

Progress in the Second Year of Patients with Quiescent Pulmonary Tuberculosis after a Year of Domiciliary Chemotherapy, and Influence of Further Chemotherapy on the Relapse Rate *

S. VELU, R. H. ANDREWS, J. H. ANGEL, S. DEVADATTA,
WALLACE FOX, P. R. J. GANGADHARAM, A. S. L. NARAYANA,
C. V. RAMAKRISHNAN, J. B. SELKON & P. R. SOMASUNDARAM

This study from the Tuberculosis Chemotherapy Centre, Madras, summarizes the progress during the second year of those patients in a 1-year comparison of four domiciliary chemotherapeutic regimens (isoniazid plus PAS and three regimens of isoniazid alone) whose pulmonary tuberculosis had attained bacteriological quiescence at the end of the year of chemotherapy. During the second year, about half of the patients received further chemotherapy, with isoniazid alone, and the remainder received a placebo, calcium gluconate. The main objects of the study were to determine the influence on the progress during the second year of (a) a second year of chemotherapy with isoniazid alone, (b) residual cavitation at the end of the first year, and (c) the chemotherapeutic regimen received during the first year, and to compare the results with those obtained in an earlier study by the Centre of the progress during the second year of patients with quiescent pulmonary tuberculosis after a year's chemotherapy with isoniazid plus PAS at home or in sanatorium.

The results of the present study, which was planned on the same lines as the earlier one, showed that relapse in the second year was unrelated to the chemotherapeutic regimen received in the first year, and it was therefore permissible to amalgamate the findings in the two studies. The amalgamated results showed that the relapse rate in the second year was low (5.9%) and that a second year of treatment with isoniazid alone was of definite value for the patients with no residual cavitation at the end of the first year, but had no effect on the relapse rate of those with residual cavitation. The combined data from the two studies have thus clarified the position with regard to the effectiveness of isoniazid in preventing bacteriological relapse in patients without residual cavitation, slight evidence of which was apparent in the earlier study.

In two previous reports from the Tuberculosis Chemotherapy Centre, Madras, the merits of a second and of a third year of chemotherapy with isoniazid alone have been studied in patients with bacteriologically quiescent disease at the end of a year of chemotherapy with isoniazid plus *p*-aminosalicylic acid (PAS), either at home or in

sanatorium (Velu et al., 1960; Devadatta et al., 1961). It was found that there was relatively little difference between the bacteriological relapse rate of patients who had one year of chemotherapy and that of patients who had two or three years of chemotherapy. Further, there was little difference between those who were treated at home and those who were treated in sanatorium in the first year. In a subsequent study (Tuberculosis Chemotherapy Centre, 1960) a controlled comparison was undertaken of four different domiciliary regimens of chemotherapy for a year. One of the regimens was the same standard combina-

* From the Tuberculosis Chemotherapy Centre, Madras, India. The Centre is under the joint auspices of the Indian Council of Medical Research, the Madras State Government, the World Health Organization and the Medical Research Council of Great Britain.

tion of isoniazid plus PAS; the other three were regimens of isoniazid alone. At the end of the year the patients with bacteriologically quiescent disease were allocated at random to treatment with isoniazid alone for a second year, or to a placebo. The reasons for using isoniazid alone have been given elsewhere (Velu et al., 1960).

The objects of the present report are:

(1) to study the progress in the second year of the patients who had bacteriologically quiescent disease at one year, with particular reference to the

influence of (a) a second year of chemotherapy with isoniazid alone, (b) residual cavitation at one year and (c) the chemotherapeutic regimen in the first year;

(2) to study the progress in the second year of the patients whose disease status at the end of a year was bacteriologically in doubt.

The progress in the second year of the patients who had bacteriologically active disease at the end of the first year will be the subject of a later report (Ramakrishnan et al., 1962).

I. GENERAL PLAN AND CONDUCT OF THE STUDY

The patients whose disease had attained bacteriological quiescence (see definition below) at the end of a year of chemotherapy were allocated at random to treatment for a second year with daily isoniazid or with a placebo, calcium gluconate. All the patients were treated at home.

Three separate comparisons have been made of the progress of the patients in the second year—namely, between:

(1) those who received chemotherapy with isoniazid for the second year and those who received the placebo, calcium gluconate;

(2) those with definite residual cavitation at one year and those with no definite evidence of residual cavitation;

(3) the patients in the four treatment series in the first year.

CHEMOTHERAPY DURING THE FIRST YEAR

Four regimens were studied for the first year, namely:

PH. Isoniazid, 3.9-5.5 mg/kg body-weight, plus PAS sodium, 0.2-0.3 g/kg, daily, divided into two doses by mouth—i.e., 200 mg of isoniazid plus 10 g of PAS sodium a day for a patient weighing 100 lb.¹

HI-1. Isoniazid alone, 7.8-9.6 mg/kg daily, in one dose by mouth—i.e., 400 mg of isoniazid a day for a patient weighing 100 lb.

HI-2. Isoniazid alone, 7.8-9.6 mg/kg daily, divided into two doses by mouth—i.e., 400 mg of isoniazid a day for a patient weighing 100 lb.

H. Isoniazid alone, 3.9-5.5 mg/kg daily, divided into two doses by mouth—i.e., 200 mg of isoniazid a day for a patient weighing 100 lb.

DEFINITION OF BACTERIOLOGICAL QUIESCENCE AT ONE YEAR

A patient's disease was classified as bacteriologically quiescent at one year if all the cultures for at least the last three monthly examinations, that is, after 10, 11 and 12 months of treatment, had been negative. The patients had been intensively investigated and had usually had seven to nine negative cultures at the last three monthly examinations.

ASSESSMENT OF CAVITATION AT ONE YEAR

The division of the patients into those with definite residual cavitation at one year and those without evidence of residual cavitation was made by an independent assessor (Dr Raj Narain) on the basis of the postero-anterior radiographs and tomographic series taken at 12 months.

ALLOCATION OF TREATMENT FOR THE SECOND YEAR

The patients had originally been admitted to treatment in the period 5 October 1957 to 6 December 1958.

Each patient who completed a year of chemotherapy, and had quiescent disease, on the evidence of the then available bacteriological data (the culture results at 11 and 12 months were usually not available at that time), was allocated to treatment for the second year, usually within a week of the completion of the first year's therapy. The random allocation to calcium gluconate or isoniazid was made from two pre-arranged lists, one for the patients with

¹ 1 lb. = 0.45 kg.

residual cavitation and the other for the patients without residual cavitation. These lists were based on random sampling numbers and had been incorporated in two series of numbered, sealed envelopes. The allocation was made by the Centre's statistical staff from the next envelope in the appropriate series. The medical and the statistical staff had no prior knowledge of which treatment any individual patient would receive.

NUMBERS IN THE SECOND-YEAR STUDY

In the main analysis of the earlier report (Tuberculosis Chemotherapy Centre, 1960), 192 patients were classified as having bacteriologically quiescent disease at one year. Of these, 181 patients (70 PH, 41 HI-1, 36 HI-2, 34 H) were allocated at random to calcium gluconate (88 patients) or to isoniazid (93 patients), 55 having residual cavitation at one

TABLE 1
NUMBERS OF PATIENTS IN THE 16 SUB-GROUPS
IN THE MAIN ANALYSIS

Chemotherapy during the first year	Cavitation status at one year	Treatment during the second year	Number of patients
PH	Cavitated	Calcium	12
		Isoniazid	14
	Non-cavitated	Calcium	21
		Isoniazid	23
HI-1	Cavitated	Calcium	7
		Isoniazid	7
	Non-cavitated	Calcium	16
		Isoniazid	11
HI-2	Cavitated	Calcium	2
		Isoniazid	5
	Non-cavitated	Calcium	15
		Isoniazid	14
H	Cavitated	Calcium	2
		Isoniazid	6
	Non-cavitated	Calcium	13
		Isoniazid	13
All patients			181

year and 126 showing no evidence of residual cavitation. They form the basis of the main analysis in this report (Table 1). The remaining 11 patients (4 PH, 2 HI-1, 1 HI-2, 4 H) were not included in the random allocation to treatment for the second year, for the reasons given on page 424.

A further nine patients (4 PH, 4 HI-1, 1 HI-2) with disease whose bacteriological status at one year was in doubt (Tuberculosis Chemotherapy Centre, 1960) are the subject of a subsidiary analysis in this report (see page 424).

TREATMENT IN THE SECOND YEAR

All the patients were treated at home in the second year. The dosages of the two regimens were:

Isoniazid

200 mg daily, for patients weighing 100 lb. or more (4.4 mg/kg body-weight or less);

175 mg daily, for patients weighing 80-99 lb. (3.9-4.8 mg/kg body-weight);

150 mg daily, for patients weighing less than 80 lb. (4.2 mg/kg body-weight or more).

The daily dosage was taken as one pill in the morning. If a patient increased in weight and moved into a higher weight category, the dosage of isoniazid was increased at the next monthly examination; if, however, the patient lost weight and moved into a lower weight category, the dosage was not decreased.

Calcium

500 mg of calcium gluconate a day, taken as one pill in the morning.

GENERAL MANAGEMENT IN THE SECOND YEAR

During the second year the patients attended the Centre monthly for a month's supply of their medicine and for a routine examination. Their homes were usually visited twice a month, one visit to deliver a bottle for a sputum specimen and the other, a surprise visit, to count the stock of pills and, for the patients receiving isoniazid, to collect a specimen of urine, in order to check, by the naphthoquinone-mercuric chloride test (Short & Case, 1957; Gangadharam et al., 1958), that the drug was being taken. The patients were encouraged to undertake their normal occupations and were often not at home when visits were made.

COLLAPSE THERAPY AND RESECTION

None of the patients who are considered in this report had any form of collapse therapy or resection during the two years.

CLINICAL INVESTIGATIONS

Examinations and assessments were undertaken monthly and included (a) a postero-anterior radiograph, (b) measurement of the weight (lb.) and (c) an assessment of the degree of physical activity and of the working capacity. The erythrocyte sedimentation rate (ESR Westergren, one-hour reading) was measured every three months. At the end of two years a series of tomographs was taken.

BACTERIOLOGICAL INVESTIGATIONS

The patients were asked to bring an overnight sputum specimen to the Centre each month. If, on inspection, it appeared to be only saliva, it was discarded and a pair of laryngeal swabs (regarded as a single specimen) was obtained instead. At two years, two overnight sputum specimens and a pair of laryngeal swabs were examined for each patient. The standard procedure was, therefore, to obtain 14 bacteriological specimens from each patient during the second year. Occasionally, extra specimens were examined, especially if a positive result had recently been obtained. (If a patient relapsed bacteriologically (see definition below) extra specimens were usually ordered.) The sputum specimens were examined by smear and culture, and the pairs of laryngeal swabs by culture only. Tests of sensitivity to isoniazid were performed on one positive culture each month. The techniques have been described in an earlier report (Tuberculosis Chemotherapy Centre, 1959).

DEFINITION OF BACTERIOLOGICAL RELAPSE

Patients who yielded two or more positive cultures in a period of six months, that is, in seven consecutive monthly examinations, have been considered to have relapsed bacteriologically. (This definition of relapse is the one used by Devadatta et al. (1961), and is more stringent than that used by Velu et al. (1960).)

INDEPENDENT ASSESSMENT OF THE RADIOGRAPHS

All the radiographic series for the second year were shown to an independent assessor (Dr Raj Narain) who was unaware of the treatment allocated to any patient in the first or the second year. Apart from the cavitation assessments (for which tomographic series as well as postero-anterior radiographs were studied), the assessments were made only from postero-anterior radiographs. The assessor classified (a) the extent of residual disease at one year on the basis of the lung-zone involvement, using standard

definitions (Daniels et al., 1948), (b) the lesions at one year as unilateral or bilateral, (c) the total extent of residual disease at one year as nil, trivial, slight, limited, moderate, extensive or gross (for definitions, see Appendix), (d) the cavitation at one year as extensive, moderate, slight or nil, (e) the cavitation at two years as more, unchanged, less or disappeared, in relation to the cavitation at the end of one year, and (f) the radiographic changes in the second year as exceptional, considerable, moderate, or slight improvement; as no change; or as slight, moderate, or considerable deterioration, viewing the postero-anterior radiographs at one and two years.

PLAN OF THE REST OF THE REPORT

Sections II to VII deal with patients all of whom had bacteriologically quiescent disease at one year.

Section II

A comparison of the progress in the second year of the 88 patients who received one year of chemotherapy (calcium series) with that of the 93 patients who received two years of chemotherapy (isoniazid series).

Section III

A comparison of the progress in the second year of the 55 patients with definite residual cavitation at one year with that of the 126 patients without residual cavitation at one year.

Section IV

A comparison of the progress in the second year of the 70 patients who received the PH regimen in the first year with that of the 41 patients who received the HI-1, the 36 who received the HI-2 and the 34 who received the H regimen.

Section V

(a) The results in the 16 sub-groups of the three main comparisons in sections II, III and IV (Table 1).

(b) The results for all the 181 patients in the 16 sub-groups combined.

Section VI

The regularity of self-administration of the medications.

Section VII

The results for the 11 patients not allocated at random to treatment for the second year.

Section VIII

The progress in the second year of the nine patients whose bacteriological status at one year was in doubt.

II. COMPARISON OF THE CALCIUM AND THE ISONIAZID SERIES

CLINICAL AND RADIOGRAPHIC CONDITION AT THE START OF THE FIRST YEAR

A large proportion of the patients had serious disease on their admission to the first-year study. Thus, 76% of the calcium and 78% of the isoniazid series had bilateral disease at the start of the first year; 67% of the calcium and 63% of the isoniazid series had a radiographic lesion whose total extent was classified as moderate, extensive or gross—that is, it involved, as a minimum, a total area of lung greater than that occupied by the right upper lobe as visualized on a postero-anterior radiograph (see Appendix); and 94% of the calcium and 87% of the isoniazid series had cavitated lesions. Tubercle bacilli were cultured from the sputum of all the patients. Considering the results of a *single* collection specimen, 75% of the calcium and 76% of the isoniazid patients had a positive result on direct smear examination.

AGE AND SEX

The distributions of estimated age (not tabulated here) were broadly similar, although more of the patients in the calcium than in the isoniazid series were aged 45 years or more—namely, 22% as compared with 10%. At the other extreme 25% and 30%, respectively, were less than 25 years old. Considering the sex distributions, 70% of the calcium and 62% of the isoniazid series were males.

RADIOGRAPHIC CONDITION AT ONE YEAR

The assessments of the radiographic condition at one year are given for the calcium and the isoniazid series in Table 2, Part A. Of the 88 calcium patients 60% had bilateral disease, as compared with 62% of the 93 isoniazid patients; 3% and 4%, respectively, had no residual radiographic lesion. The proportions of the patients with three or more lung zones involved in residual disease were 39% for the calcium and 41% for the isoniazid series. Considering the total extent of disease, 11% of each series had moderate or extensive disease and 57% and 66%, respectively, had lesions of limited extent. In the calcium series 26% of the patients had residual cavitation, as compared with 34% in the isoniazid series.

In summary, the two series were similar at the start of the second year.

CLINICAL RESULTS IN THE SECOND YEAR

Death

One patient (isoniazid, non-cavitated, HI-1) had a persistently negative sputum up to 19 months. He left Madras in the 20th month and was supplied with isoniazid by post. He died two-and-a-half months later, having had diarrhoea and oedema of the lower extremities. The residual lesion at 12 months was classified by the independent assessor as being trivial and involving one lung zone, and there was no change in the radiographic appearances at 19 months. It seems unlikely that this patient died of tuberculosis.

Changes in weight

Of 86 calcium and 92 isoniazid patients who followed the allocated regimen uninterruptedly for the second year, 38% and 45%, respectively, gained weight; 52% of the calcium and 49% of the isoniazid patients lost weight. The average weight change was a loss of 0.7 lb. for the calcium series and of 0.1 lb. for the isoniazid series.

Changes in radiographic appearances

The considerable majority of patients—namely, 65 (74%) of the calcium and 73 (78%) of the isoniazid series—showed no change in the radiographic appearances in the second year; 12% of the calcium and 13% of the isoniazid series showed radiographic improvement (Table 3, Part A).

Changes in cavitation

Considering the patients with residual cavitation at one year, cavitation disappeared in seven of 23 patients in the calcium series and was less in nine more, as compared with 10 and 11, respectively, of 32 patients in the isoniazid series (Table 4, Part A). There were 65 patients in the calcium series with no residual cavitation at one year. Cavitation was present at two years in three and two more had had their treatment changed on account of a bacteriological relapse with a radiographic deterioration. The corresponding figures for the 61 patients in the isoniazid series were 4 and 0, respectively; one patient in the isoniazid series died.

TABLE 2
RADIOGRAPHIC CONDITION AT ONE YEAR

	Part A				Part B				Part C							
	Treatment during the second year				Cavitation status at one year				Chemotherapy during the first year							
	Calcium		Isoniazid		Cavitated		Non-cavitated		PH		HI-1		HI-2		H	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
<i>Extent of radiographic lesion:</i>																
Nil	3	3	4	4	0	0	7	6	4	6	0	0	1	3	2	6
Unilateral	32	36	31	33	9	16	54	43	21	30	15	37	17	47	10	29
Bilateral	53	60	58	62	46	84	65	52	45	64	26	63	18	50	22	65
<i>Number of lung zones involved in disease:</i>																
0 or 1	29	33	27	29	5	9	51	40	20	29	10	24	15	42	11	32
2	25	28	28	30	15	27	38	30	19	27	12	29	11	31	11	32
3	25	28	29	31	25	45	29	23	22	31	14	34	10	28	8	24
4	6	7	9	10	9	16	6	5	7	10	5	12	0	0	3	9
5 or 6	3	3	0	0	1	2	2	2	2	3	0	0	0	0	1	3
<i>Total extent of disease:</i>																
Nil or trivial	17	19	16	17	0	0	33	26	12	17	7	17	8	22	6	18
Slight	11	12	6	6	2	4	15	12	4	6	5	12	2	6	6	18
Limited	50	57	61	66	37	67	74	59	42	60	26	63	25	69	18	53
Moderate	9	10	10	11	15	27	4	3	12	17	3	7	1	3	3	9
Extensive	1	1	0	0	1	2	0	0	0	0	0	0	0	0	1	3
<i>Extent of cavitation:</i>																
Nil	65	74	61	66	0	0	126	100	44	63	27	66	29	81	26	76
Slight	9	10	13	14	22	40	0	0	11	16	7	17	1	3	3	9
Moderate	12	14	14	15	26	47	0	0	9	13	7	17	6	17	4	12
Extensive	2	2	5	5	7	13	0	0	6	9	0	0	0	0	1	3
Total patients	88	100	93	100	55	100	126	100	70	100	41	100	36	100	34	100

BACTERIOLOGY IN THE SECOND YEAR

Number of culture results

Table 5 sets out the number of culture results in the second year. It will be seen from Part A that the majority of patients in both series—namely, 66% of the calcium and 73% of the isoniazid patients—had 11 to 14 culture results during the year; 31% of the calcium and 23% of the isoniazid patients had more than 14 culture results. The average number

of culture results was similar, being 13.8 for the calcium and 13.6 for the isoniazid series.

Culture results

The results of the culture examinations for tubercle bacilli during the second year are given in Table 6, Part A. Seventy-six (86%) of the 88 calcium and 86 (92%) of the 93 isoniazid patients yielded only negative cultures during the second year; three (3%) of the calcium and six (6%) of the isoniazid

TABLE 3
CHANGES IN RADIOGRAPHIC APPEARANCES DURING THE SECOND YEAR

	Patient series	Total patients		Improvement				No change		Deterioration		Change of treatment ^a		Death				
				Moderate		Slight				Slight	Moderate	No.	%					
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%					
Part A	Treatment during the second year	Calcium	88	99	0	0	11	12	65	74	7	8	3	3	2	2	0	0
		Isoniazid	93	100	1	1	11	12	73	78	7	8	0	0	0	0	1	1
Part B	Cavitation status at one year	Cavitated	55	100	1	2	4	7	42	76	7	13	1	2	0	0	0	0
		Non-cavitated	126	101	0	0	18	14	96	76	7	6	2	2	2	2	1	1
Part C	Chemotherapy during the first year	PH	70	100	0	0	10	14	55	79	2	3	1	1	2	3	0	0
		HI-1	41	99	1	2	4	10	30	73	4	10	1	2	0	0	1	2
		HI-2	36	101	0	0	5	14	29	81	2	6	0	0	0	0	0	0
		H	34	101	0	0	3	9	24	71	6	18	1	3	0	0	0	0
Part D	All patients		181	100.1	1	0.6	22	12.2	138	76.2	14	7.7	3	1.7	2	1.1	1	0.6

^a On account of a radiographic deterioration (confirmed by an independent assessor) associated with a bacteriological relapse.

patients yielded a single positive culture. The isolated positive cultures in the calcium patients were produced at 15, 16 and 17 months and were growths of one, four and two colonies, respectively. The isoniazid patients yielded positive cultures at 14, 15, 17, 19, 20 and 21 months which were 1-plus

growth (20-100 colonies), one colony, two colonies, one colony, 1-plus growth and 1-plus growth, respectively. Nine (10%) calcium patients and one (1%) isoniazid patient yielded more than one positive culture during the second year. In summary, the large majority of patients in both series yielded only

TABLE 4
CHANGES IN CAVITATION STATUS DURING THE SECOND YEAR^a

	Patient series	Total patients with cavitation at one year	Disappearance of cavitation	Cavities smaller or fewer	No change	Cavities larger or more numerous	Total patients without cavitation at one year	Appearance of cavitation	Change of treatment ^b	Death	
											Part A
		Isoniazid	32	10	11	7	4	61	4	0	1
Part B	Chemotherapy during the first year	PH	26	8	9	5	4	44	2	2	0
		HI-1	14	6	5	0	3	27	1	0	1
		HI-2	7	2	4	1	0	29	3	0	0
		H	8	1	2	5	0	26	1	0	0
Part C	All patients		55	17	20	11	7	126	7	2	1

^a Assessments on standard radiographs and tomographic series at one and at two years.

^b On account of a radiographic deterioration (confirmed by an independent assessor) associated with a bacteriological relapse.

TABLE 5
NUMBER OF CULTURE RESULTS DURING THE SECOND YEAR

Total number of culture results	Part A		Part B		Part C				Part D
	Treatment during the second year		Cavitation status at one year		Chemotherapy during the first year				All patients
	Calcium	Isoniazid	Cavitated	Non-cavitated	PH	HI-1	HI-2	H	
	No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %
10 or less	2 2	4 4	2 4	4 3	2 3	2 5	1 3	1 3	6 3.4
11-14	57 66	67 73	38 69	86 70	49 72	29 72	21 58	25 74	124 69.7
15 or more	27 31	21 23	15 27	33 27	17 25	9 22	14 39	8 24	48 27.0
Total patients ^a	86 99	92 100	55 100	123 100	68 100	40 99	36 100	34 101	178 100.1
Average number of culture results	13.8	13.6	13.7	13.7	13.6	13.5	14.1	13.6	13.7

^a Excluding two patients (both calcium; both non-cavitated; both PH) who had their treatment changed on account of a bacteriological relapse with a radiographic deterioration and one patient (isoniazid, non-cavitated, HI-1) who died.

negative cultures. Isolated positive cultures were more frequent in the isoniazid series and multiple positive cultures in the calcium series.

Sensitivity test results

Isoniazid-sensitivity test results were available in the second year for the three calcium patients (all non-cavitated; 1 HI-2, 2 H) who yielded isolated positive cultures. All were sensitive. Results were also available for four of the six isoniazid patients

with isolated positive cultures; two (both non-cavitated; 1 PH, 1 HI-1) were isoniazid-sensitive and two (both non-cavitated; 1 PH, 1 HI-2) were highly resistant.

Considering the nine patients in the calcium series who relapsed bacteriologically (Table 8), eight had isoniazid-sensitive strains and the ninth had a highly resistant strain. The patient on isoniazid who relapsed bacteriologically did so with a strain which had a low level of resistance to isoniazid.

TABLE 6
RESULTS OF CULTURE EXAMINATIONS FOR TUBERCLE BACILLI DURING THE SECOND YEAR

Results of culture examinations	Part A		Part B		Part C				Part D
	Treatment during the second year		Cavitation status at one year		Chemotherapy during the first year				All patients
	Calcium	Isoniazid	Cavitated	Non-cavitated	PH	HI-1	HI-2	H	
	No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %
All cultures negative	76 86	86 ^a 92	50 91	112 ^a 89	63 90	38 ^a 93	32 89	29 85	162 ^a 89.5
One culture positive	3 3	6 6	1 2	8 6	2 3	1 2	2 6	4 12	9 5.0
More than one culture positive	9 10	1 1	4 7	6 5	5 7	2 5	2 6	1 3	10 5.5
Total patients	88 99	93 99	55 100	126 100	70 100	41 100	36 101	34 100	181 100.0

^a Including the one patient who died (see page 413).

TABLE 7
DISEASE STATUS IN THE SECOND YEAR

Finding	Part A				Part B				Part C								Part D	
	Treatment during the second year				Cavitation status at one year				Chemotherapy during the first year								All patients	
	Calcium		Isoniazid		Cavitated		Non-cavitated		PH		HI-1		HI-2		H			
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
<i>Quiescent disease</i>																		
All cultures negative	76	86	85	91	50	91	111	88	63	90	37	90	32	89	29	85	161	89.0
Isolated positive culture	3	3	6	6	1	2	8	6	2	3	1	2	2	6	4	12	9	5.0
<i>Relapsed disease</i>																		
Bacteriological relapse (two or more positive cultures) without radiographic deterioration	7	8	1	1	4	7	4	3	3	4	2	5	2	6	1	3	8	4.4
Bacteriological relapse with radiographic deterioration necessitating a change of treatment	2	2	0	0	0	0	2	2	2	3	0	0	0	0	0	0	2	1.1
<i>Death</i>																		
	0	0	1	1	0	0	1	1	0	0	1	2	0	0	0	0	1	0.6
Total patients	88	99	93	99	55	100	126	100	70	100	41	99	36	101	34	100	181	100.1

TABLE 8
PATIENTS WHO RELAPSED BACTERIOLOGICALLY DURING THE SECOND YEAR

Patient's serial number	Chemotherapy during the first year	Treatment during the second year	Cavitated at one year	Treatment changed in the second year (on account of radiographic deterioration)	Months of all the positive cultures	Results of isoniazid-sensitivity tests ^a
A 146	PH	Calcium	Yes	No	19, 20, 21, 22(2), ^b 23, 24(2)	R, R, R, R, R, R
A 287	PH	Calcium	Yes	No	24(2)	S
A 18	PH	Calcium	No	No	18, 20(2), 22, 24	S, S, S, NT
A 38	PH	Calcium	No	Yes	20, 21(3), 22	S, NT, S
A 156	PH	Calcium	No	Yes	18, 19(3)	S, NT
A 19	HI-1	Calcium	Yes	No	23, 24(3)	S, S
A 61	HI-1	Calcium	No	No	14, 15	S, S
A 275	HI-2	Calcium	No	No	19, 20, 23	S, S, S
A 20	H	Calcium	No	No	20, 21, 22, 23(2), 24	S, S, S, S, S
A 229	HI-2	Isoniazid	Yes	No	14(2), 15, 19, 24(2)	R, R, R, NT

^a R = Resistant; S = Sensitive; NT = Not tested.

^b The figures in parentheses indicate the number of positive cultures obtained in the month.

Disease status in the second year

Of the calcium series 76 (86%) patients and of the isoniazid series 85 (91%) patients yielded only negative cultures in the second year (Table 7, Part A); three (3%) of the former series and six (6%) of the latter series yielded an isolated positive culture. If these isolated positive findings are regarded as unimportant (Raleigh, 1957; Velu et al., 1960; Devadatta et al., 1961), the proportion of patients with bacteriologically quiescent disease throughout the period was 90% for the calcium and 98% for the isoniazid series. Bacteriological relapse occurred in nine (10%) of the calcium and one (1%) of the isoniazid patients, a statistically significant difference

($P < 0.01$). Two of the patients in the calcium series had a radiographic deterioration, confirmed by an independent assessor (Dr K. S. Sanjivi), necessitating a change of treatment. The details of the 10 patients who relapsed bacteriologically are set out in Table 8. Of the nine patients in the calcium series five had received the PH regimen in the first year, two the HI-1, one the HI-2 and one the H regimen; the patient in the isoniazid series had received the HI-2 regimen. The time when the first positive culture of the relapse was obtained ranged from the 14th to the 24th month for the patients in the calcium series and was the 14th month for the patient in the isoniazid series.

III. COMPARISON OF THE CAVITATED AND THE NON-CAVITATED SERIES

In this section the progress in the second year of the 55 patients with residual cavitation at one year is compared with that of the 126 patients who had no definite evidence of residual cavitation. Before considering the second-year findings, the clinical and other radiographic features at one year are compared to see whether the cavitated and the non-cavitated series differed in other respects also.

AGE AND SEX

There was little difference between the two series in the distributions of estimated age. Of the patients in the cavitated series 22% were under 25 years of age, as compared with 30% of the non-cavitated series; 35% and 33%, respectively, were in the 25-34 age-group and 16% and 15%, respectively, were aged 45 years or more. There were more males in the cavitated than in the non-cavitated series—namely, 78% as compared with 61%. These findings differ from those in the report of Velu et al. (1960) in which the non-cavitated series contained many more young patients and slightly more male patients than the cavitated series.

RADIOGRAPHIC CONDITION AND THE ESR AT ONE YEAR

The assessments of the radiographic condition at one year are given in Table 2, Part B. Of the patients in the cavitated series 84% had bilateral disease, as compared with 52% in the non-cavitated series; 29% of the former series and 3% of the latter had moderate or extensive disease. At the other extreme, 4% and 38%, respectively, had slight, trivial, or no

residual disease. The number of lung zones involved in disease was three or more in 64% of the cavitated and 29% of the non-cavitated series. In summary, the cavitated series had more extensive residual radiographic lesions than the non-cavitated series.

In an earlier study (Velu et al., 1960) the patients with residual cavitation had higher ESRs at one year than the patients without residual cavitation. In the present study, however, the distributions for the two series at one year were similar, 34% and 32%, respectively, having normal ESRs (0-10 mm) and 14% and 13%, respectively, ESRs of 51 mm or more.

CLINICAL RESULTS IN THE SECOND YEAR

Death

One patient (non-cavitated) died. His case is summarized on page 413.

Changes in weight

Of 55 patients assessed in the cavitated series 51% lost weight, as compared with 50% of 123 assessed in the non-cavitated series. The average change in weight was a loss of 0.5 lb. for the cavitated and 0.3 lb. for the non-cavitated series.

Changes in radiographic appearances

The majority of the patients (76% of each series) showed no radiographic change in the second year (Table 3, Part B). In the cavitated series eight (15%) of the patients had a radiographic deterioration, as compared with 11 (9%) in the non-cavitated series; in two (2%) of the latter series the deteriorations led

to a change of treatment. Thus, the differences in the radiographic progress of the two series in the second year were small.

Changes in cavitation

Of the 55 patients with cavitated lesions, the cavitation had disappeared in 17 and was less in 20 (Table 4, Part C). Of the 126 patients assessed as having no residual cavitation at one year, seven had cavitation at two years and two more had had a bacteriological relapse with a radiographic deterioration necessitating a change of treatment; one had died (Table 4). It may be concluded that there was a tendency towards further improvement in the cavitated series and that the great majority of patients without residual cavitation at one year remained without cavitation during the second year.

BACTERIOLOGY IN THE SECOND YEAR

Number of culture results

Table 5, Part B, sets out the distributions of the number of culture results during the second year for

the two series. The distributions were closely similar and the average number of cultures was 13.7 for both the cavitated and the non-cavitated series.

Culture results

Of the 55 patients in the cavitated series, 91% yielded negative cultures throughout the second year, as compared with 89% of the 126 patients in the non-cavitated series; 2% and 6%, respectively, yielded an isolated positive culture, and 7% and 5%, respectively, yielded more than one positive culture (Table 6, Part B).

Disease status in the second year

Of the cavitated series 93%, and of the non-cavitated series 94%, had quiescent disease throughout the second year, and four (7%) and six (5%), respectively, had bacteriologically relapsed disease two of the latter having, in addition, a radiographic deterioration necessitating a change of treatment (Table 7, Part B). Eight of the patients were excreting isoniazid-sensitive organisms and the remaining two (both cavitated), isoniazid-resistant organisms (Table 8).

IV. COMPARISON IN THE SECOND YEAR OF THE FOUR TREATMENT SERIES OF THE FIRST YEAR

In this section the progress in the second year of the 70 patients in the PH series with bacteriologically quiescent disease at one year is compared with that of the 41 HI-1, 36 HI-2 and 34 H patients. Before considering the findings, the four series are compared at the beginning of the first year, the time when the original random allocation was made, and also at the end of the first year.

RADIOGRAPHIC AND BACTERIOLOGICAL CONDITION AT THE START OF THE FIRST YEAR

The proportions with bilateral disease were 80% for the PH, 78% for the HI-1, 72% for the HI-2 and 76% for the H series; 73% of the PH, 68% of the HI-1, 56% of the HI-2 and 56% of the H series had a total extent of disease classified as moderate, extensive or gross. Four or more lung zones were involved in disease in 66% of the PH, 63% of the HI-1, 53% of the HI-2 and 50% of the H series. The proportions with cavitated disease were 90%, 98%, 89% and 85%, respectively, and the cavitation

was extensive in 13%, 2%, 0% and 0%, respectively. The proportions positive on direct smear examination of a single collection specimen of sputum were 74%, 85%, 78% and 65%, respectively, for the four series. It may be concluded that there was evidence that the PH and HI-1 series contained more patients who had been severely ill on their original admission to treatment than did the HI-2 and H series. This finding is not surprising since the proportion of patients who attained bacteriological quiescence was greater in the PH and HI-1 series than in the HI-2 and H series (Tuberculosis Chemotherapy Centre, 1960).

AGE

There were differences between the age distributions in the four series. Thus, 34% of the PH, 24% of the HI-1, 31% of the HI-2 and 15% of the H series were under the age of 25 years. At the other extreme, 21%, 12%, 6% and 18%, respectively, were 45 years or older.

RADIOGRAPHIC CONDITION AT ONE YEAR

The proportions of the patients in the four series with bilateral disease were 64% for the PH, 63% for the HI-1, 50% for the HI-2 and 65% for the H series (Table 2, Part C). The distributions of the total extent of disease were broadly similar, although 17%, 7%, 3% and 12%, respectively, had moderate or extensive disease. The proportions with three or more lung zones involved were 44% for the PH, 46% for the HI-1, 28% for the HI-2 and 35% for the H series, and the proportions with residual cavitation were 37%, 34%, 19% and 24%, respectively. There was, thus, evidence that the HI-2 series had smaller residual lesions than the other three series.

CLINICAL RESULTS IN THE SECOND YEAR

Death

One patient (HI-1) died. His case is summarized on page 413.

Changes in weight

Of 68 patients in the PH series with observations available, 59% gained weight, as compared with 25% of 40 HI-1, 42% of 36 HI-2 and 26% of 34 H patients. The average change in weight was a gain of 1.8 lb. for the PH series, a loss of 3.5 lb. for the HI-1, a gain of 0.3 lb. for the HI-2 and a loss of 1.7 lb. for the H series.

Changes in radiographic appearances

The majority of the patients in all four series—namely, 79% of the PH, 73% of the HI-1, 81% of the HI-2 and 71% of the H series—showed no change in the radiographic appearances (Table 3, Part C); the proportions showing improvement were 14%, 12%, 14% and 9%, respectively. There were, thus, no major differences between the four series in the second year.

Changes in cavitation

Of 26 patients in the PH series with cavitation at one year (Table 4, Part B), cavitation had disap-

peared in eight and in nine more it was less, as compared with six and five, respectively, of 14 HI-1 patients, two and four of seven HI-2 patients and one and two of eight H patients. Considering the patients with no cavitation at one year, cavitation appeared in two of 44 patients in the PH series and two more had their treatment changed on account of a radiographic deterioration associated with a bacteriological relapse. Cavitation appeared in one of 27 HI-1 patients, three of 29 HI-2 and one of 26 H patients.

BACTERIOLOGY IN THE SECOND YEAR

Number of culture results

The numbers of culture examinations are set out in Table 5, Part C. The majority of patients in all four series had 11-14 cultures, but the HI-2 series had a considerably higher proportion of patients with 15 cultures or more than the other series (39%, as compared with 25% of the PH series, 22% of the HI-1 and 24% of the H series). Even so, the average numbers of cultures for the four series were very similar—namely, 13.6 for the PH, 13.5 for the HI-1, 14.1 for the HI-2 and 13.6 for the H series.

Culture results

All the cultures were negative in 90% of the PH, 93% of the HI-1, 89% of the HI-2 and 85% of the H series (Table 6, Part C); the proportions with more than one positive culture were 7%, 5%, 6% and 3%, respectively. The differences between the four series were thus minor.

Disease status in the second year

The disease was quiescent throughout the second year in 93% of the PH, 93% of the HI-1, 94% of the HI-2 and 97% of the H patients (Table 7, Part C). The disease relapsed in five (7%), two (5%), two (6%) and one (3%), respectively. Two of these patients (both PH) had a radiographic deterioration in addition (Table 8). All except two (1 PH, 1 HI-2) relapsed with isoniazid-sensitive organisms (Table 8).

V. SEPARATE AND AMALGAMATED RESULTS IN THE 16 SUB-GROUPS OF THE THREE MAIN COMPARISONS

RESULTS IN THE 16 SUB-GROUPS OF THE THREE MAIN COMPARISONS

The 181 patients with bacteriologically quiescent disease at one year who were allocated at random

to calcium gluconate or to isoniazid may be classified into 16 sub-groups according to three factors—namely, the chemotherapy in the first year, the cavitation status at one year and the treatment during the second year (Table 9). The number of

TABLE 9
NUMBERS OF PATIENTS IN THE 16 SUB-GROUPS WITH BACTERIOLOGICALLY QUIESCENT DISEASE THROUGHOUT THE SECOND YEAR

Chemotherapy during the first year	Cavitation status at one year	Treatment during the second year	All patients	Patients with bacteriologically quiescent disease throughout the second year	
				No.	%
PH	Cavitated	Calcium	12	10	(83) ^a
		Isoniazid	14	14	(100)
	Non-cavitated	Calcium	21	18	(86)
		Isoniazid	23	23	(100)
HI-1	Cavitated	Calcium	7	6	(86)
		Isoniazid	7	7	(100)
	Non-cavitated	Calcium	16	15	(94)
		Isoniazid	10 ^b	10	(100)
HI-2	Cavitated	Calcium	2	2	(100)
		Isoniazid	5	4	(80)
	Non-cavitated	Calcium	15	14	(93)
		Isoniazid	14	14	(100)
H	Cavitated	Calcium	2	2	(100)
		Isoniazid	6	6	(100)
	Non-cavitated	Calcium	13	12	(92)
		Isoniazid	13	13	(100)
Total patients			180 ^b	170	94.4

^a The parentheses indicate percentages based on fewer than 25 observations.

^b Excluding the one patient who died with quiescent tuberculosis (see page 413).

patients with bacteriologically quiescent disease throughout the second year in each sub-group is given in the table. Although the figures are small they do not suggest that there were major differences between any of the sub-groups contributing to the three main comparisons already presented. It is evident, however, that the patients who had no residual cavitation and were treated with calcium fared less well than those who received isoniazid, six (9%) of 65 of the former, as compared with none of 60 of the latter, having relapsed bacteriologically in the second year—a statistically significant difference ($P < 0.02$).

AMALGAMATED RESULTS OF THE 16 SUB-GROUPS

In view of the finding that there were no *major* differences, as far as could be judged from the available numbers, in the response of the patients in the 16 sub-groups contributing to the three main comparisons, the findings were amalgamated for all the 181 patients. These findings may be summarized as follows:

Radiographic changes

Of the 181 patients (Table 3, Part D) 76.2% showed no change in the radiographic appearances

during the second year, 9.4% showed radiographic deterioration and 1.1% had had treatment changed following a bacteriological relapse with a radiographic deterioration. One patient had died.

Changes in cavitation

Of the 55 patients with cavitation at one year, the cavitation had disappeared in 17 (31%), was less in 20 (36%) and was unchanged or more in 18 (33%) (Table 4, Part C). Of the 126 patients with no residual cavitation at one year, cavitation was apparent at two years in seven (6%), two patients had had their treatment changed and one patient had died.

Culture results

The patients were investigated intensively, the average number of cultures being 13.7 (Table 5, Part D). Of the 181 patients, 162 (89.5%) yielded only negative cultures, nine (5.0%) had one positive culture and 10 (5.5%) had more than one positive culture (Table 6, Part D).

Disease status in the second year

In all, 93.9% of the patients had quiescent disease throughout the second year and 5.5% had bacteriologically relapsed disease.

In summary, the over-all findings in the second year for the patients who had bacteriologically quiescent disease at one year was very satisfactory, the relapse rate being 5.5%.

Prognostic factors

An analysis (not tabulated here) was undertaken to investigate factors of possible prognostic importance in the 10 patients whose disease relapsed bacteriologically in the second year. There was a suggestion that these patients had more extensive disease on their original admission to treatment than those whose disease remained quiescent. Thus, on admission, eight of the 10 patients had four, five or six lung zones involved in disease, as compared with 58% of the 170 patients with persisting quiescent disease, and five of the 10 had a 3-plus (heavy) positive result on smear examination of the sputum, as compared with 28% of the 170. On the other hand, the initial cavitation, the total extent of disease (see Appendix), the ESR and the age were not factors of prognostic importance. Of the 10 patients who relapsed six were males, as compared with 113 (66%) of those whose disease remained quiescent.

There was little difference in the month of the original sputum conversion in the first year, eight of the patients whose disease relapsed having had their sputum converted to negativity within the first four months, as compared with 143 (84%) of those with quiescent disease.

Considering the disease status at one year, there was little difference in terms of either the radiographic factors—namely, the extent of cavitation, the number of lung zones involved in disease and the total extent of the disease—or the ESRs.

VI. REGULARITY OF SELF-ADMINISTRATION OF THE MEDICINE

Two methods were used to check the regularity with which the patients took the medicaments—namely, counts of the pill stocks at surprise visits to the home for all the patients, and, for the patients who received isoniazid, tests for the presence of the drug in specimens of urine obtained at the Centre and at surprise visits to the home. As pointed out elsewhere (Tuberculosis Chemotherapy Centre, 1960), the tests on specimens obtained at visits to the Centre permit valid comparisons of the regularity of self-administration, whereas the interpretation of the results of tests on specimens obtained at surprise visits to the home and of pill counts at surprise visits is open to bias.

PILL COUNTS

Table 10 sets out the findings for the counts of the patients' stocks of pills at surprise visits to the home. The average number of counts for the patients in the calcium series was 10.8 and for those in the isoniazid series 12.1. Of the total of 895 counts in the calcium series 20.4% disclosed incorrect stocks, as compared with 15.9% of 1111 counts for the isoniazid series. There were differences between the four treatment series; the percentage of incorrect stocks ranged from 14.4% in the HI-1 series to 23.0% in the H series. The male patients had incorrect stocks at 18.3% of the counts and the

TABLE 10
REGULARITY OF SELF-ADMINISTRATION OF MEDICINE DURING THE SECOND YEAR
(AS ASSESSED BY PILL COUNTS AT SURPRISE VISITS TO THE HOME)

	Treatment during the second year		Cavitation status at one year		Chemotherapy during the first year				Sex	
	Calcium	Isoniazid	Cavitated	Non-cavitated	PH	HI-1	HI-2	H	M	F
Number of patients with one or more pill counts ^a	83	92	54	121	67	39	35	34	117	58
Total number of occasions on which pills were counted	895	1111	599	1407	739	499	386	382	1238	768
Average number of pill counts per patient	10.8	12.1	11.1	11.6	11.0	12.8	11.0	11.2	10.6	13.2
Number of occasions on which incorrect pill stocks were found	183	177	115	245	133	72	67	88	227	133
Percentage of occasions on which incorrect pill stocks were found	20.4	15.9	19.2	17.4	18.0	14.4	17.4	23.0	18.3	17.3

^a Excluding two patients (both calcium; both non-cavitated; both PH; 1 male, 1 female) who had their treatment changed on account of a bacteriological relapse with a radiographic deterioration, and one patient (isoniazid, non-cavitated, HI-1, male) who died.

female patients at 17.3% of the counts. It will be noted that the average number of counts in the male patients was 10.6 and in the female patients 13.2, indicating that female patients were more often at home and their stocks of pills were, therefore, more readily accessible for checking.

URINE TESTS

The urine was tested by the naphthoquinone-mercuric chloride test (Short & Case, 1957) and, if a negative result was obtained, a hydrolysis test was performed (Gangadharam et al., 1958). Table 11 sets out the results of the tests on the urine specimens.

TABLE 11
REGULARITY OF SELF-ADMINISTRATION OF ISONIAZID DURING THE SECOND YEAR
(AS ASSESSED BY THE NAPHTHOQUINONE-MERCURIC CHLORIDE TEST ON URINE SPECIMENS)

	Specimens obtained at visits to the Centre								Specimens obtained at surprise visits to the home							
	Cavitation status at one year		Chemotherapy during the first year				Sex		Cavitation status at one year		Chemotherapy during the first year				Sex	
	Cav.	Non-cav.	PH	HI-1	HI-2	H	M	F	Cav.	Non-cav.	PH	HI-1	HI-2	H	M	F
Number of patients with one or more test results ^a	32	60	37	17	19	19	57	35	31	57	35	17	17	19	53	35
Total number of test results	512	945	576	284	297	300	894	563	276	535	301	177	157	176	361	450
Average number of test results per patient	16.0	15.8	15.6	16.7	15.6	15.8	15.7	16.1	8.9	9.4	8.6	10.4	9.2	9.3	6.8	12.9
Number of test results which were negative	113	244	142	71	76	68	193	164	65	189	78	73	45	58	85	169
Percentage of test results which were negative	22.1	25.8	24.7	25.0	25.6	22.7	21.6	29.1	23.6	35.3	25.9	41.2	28.7	33.0	23.5	37.6

^a Excluding the one patient (non-cavitated, HI-1, male) who died.

Considering the specimens obtained at visits to the Centre, the proportion of negative test results ranged from 22.7% in the H series to 25.6% in the HI-2 series. The males had a smaller proportion of negative test results (21.6%) than the females (29.1%). Considering the results for specimens obtained at surprise visits the findings ranged from 25.9% of results negative in the PH series to 41.2% in the HI-1

series. The male patients yielded negative results in 23.5% and the females in 37.6% of the tests. In summary, approximately a quarter of all the specimens obtained at the Centre were negative, the females being more irregular in taking their medicine than the males, and there was evidence of greater irregularity, especially among the females, at surprise visits to the home.

VII. RESULTS IN THE 11 PATIENTS NOT ALLOCATED TO TREATMENT AT RANDOM

There were 11 eligible patients who were not included in the random allocation. Six patients (2 PH, both cavitated; 1 HI-1, cavitated; 3 H, 1 cavitated, 2 non-cavitated) who had quiescent disease at one year, according to the definition adopted in this report, were misclassified as having active disease at one year, because the results of the cultures at 11 and 12 months were not available at that time. All of them, therefore, continued on the first-year treatment for the second year also. Five had quiescent disease throughout the second year, but one (H, cavitated) relapsed bacteriologically in the 14th month, with isoniazid-resistant organisms. There were four patients (2 PH, both non-cavitated; 1 HI-1, non-cavitated; 1 H, cavitated) who were

regarded as unlikely to co-operate and were, therefore, prescribed non-random calcium gluconate in the second year. Of these, one (PH) relapsed bacteriologically in the 17th month with isoniazid-sensitive organisms. The other three had quiescent disease throughout the second year. The eleventh patient (HI-2, non cavitated) who had quiescent disease at one year continued, in error, to receive the HI-2 regimen until 15 months and then received calcium gluconate. The disease was quiescent throughout the second year.

In summary, two (1 non-cavitated, calcium in second year; 1 cavitated, isoniazid in second year) of the 11 patients had a bacteriological relapse.

VIII. PATIENTS WITH DISEASE OF DOUBTFUL BACTERIOLOGICAL STATUS AT ONE YEAR

As reported earlier (Tuberculosis Chemotherapy Centre, 1960) nine patients (4 PH, 4 HI-1, 1 HI-2) were classified as having disease of doubtful bacteriological status at one year. These were patients whose cultures were all negative at three or more consecutive monthly examinations, but who produced an isolated positive culture at one of the last three monthly examinations, that is, at 10, 11 or 12 months. These nine patients represented 2.9% of the total of 315 patients in the main analysis.

One patient (PH, cavitated) was regarded as unlikely to co-operate and received non-random calcium gluconate. The remaining patients were allocated, at random, to calcium gluconate (five patients) or to isoniazid (three patients). Of the five patients who received calcium gluconate one (PH) had cavitated disease and the other four (2 PH, 2

HI-1) had non-cavitated disease at one year. Of the three patients who received isoniazid one (HI-1) had cavitated disease and the other two (1 HI-1, 1 HI-2) had non-cavitated disease at one year.

Of these nine patients, classified as having disease of doubtful status at one year, seven had quiescent disease throughout the second year, and one (isoniazid, non-cavitated, HI-2) yielded a single colony of isoniazid-resistant tubercle bacilli at 24 months. Only one (isoniazid, non-cavitated, HI-1) had a bacteriological relapse. This occurred in the 17th month with organisms highly resistant to isoniazid. It may be concluded that an isolated positive culture in the last three months of the *first* year of treatment for this group of patients under *intensive* bacteriological investigation did not carry a bad prognosis in the second year.

IX. DISCUSSION

This report is mainly concerned with the progress in the second year of the 192 patients in a 1-year comparison of four different regimens of domiciliary chemotherapy whose pulmonary tuberculosis had attained bacteriological quiescence by the end of the period (Tuberculosis Chemotherapy Centre, 1960). All the patients had bacteriologically confirmed tuberculosis on their original admission to treatment, and the great majority had advanced disease. They were drawn from the same ill-housed, overcrowded, malnourished, low-income or unemployed section of the community in Madras City as those admitted to an earlier study of treatment at home or in sanatorium for a year with isoniazid plus PAS (Tuberculosis Chemotherapy Centre, 1959).

Considering the findings for the 181 patients (from all four first-year regimens combined) in the present study who were allocated at random to treatment for the second year, 90% of 88 who received the placebo, calcium gluconate, and 98% of 93 who received isoniazid had quiescent disease throughout the second year. There was thus suggestive evidence that a second year of isoniazid had some effect in preventing relapse.

Of the 181 patients, 55 had residual cavitation at one year, the "open-negative" syndrome, and 126 had no residual cavitation; 93% of the former and 94% of the latter had quiescent disease throughout the second year, closely similar findings.

Considering the progress of the patients in the second year according to their chemotherapeutic regimen in the first year, 93% of those who received the standard combination of isoniazid plus PAS had quiescent disease throughout the second year, as compared with 93% of those on the moderate daily dosage of isoniazid in one dose a day, 94% of those who received the same moderate dosage of isoniazid but in two doses a day and 97% of the patients who received a small dosage of isoniazid in two doses a day; the differences between the four first-year treatment series were thus only minor.

The plan of the second-year study reported here and the protocol followed were the same as in an earlier study of a second year of chemotherapy (Velu et al., 1960). Consequently, the two medications (isoniazid and placebo) and their dosages, the supervision of the patients, the clinical and bacteriological investigations, and the intensity with which they were performed, were the same. Thus, the

average number of culture results in the second year was 13.4 in the earlier study (Velu et al., 1960) and 13.7 in the present study. Further, the relapse rates in the second year were not influenced by the chemotherapeutic regimens in the first year, which were isoniazid plus PAS in the earlier study, and the same combination and three regimens of isoniazid alone in the present study. It is therefore permissible to amalgamate the findings of the present study with those of the earlier study (Velu et al., 1960; Devadatta et al., 1961) in which 126 patients with quiescent disease at the end of a year's treatment with isoniazid plus PAS were allocated at random for a second year, 61 to calcium gluconate and 65 to isoniazid, and so obtain consolidated results.

Amalgamating the two studies, there were 149 patients who received calcium gluconate in the second year and 91% maintained quiescence, as compared with 96% of 158 patients who received isoniazid, a difference which attains statistical significance at the 5% level (see below). Of the 97 patients with cavitated disease at one year the disease remained quiescent in 91%, as compared with 95% of 210 with non-cavitated disease.

In the earlier study, for reasons given by Devadatta et al. (1961), no definite conclusions could be reached about the role of isoniazid in the prevention of bacteriological relapse, although there was some evidence that it might be effective in lesions without residual cavitation but not in lesions with residual cavitation. The additional data from the present study have clarified the position. Thus, considering the patients with residual cavitation at one year in both studies combined (Table 12), four of 42 patients who received the placebo in the second year relapsed bacteriologically, as compared with four of 55 patients who received isoniazid, very similar findings. The corresponding figures for the patients with no residual cavitation at one year were 10 relapses among 107 patients who received the placebo and no relapses among 103 patients who received isoniazid, a highly significant difference ($P < 0.005$). Thus, the evidence indicates that isoniazid alone in the second year did not influence the relapse rate in patients with the open-negative syndrome, but that for the patients with no residual cavitation, there was a definite benefit from isoniazid therapy in the second year.

The findings have implications not only for the developing countries but also for the countries with

TABLE 12
EFFECT OF TREATMENT DURING THE SECOND YEAR ON THE RELAPSE RATE OF THOSE WITH AND THOSE WITHOUT RESIDUAL CAVITATION AT ONE YEAR (TWO STUDIES COMBINED)

Cavitation status at one year	Treatment during the second year	Velu et al. (1960)			Present study			Both studies combined		
		All patients	Patients who relapsed in the second year		All patients	Patients who relapsed in the second year		All patients	Patients who relapsed in the second year	
			No.	%		No.	%		No.	%
Cavitated	Calcium	19	1	(5) ^a	23	3	(13)	42	4	10
	Isoniazid	23	3	(13)	32	1	3	55	4	7
Non-cavitated	Calcium	42	4	10	65	6	9	107	10	9
	Isoniazid	42	0	0	61	0	0	103	0	0
Total patients . . .		126	8	6.3	181	10	5.5	307	18	5.9

^a The parentheses indicate percentages based on fewer than 25 observations.

extensive resources for treating tuberculosis. The optimum duration of chemotherapy is generally regarded to be many months and, indeed, it has even been recommended that chemotherapy for tuberculosis should, in selected cases, continue for life (*Lancet*, 1953) or indefinitely (Dooneief, Hite & Bloch, 1955). For the open-negative syndrome other workers also recommend indefinitely prolonged chemotherapy, either with combinations of drugs (Pfuetze, Watson & Pyle, 1960), with combined therapy and then isoniazid alone (Worobec, Krasner & Fox, 1960), or with isoniazid alone (Hyde, 1960). Although these may be extreme views, many authorities would regard 18 months to two years as the minimum required for disease as far advanced as that under consideration in this study (Smart & Gough, 1958; Tucker, 1958; American Trudeau Society, 1958) or for any type of lesion (Ross et al., 1958; Ross, 1959; Crofton, 1960). The absence of relapses among the patients who had had no evidence of residual cavitation at one year and received isoniazid treatment in the second year suggests that two years of chemotherapy may be the *maximum* necessary for such patients, even if they had extensive bilateral cavitated disease when first diagnosed. The relapse rate in the third year, which is very relevant to an assessment of the maximum period of chemotherapy required, is not yet known for the combined group, but for the patients in the earlier study it was very low (Devadatta et al., 1961). It would be surprising if

these findings with extensive disease did not apply to less extensive lesions. The findings should, therefore, have relevance also to the highly developed countries, where more and more cases are diagnosed by community survey techniques (Seiler, Welstead & Williamson, 1958) and extensive lesions are becoming increasingly uncommon.

For the patients with residual cavitation at one year, therapy with isoniazid alone in the second year, at the dosage used in this study, has not, apparently, prevented bacteriological relapse. This suggests that in countries with adequate supplies of antituberculosis medicaments *combined* chemotherapy should be used, not only in the first, but also in the second year. For the developing countries, with their limited resources, this is rarely practicable. For them, however, it might be profitable to investigate whether a higher dosage of isoniazid would be effective. Unfortunately, a comparatively small increase in the dosage is all that would be permissible in the Madras community without vitamin supplements, for if the dosage is approximately doubled peripheral neuritis becomes a problem (Devadatta et al., 1960).

The over-all bacteriological relapse rate during the second year was 6.3% in the earlier study (Velu et al., 1960; Devadatta et al., 1961) and 5.5% in the present study. Under the social conditions in which these studies were undertaken and considering the severity of the disease initially, these proportions

are low. Even so, the findings could, in all probability, have been improved upon substantially merely by giving isoniazid to all the patients with no residual cavitation at one year instead of to approximately half of them, as in both the earlier and the present study. This would be expected to have resulted in a reduction of the relapse rate to about 3% in the earlier study and 2% in the present study.

The present study confirms the observations made by Raleigh (1957), Velu et al. (1960) and Devadatta et al. (1961) that an *isolated* positive culture in a patient with quiescent disease who is under intensive bacteriological supervision is unimportant.

An increasing body of evidence on the problem of self-administration of medicaments has been accumulated at the Centre (Fox, 1958; Tuberculosis Chemotherapy Centre, 1959, 1960; Velu et al.,

1960; Devadatta et al., 1961). It has been shown in these studies that self-administration presents problems with cachets containing isoniazid plus PAS, with tablets of isoniazid, whether prescribed as several a day (either as one dose or as two doses) or as one tablet a day, or with a placebo, calcium gluconate, also prescribed as one tablet a day. The present study has confirmed the observations for isoniazid prescribed as a single tablet a day and for calcium gluconate; it seems likely that at least a fifth of the doses were not being taken by the patients.

The study is continuing and, like the earlier study (Tuberculosis Chemotherapy Centre, 1959), is planned to continue for five years. When the follow-up is complete for both the studies, it will be possible to make a long-term evaluation of the role of chemotherapy in a developing country on the basis of substantial numbers of patients.

X. SUMMARY

1. In the main analysis of a year's study of isoniazid plus PAS in comparison with three different regimens of isoniazid alone under domiciliary conditions, it was reported that 192 patients had attained bacteriological quiescence at one year (Tuberculosis Chemotherapy Centre, 1960). Of these, 181 were allocated at random to treatment at home for a second year, either with isoniazid alone or with a placebo, calcium gluconate. The daily dosage of isoniazid was 200 mg for patients weighing 100 lb. or more, 175 mg for patients weighing 80-99 lb. and 150 mg for patients weighing less than 80 lb. The daily dosage of calcium gluconate was 500 mg.

2. Three main comparisons have been made for the 181 patients for the second year—namely, between (a) the 88 calcium and 93 isoniazid patients; (b) the 55 patients with residual cavitation and the 126 patients without residual cavitation at one year; (c) the 70 patients who received the combination of isoniazid plus PAS (PH regimen) in the first year and the 41 who received a moderate daily dosage of isoniazid in the first year in one dose (HI-1 regimen), the 36 who received the same moderate daily dosage but in two doses (HI-2 regimen) and the 34 who received a small daily dosage of isoniazid in two doses (H regimen).

3. In addition, the progress of the nine patients whose bacteriological status at one year was in doubt has been studied.

4. One patient (isoniazid, non-cavitated, HI-1) died, probably of a non-tuberculous condition.

5. The patients in the calcium and isoniazid series were similar both on their original admission to treatment, when the great majority had far advanced disease, and also at the start of the second year. During the second year 10% of the calcium and 1% of the isoniazid series relapsed bacteriologically, a statistically significant difference ($P < 0.01$).

6. Comparing the cavitated and non-cavitated series, the cavitated series also had other evidence of more extensive residual lesions at one year; 84% of the former, as compared with 52% of the latter, had bilateral disease and 29% and 3%, respectively, had moderate or extensive disease. During the second year 7% of the cavitated and 5% of the non-cavitated series relapsed bacteriologically. All the relapses in the non-cavitated series occurred in patients receiving the placebo.

7. The PH and HI-1 series contained a greater proportion of patients who had been severely ill on their original admission to treatment than did the HI-2 and H series. At the beginning of the second year the HI-2 series had smaller residual lesions than the other three series. The relapse rates were 7% for the PH, 5% for the HI-1, 6% for the HI-2 and 3% for the H series.

8. Eight of the nine patients on calcium gluconate who relapsed bacteriologically did so with isoniazid-

sensitive organisms. The only isoniazid patient who relapsed did so with resistant organisms. Three calcium patients yielded isolated positive cultures; all were isoniazid-sensitive. Results of sensitivity tests were available for four of the six isoniazid patients with isolated positive cultures; two were sensitive.

9. The self-administration of the medicaments was checked by counting the stocks of pills and by urine tests for isoniazid. Pill counting at surprise visits to the home revealed incorrect stocks in approximately a fifth of the counts, there being hardly any difference between the males and the females. The results of tests on urine specimens obtained at visits to the Centre revealed that approximately a quarter of the doses of isoniazid were not being taken. Tests on surprise specimens of urine showed

a greater degree of irregularity, particularly among the females.

10. Of the nine patients whose bacteriological status at one year was in doubt, one (isoniazid) patient relapsed bacteriologically in the second year.

11. Amalgamating the results of the present and an earlier study in the Madras community, it is concluded that in the second year the relapse rate is low, that a second year of isoniazid alone is of value in patients with no evidence of residual cavitation but not in patients with residual cavitation, and that the chemotherapeutic regimen in the first year does not influence the relapse rates in the second year.

12. The longer term progress of the patients in the present study and the attack rate of tuberculosis in their close family contacts will be the subject of further reports.

RÉSUMÉ

L'analyse des résultats du traitement antituberculeux durant une année, au moyen d'isoniazide + PAS, comparés à ceux obtenus avec 3 régimes différents d'isoniazide seul, chez les malades soignés à domicile, ont montré que 192 malades avaient atteint le stade de quiescence bactériologique à la fin de la première année. Sur ce nombre, 181 furent répartis au hasard pour recevoir à domicile, et pendant une année encore, les uns de l'isoniazide seul, les autres un placebo (gluconate de calcium). La posologie journalière était de 200 mg d'isoniazide pour les malades pesant 45 kg ou plus, de 175 mg pour un poids de 36-44 kg et de 150 mg pour un poids inférieur à 36 kg. La dose de gluconate était de 500 mg par jour.

Les comparaisons principales effectuées sur les 181 malades de deuxième année, ont porté sur les sujets suivants: a) 88 malades recevant du gluconate et 93 de l'isoniazide; b) 55 malades cavitaires et 126 non cavitaires à la fin de la première année; c) 70 malades au régime PH (isoniazide + PAS) durant la première année et 41 malades au régime HI-1 (dose moyenne d'isoniazide quotidienne en une fois), 36 malades au régime HI-2 (dose moyenne quotidienne d'isoniazide en deux fois) et 34 malades au régime H (faible dose quotidienne d'isoniazide en deux doses).

En outre, on a suivi l'évolution de 9 malades dont l'état, du point de vue bactériologique, était douteux.

Un malade au régime HI-1, non cavitaire, mourut, mais pas de tuberculose probablement.

Les groupes de malades recevant les uns du gluconate, les autres de l'isoniazide étaient semblables, tant lors de leur admission au traitement (la plupart étaient gravement atteints) qu'au début de la seconde année. Au cours de cette deuxième année, 10% des malades de la série

recevant du gluconate eurent une rechute bactériologiquement confirmée, contre 1% dans la série recevant de l'isoniazide, différence statistiquement significative ($P < 0,01$).

Les sujets cavitaires présentaient en outre des lésions résiduelles plus étendues, à la fin de la deuxième année, que les sujets non cavitaires. 84% des premiers, contre 52% des seconds avaient des lésions bilatérales, et 29% et 3% avaient une infection modérée ou étendue, respectivement. Durant la deuxième année, 7% des sujets cavitaires eurent une rechute bactériologique contre 5% chez les non cavitaires. Toutes les rechutes chez les non cavitaires survinrent dans la série recevant le placebo.

Les séries PH et HI-1 comportaient une plus forte proportion de malades graves lors de leur admission au traitement que les séries HI-2 et H. Au début de la deuxième année, la série HI-2 avait des lésions résiduelles plus faibles que les trois autres séries. Le taux des rechutes a été de 7% pour la série PH, 5% pour HI-1, 6% pour HI-2 et 3% pour H.

Huit des 9 malades recevant le placebo présentèrent, lors de leur rechute bactériologique, des bacilles sensibles à l'isoniazide. Le seul malade traité par l'isoniazide, qui eut une rechute, présentait les bacilles résistants à l'isoniazide. Des crachats de trois malades recevant du gluconate, il a été possible d'isoler des bacilles tuberculeux, tous sensibles à l'isoniazide. Chez 4 des 6 malades traités à l'isoniazide dont on put obtenir des cultures positives, 2 de ces dernières étaient sensibles au médicament.

On a évalué dans quelle mesure les médicaments ont été réellement ingérés par les malades, en comptant les comprimés restants et en dosant l'isoniazide dans l'urine. La première méthode, appliquée lors de visites-surprises, a révélé une administration incorrecte dans $\frac{1}{6}$ des cas,

sans différence appréciable entre hommes et femmes. Par l'analyse de l'urine, on a pu se rendre compte qu'un quart environ des doses prescrites n'étaient pas ingérées. Des tests-surprises de l'urine montrèrent une irrégularité plus grande encore, surtout chez les femmes.

Des 9 malades dont l'état bactériologique était incertain, un (traité à l'isoniazide) eut une rechute la deuxième année.

L'ensemble des résultats de cette étude et des précédentes permet de conclure que, durant la deuxième année, le taux de rechute est faible, qu'un traitement à l'isoniazide seul durant la deuxième année peut être utile aux malades non cavitaires, mais non pas à ceux qui ont des cavités résiduelles, et que le régime thérapeutique appliqué durant la première année n'influe pas sur le taux des rechutes au cours de la deuxième année.

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APPENDIX

The total extent of the radiographic lesion as seen on a full-plate postero-anterior radiograph was classified in six grades by an independent assessor (Dr Raj Narain) as follows:

- (1) trivial, that is, minimal lesions which the assessor regarded, purely on radiographic grounds, as inactive;
- (2) slight, that is, minimal or rather larger lesions which he regarded as radiographically active;
- (3) limited, that is, lesions of greater extent than in (2) but involving a total area of lung less than that

occupied by the right upper lobe as visualized on a postero-anterior radiograph;

- (4) moderate, that is, lesions of greater extent than in (3) but whose total extent, even if bilateral, did not exceed an area equivalent to the whole of one lung;
- (5) extensive, that is, lesions which involved an area of more than the whole of one lung; and
- (6) gross, that is, very extensive bilateral disease.

The assessor checked the consistency of the grading by reviewing the films in batches, grade by grade.