 mg of isoniazid is low. Furthermore, even the 2 cases of peripheral neuropathy observed at this Centre could have been due to, or precipitated by, a nutritional deficiency, since 1 of 176 patients who received a placebo developed symptoms suggestive of peripheral neuropathy (page 609), and tuberculosis patients attending this Centre are known to have a vitamin deficiency (Ramakrishnan et al., 1961, 1966; Krishnamurthy et al., 1967).

In conclusion, it may be stated that, in patients with bacteriologically quiescent disease and residual cavitation at 1 year, isoniazid alone in a single daily dose of 400 mg throughout the second year was not highly satisfactory, although it was of some value. In patients with bacteriologically quiescent disease and no residual cavitation at 1 year, isoniazid alone in a single daily dose of 300 mg for 6 months in the second year was of some value, but was considerably less satisfactory than 150–200 mg given in a single daily dose throughout the second year.

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RÉSUMÉ

DEUX ÉTUDES CONTRÔLÉES SUR L'EFFICACITÉ D'UN TRAITEMENT PAR L'ISONIAZIDE SEUL DANS LA PRÉVENTION DES RECHUTES CHEZ DES MALADES ATTEINTS DE TUBERCULOSE PULMONAIRE BACTÉRIOLOGIQUEMENT INACTIVE APRÈS UN AN DE CHIMIOTHÉRAPIE

La première étude a porté sur des malades donnant à l'issue d'un traitement d'un an des cultures négatives, mais porteurs de cavernes résiduelles. Ils ont été répartis, sur une base aléatoire, en deux groupes: 63 ont reçu une dose quotidienne unique de 400 mg d'isoniazide (avec 6 mg de pyridoxine) pendant la 2e année; 58 (groupe témoin) ont reçu un placebo (500 mg de gluconate de calcium ou 500 mg de lactose) pendant la même période. Tous ont été suivis pendant 4 ans.

Huit malades (14%) du groupe témoin et 4 (6%) du groupe isoniazide ont souffert d'une rechute bactériologique exigeant un traitement, dont 5 et 2, respectivement, durant la 2e année de traitement (1re année d'observation). Sur 2 malades traités par l'isoniazide au moment de la rechute, 1 était porteur de bacilles résistants à ce médicament; parmi les 10 autres cas de rechute, on trouvait 9 excréteurs de bacilles sensibles à l'isoniazide.

Des malades porteurs de lésions tuberculeuses bactériologiquement inactives, sans cavernes résiduelles, après un an de chimiothérapie, ont participé à la seconde étude: 127 ont reçu une dose quotidienne unique de 300 mg d'isoniazide (sans pyridoxine) pendant 6 mois, puis le placebo pendant 6 mois; 118 (groupe témoin) ont reçu le placebo pendant un an. Ils ont été également suivis pendant 4 ans.

On a enregistré une rechute bactériologique exigeant un traitement chez 14 malades (12%) du groupe témoin et chez 6 malades (5%) du groupe isoniazide, dans 7 et 1 cas, respectivement, durant la 2e année. Un autre malade du groupe isoniazide a dû être repris en traitement au 48e mois pour tuberculose vertébrale. Aucun des 20 malades ayant présenté une récidive bactériologique n'était traité par l'isoniazide au moment de la rechute; tous, sauf 3, excrétaient des bacilles sensibles à l'isoniazide.

Chez les malades à affection bactériologiquement inactive après un an qui n'ont pas bénéficié ultérieurement de la chimiothérapie, l'étendue globale des signes radiologiques avant le traitement initial et après un an, ainsi que la rapidité avec laquelle l'expectoration s'est négativée au cours de la 1re année, ont nettement influé sur le risque d'une rechute justiciable d'un traitement. En revanche, aucun de ces facteurs ne s'est révélé décisif du point de vue pronostique chez les malades traités par l'isoniazide seul pendant 6 ou 12 mois au cours de la 2e année. L'irrégularité de la prise du médicament a favorisé la survenue de rechutes requérant un traitement.

Les résultats de ces études et de recherches précédentes indiquent que: *a*) chez les malades présentant, après un an de traitement, une affection bactériologiquement stabilisée et des lésions cavitaires résiduelles, l'isoniazide seul donné à la dose quotidienne de 400 mg pendant une 2e année, bien que non dépourvu d'action, ne témoigne pas d'une très grande efficacité dans la prévention des rechutes; *b*) chez les malades à cultures négatives et indemnes de lésions cavitaires résiduelles après un an de traitement, l'isoniazide seul, donné à la dose quotidienne de 300 mg pendant 6 mois, donne certains résultats qui sont cependant très inférieurs à ceux obtenus par l'administration d'une dose quotidienne de 150-200 mg pendant toute la 2e année.

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