

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

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A recent report by the Tuberculosis Chemotherapy Centre, Madras, showed that the response of patients to a year's domiciliary treatment for pulmonary tuberculosis with isoniazid plus p-aminosalicylic acid closely approached that of patients to a year's sanatorium treatment with the same combination of drugs. The present report summarizes the findings of a second year's study, carried out on those patients in the first-year study whose disease had attained bacteriological quiescence by the end of the year of combined chemotherapy. The main objects of this follow-up study were to determine (a) whether relapse in the second year was more frequent among the patients originally treated at home than among those originally treated in sanatorium, (b) whether a second year of antituberculosis chemotherapy, with isoniazid alone, would reduce the relapse rate and (c) the influence of residual cavitation at one year, the so-called "pen negative" syndrome, on the results in the second year. During the second year all the patients were treated at home, either with isoniazid or with a placebo, calcium gluconate; in each case the medicine was administered by the patients themselves. It was found that there was very little difference in the relapse rates of "home" and "sanatorium" groups, that a second year of treatment with isoniazid alone did not influence the likelihood of relapse, and that patients with the open negative syndrome fared slightly less well in the second year than patients without residual cavitation.

An earlier report from the Tuberculosis Chemotherapy Centre, Madras, gave the findings of a controlled comparison of combined chemotherapy with isoniazid and p-aminosalicylic acid (PAS) for patients treated at home with the same treatment in sanatorium (Tuberculosis Chemotherapy Centre, 1959). It was found that the response of the domiciliary patients to a year's treatment closely approached the results in the patients treated in sanatorium. It has also been shown (Andrews et al., 1960¹) that the treatment of the patients at home did not expose their contacts to any special risk of contracting the disease during

the year as compared with the risks to contacts of the patients segregated in sanatorium.

Although both these conclusions are encouraging to the use of mass domiciliary treatment of tuberculosis in under-developed countries, they leave unanswered two important issues. These are (a) whether bacteriological relapse and radiographic spread of disease are more frequent in patients who have attained bacteriological quiescence under treatment at home, and (b) whether, in patients who have attained quiescence after one year with combined chemotherapy, a second year of antituberculosis chemotherapy with isoniazid alone gives results at the end of two years superior to those obtained if chemotherapy is stopped at the end of the first year. This report is primarily concerned with these two issues. In addition, it studies (c) the

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¹ See article on page 463 of this issue.

influence of residual cavitation at one year, the so-called "open negative" syndrome, on the results in the second year, and (d) the progress of the patients whose bacteriological status at one year was in doubt because an isolated positive culture had been obtained late in the course of the first year of treatment.

All the patients who form the subject of this report were managed at home in the second year, where they received either a placebo or isoniazid. For several reasons, isoniazid alone was given for the second year instead of the combination isoniazid plus PAS. All the patients had already had a year of the combined chemotherapy, a very long period

indeed in relation to current practice in most of the under-developed countries, and had achieved quiescence. Treatment with isoniazid alone was cheaper and much less bulky and there was a possibility that the self-administration would prove more regular than had been the experience with the combination (Fox, 1958; Tuberculosis Chemotherapy Centre, 1959).

The organization of the Centre, which is under the joint auspices of the Indian Council of Medical Research (ICMR), the Madras State Government, the World Health Organization (WHO) and the Medical Research Council of Great Britain (MRC), was described in detail in the first report (Tuberculosis Chemotherapy Centre, 1959).

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 combined chemotherapy, whether at home or in sanatorium, were allocated at random to treatment for a second year with daily isoniazid or with a placebo, calcium gluconate. Randomization was from two lists, one for those with residual cavitation, the other for those without cavitation. All the patients were treated at home.

The data obtained in this study have been used to make three separate comparisons of the progress in the second year of patients who had quiescent disease at one year—namely, comparisons between:

(1) those who had been treated at home in the first year and those who had been treated in sanatorium;

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

(3) those with definite residual cavitation at one year and those with no definite evidence of residual cavitation.

CHEMOTHERAPY DURING THE FIRST YEAR

All the patients studied in the present report had received isoniazid plus PAS (sodium salt) daily for the 12 months immediately before admission to the present study, those weighing 100 lb. or more having been prescribed 200 mg and 10 mg and 8.75 g daily, and those weighing less than 80 lb. 1560 mg and 7.5 g daily.

DEFINITION OF BACTERIOLOGICAL QUIESCENCE AT THE END OF THE FIRST YEAR

As stated in the first report (Tuberculosis Chemotherapy Centre, 1959), a patient's disease was classified as bacteriologically quiescent at the end of the first year if all the culture for at least the last three monthly examinations, after 10, 11 and 12 months of treatment, had been negative. The patients had all been intensively investigated bacteriologically and had an average of nearly three cultures a month; thus, a patient with quiescent disease at one year had usually had seven to nonnegative cultures at the last three monthly examinations.

ASSESSMENT OF CAVITATION AT ONE YEAR

At the end of the first year of treatment, in addition to a postero-anterior radiograph, every patient had had a tomographic series which was viewed by two members of the medical staff, and, if there was any doubt as to its interpretation, by a third, fourth or even a fifth clinician. Only patients considered to have definite cavitation were classified as having residual cavitation.

ALLOCATION OF TREATMENT FOR THE SECOND YEAR

Each patient who completed the first year of treatment, whether at home or in sanatorium, and had, on the evidence of the then available bacteriological data (the culture results of the eleventh and twelfth months were usually not

available at that time), quiescent disease was allocated to treatment for the second year, within a week of the completion of the first year's therapy. The allocation was made from two pre-arranged lists, one for the patients with residual cavitation and the other for 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 Center's statistical staff from the next envelope in the appropriate series. The medical and statistical staff had no prior knowledge of the treatment which any individual patient would receive.

The patients had originally been allocated to treatment at home or in sanatorium in the period 24 September 1956 to 24 September 1957. The period of intake for the present study, therefore, extended from September 1957 to September 1958.

NUMBERS IN THE SECOND-YEAR STUDY

A total of 130 patients in the main analysis of the earlier report (Tuberculosis Chemotherapy Centre, 1959) were classified as having bacteriologically quiescent disease at the end of the first year. Of these, 126 patients (57 home, 69 sanatorium) were allocated at random to calcium gluconate (61 patients) or to isoniazid (65 patients), 42 having residual cavitation and 84 showing no evidence of residual cavitation. They form the basis of the main analyses in this report (Table 1). The remaining four patients (three home, one

sanatorium) were not included in the random allocation to treatment for the second year (see page 526).

A further 10 patients (seven home, three sanatorium), with disease whose bacteriological status at one year was in doubt (Tuberculosis Chemotherapy Centre, 1959, are the subject of a subsidiary analysis in this report (see page 528).

TREATMENT IN THE SECOND YEAR

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

Isoniazid

200mg daily, for patients weighing 100lb. or more;

175mg daily, for patients weighing 80-99 lb.;

150mg daily for patients weighing less than 80lb.

The daily dose 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 lowered.

Calcium;

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

GENERAL MANAGEMENT IN 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-mercurei 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 either the first or the second year.

TABLE 1
NUMBERS OF PATIENTS IN THE EIGHT SUB-GROUPS IN
THE MAIN ANALYSES

Place of treatment during the first year	Cavitation status at the end of the first year	Treatment during the second year	Number of patients
Home	Cavitated	Calcium	11
		Isoniazid	10
	Non-cavitated	Calcium	18
		Isoniazid	18
Home	Cavitated	Calcium	8
		Isoniazid	13
	Non-cavitated	Calcium	24
		Isoniazid	24
Total . . .			126

ASSESSMENT OF PROGRESS IN THE SECOND YEAR

Examinations and assessment were undertaken monthly and included (a) a postero-anterior radiograph, (b) an examination by smear and culture of an overnight sputum specimen or, if the patient had no sputum, specimen or, if the patient had no sputum, by culture of a pair of laryngeal swabs, (c) tests of sensitivity to isoniazid and PAS on positive cultures, (d) measurement of the weight (lb.) and (e) 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 the second year a series of tomographs was taken and two overnight sputum specimens were examined by smear and culture and a pair of laryngeal swabs was examined by culture.

INDEPENDENT ASSESSMENT OF THE RADIOGRAPHS

All the radiographic series were shown to an independent assessor (Dr J. H. Angel) who was unaware of the treatment allocated to any patient in the first or the second year or of the classification of the lesions by the Centre's medical staff as cavitated or non-cavitated at the end of the first year. Apart from the cavitation assessment, for which tomographic series were also used, all the assessment were made 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 cavitation at one year as extensive, moderate, slight or nil, (d) the cavitation at two years as more, unchanged, less or disappeared, in relation to the cavitation at the end of one year, (e) the radiographic changes in the second year as exceptional, considerable, moderate or slight improvement, no change, or slight, moderate or considerable deterioration, viewing the postero-anterior radiographs at one and two years, and (f) the over-all changes in the radiographic appearances in the two-year period, using the same gradings, and viewing the radiographs on admission and at two years.

There was a minor difference between the original classification of the patients by the Centre's medical staff into those with cavitation and those without cavitation at one year (the basis of the stratification for random allocation) and the subsequent classification by the independent

assessor. In three patients (one home, two sanatorium; two calcium, one isoniazid) the assessor thought a lesion was cavitated where the medical staff had not; in three others (two home, one sanatorium; one calcium, two isoniazid) the reverse applied. The independent assessor's classification has been adopted.

FINANCIAL ASSISTANCE TO FAMILIES IN THE SECOND YEAR

Limited financial assistance was given to especially needy families during the first year of the patient's treatment (Tuberculosis Chemotherapy Centre, 1959). Some families also received financial assistance during the second year. Considering the families of the former home patients, 24 (42%) of the 57 received financial assistance in the second year, as did 26 (38%) of the 69 families of former sanatorium patients. Over half (52%) of these 50 families received financial assistance for one month only. The average monthly disbursement to the former home families receiving financial assistance was Rs. 1.80¹ and for the families of the former sanatorium patients it was Rs 2.67. It may be concluded that the financial assistance had a negligible effect on the economic status of the families in the second year.

MILK POWDER IN THE SECOND YEAR

Small quantities of milk powder were given monthly to the families of all the patients, the quantities being the same as in the first year (Tuberculosis Chemotherapy Centre, 1959).

PLAN OF THE REST OF THE REPORT

The subsequent sections in this report present the following:

Section II. A comparison of the progress in the second year of the 57 patients who had been treated at home for the first year (referred to as "home patients" in this report) with the 69 who had been treated in sanatorium for the first year (referred to as "sanatorium patients").

Section III. A comparison of the progress of the 61 patients allocated calcium gluconate in the second year with that of the 65 allocated isoniazid in the second year.

Section IV. A comparison of the progress of the 42 patients with cavitated lesions at one year with

¹ Rs. 4.80 = US\$ 1.00.

that of the 84 with non-cavitated lesions at one year.

Section V. (a) Results in the eight sub-groups in the tree main comparisons above; (b) the amalgamated results of the eight sub-groups; (c) results in the four patients not allocated to treatment at random.

Section VI. Regularity of self-administration of the medicine.

Section VII. The progress during the second year of the 10 patients whose bacteriological status at one year was classified as doubtful (Tuberculosis Chemotherapy Centre, 1955).

II. COMPARISON IN THE SECOND YEAR OF THE HOME AND SANATORIUM SERIES

CLINICAL AND RADIOGRAPHIC CONDITION AT THE START OF THE FIRST YEAR

It was shown in the earlier report (Tuberculosis Chemotherapy Centre, 1959) that a large proportion of the patients had serious disease on their admission to the first year study. The same is true of those patients whose disease attained quiescence at the end of the first year's treatment and who are therefore considered in the present report. Thus, 82% of the 57 home and 72% of the 69 sanatorium patients had bilateral disease at the start of the first year; 84% of the home and 93% of the sanatorium patients had cavitated lesions, the cavitation being moderate or extensive in 68% of the home and 71% of the sanatorium patients. All the patients had tubercle bacilli in their sputum on admission. Considering the results of a single collection specimen, 89% of the home and 84% of the sanatorium patients had a positive result on a direct smear examination, 51% of the home and 33% of the sanatorium patients having a 3-plus (heavy) positive result.

CLINICAL AND RADIOGRAPHIC CONDITION AT THE END OF THE FIRST YEAR

A comparison of the clinical and radiographic features at the end of the first year are given for the home and sanatorium patients in Table 2, Part A. It will be seen that the home patients, who had had an inferior diet (Tuberculosis Chemotherapy Centre, 1959), weighed less than the sanatorium patients, 15 (26%) of the former compared with 44 (64%) of the latter weighing 100 lb. or more, and that 12% of the home patients had normal ESRs (10 mm or less) compared with 38% in the sanatorium series. Considering the radiographic features, 54% of the home patients and 43% of the sanatorium patients had residual lesions in three or more lung zones; 77% of the home and 67% of the sanatorium patients had bilateral disease; 37% of the home and 30% of the sanatorium series had residual cavitation.

In summary, at the end of the first year the home patients weighed less and had higher ESRs and rather more extensive residual radiographic lesions than the sanatorium patients.

CLINICAL RESULTS IN THE SECOND YEAR

Deaths

There was one death in the total of 126 patients. This occurred in a 48-year-old male patient (home, isoniazid, cavitated). An isolated positive culture was obtained at 15 months, the first for 13 months. It failed to grow on subculture and was followed by five negative cultures at 16 months. The patient's general condition was frail and he died suddenly late in the seventeenth month, following acute pain in his left side and severe dyspnoea. The spontaneous pneumothorax cannot be excluded. There was no clear-cut evidence of activity in the lesion and the radiographic appearances at 16 months showed that slight improvement had occurred in the preceding four months. Permission for a post-mortem examination was not obtained.

Bacteriological relapse with radiographic deterioration

Five patients (one home, four sanatorium) had graphic deterioration, necessitating a change of treatment. The radiographs were reviewed by an independent assessor (Dr K. S. Sanjivi) who was unaware of the treatment allocated to any case, either in the first or in the second year. In four cases he reported a radiographic deterioration and recommended a change of treatment. The fifth case, in which also he reported radiographic deterioration, had a haemoptysis as well, and treatment was changed on this clinical ground.

The home patient, a female aged 26 (calcium, cavitated), remained bacteriologically negative until 22 months, when a positive culture, with organisms sensitive to isoniazid and to PAS, was obtained.

TABLE 2
CONDITION OF PATIENTS AT THE END OF ONE YEAR

	Part A				Part B				Part C			
	Place of treatment during the first year				Treatment during the second year				Cavitation status at the end of the first year			
	home		sanatorium		calcium		isoniazid		cavitated		non-cavitated	
Total patients	57		69		61		65		42		84	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
<i>Weight (lb.):</i>												
60-69	2	4	0	0	1	2	1	2	0	0	2	2
70-79	8	14	2	3	6	10	4	6	5	12	5	6
80-89	15	26	9	13	7	11	17	26	7	17	17	20
90-99	17	30	14	20	15	25	16	25	12	29	19	23
100-109	9	16	24	35	19	31	14	22	9	21	24	29
110 or more	6	11	20	29	13	21	13	20	9	21	17	20
<i>ESR (mm in 1 hour):</i>												
0-10	7	12	26	38	12	20	21	32	3	7	30	36
11-20	14	25	14	20	11	18	17	26	13	31	15	18
21-50	27	47	22	32	31	51	18	28	22	52	27	32
51-100	9	16	7	10	1	11	9	14	4	10	12	14
<i>Number of lung zones involved in disease:</i>												
0	1	2	3	4	3	6	1	2	0	0	4	5
1	7	12	13	19	8	13	12	18	3	7	17	20
2	18	32	23	33	21	34	20	31	11	26	30	36
3	18	32	17	25	18	30	17	26	15	36	20	24
4	11	19	10	14	9	15	12	18	10	24	11	13
5	2	4	3	4	2	3	3	5	3	7	2	2
6	0	0	0	0	0	0	0	0	0	0	0	0
<i>Extent of radio-graphic lesion:</i>												
Nil	1	2	3	4	3	5	1	2	0	0	4	5
Unilateral	12	21	20	29	14	23	18	28	6	14	26	31
Bilateral	44	77	46	67	44	72	46	71	36	86	54	64
<i>Extent of cavitation:</i>												
Nil	36	63	48	70	42	69	42	65	0	0	84	100
Slight	9	16	11	16	10	16	10	15	20	48	0	0
Moderate	9	16	7	10	9	15	7	11	16	38	0	0
Extensive	3	5	3	4	0	0	6	9	6	14	0	0

* 1 lb. = 0.45 kg.

Positive cultures were obtained at 23 and 24 months, the lesion showed radiographic deterioration and treatment was changed.

Of the four sanatorium patients, two were males (calcium, non-cavitated). One of the males developed, in the fourteenth month, a positive sputum which persisted; his treatment was changed in the seventeenth month, at which time there was radiographic deterioration. The organisms were sensitive to isoniazid and to PAS. The second male developed a positive sputum in the seventeenth month; treatment was changed at the end of 22 months, when a radiographic deterioration was confirmed. The organisms were consistently sensitive to isoniazid and to PAS. One of the females developed a positive sputum at 18 months, organisms being sensitive to isoniazid and PAS, associated with a radiographic deterioration. She refused to cooperate in a change of treatment until the twenty-fourth month. The second female developed a positive sputum at 15 months, the organisms being resistant to isoniazid but sensitive to PAS. She had a radiographic deterioration and a haemoptysis, and her treatment was changed in the seventeenth month.

In summary, one home and four sanatorium patients had clear-cut bacteriological relapse with radiographic deterioration. Four of these patients had organisms sensitive to both drugs; one of them, had been allocated to isoniazid.

Changes in weight

Of 55 home and 65 sanatorium patients who followed the allocated regime uninterruptedly for the second year, 33% and 22% respectively, gained weight; 49% of the home and 77% of the sanatorium patients lost weight. The average weight of the home patients was unaltered at two years, whereas the sanatorium patients, who had gained considerably more weight than the home patients in the first year, lost on the average, 5.3 lb. (2.40 kg), of which 3.4 lb. (1.54kg) were lost in the first six months of the second year.

Changes in the ESR

It was pointed out in the earlier report (Tuberculosis Chemotherapy Centre, 1959) that a number of patients with bacteriologically quiescent disease at one year still had an elevated ESR at that time. Results are available at both one year and two years for 54 home and 65 sanatorium patients who followed the allocated regimen uninterruptedly

for the second year. Of these, 47 (87%) of the home and 40 (62%) of the sanatorium patients had an elevated ESR at one year. At two years a considerable proportion of both series—namely, 43 (80%) of the home and 40 (62%) of the sanatorium patients—still had elevated ESRs, the rate being higher than 20 mm in 43% of the home and 32% of the sanatorium patients. Only two patients (one home, one sanatorium) were classified as having bacteriologically relapsed disease at two years; both had normal ESRs.

Changes in radiographic appearances

Of the 57 home and 69 sanatorium patients, 81% and 80% respectively, showed no change in the radiographic appearances in the second year (Table 3, Part A); 9% of the home and 12% of the sanatorium patients had some degree of radiographic improvement, while four of the home patients and two of the sanatorium patients showed slight radiographic deterioration. In addition, one home and four sanatorium patients had their treatment changed as a result of radiographic deterioration associated with a bacteriological relapse, and one other home patient died. It may be concluded that there were comparatively few changes in the radiographic appearances in the course of the second year and that, apart from those in the patients who had their treatment changed, the radiographic changes were trivial.

The radiographic changes over the whole two-year period (not tabulated here) were assessed in order to put the findings for the second year in their proper perspective. In the two-year period 84% of the 57 home and 87% of the 69 sanatorium patients showed at least moderate improvement, the proportions with considerable or exceptional improvement being 53% and 57% respectively.

Changes in cavitation

Of the 36 home and 48 sanatorium patients who were assessed as having no cavitation at one year, one home patient (3%) and one sanatorium patient (2%) had slight cavitation at the end of two years (but two sanatorium patients had had their treatment changed). Of the patients who had had their treatment changed). Of the patients with residual cavitation at one year, and who had received the allocated treatment for the whole of the second year, two of 19 home and four of 19 sanatorium patients had no cavitation and 12 and four, respectively, had less cavitation at two years (Table 4).

TABLE 3
CHANGES IN RADIOGRAPHIC APPEARANCES DURING THE SECOND YEAR

	Patient series	Total patients		Improvement				No change		Slight deterioration		Change of treatment *		Death	
				moderate		slight									
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Part A	Place of treatment during the first year	57	101	1	2	4	7	46	81	4	7	1	2	1	2
		69	101	0	0	8	12	55	80	2	3	4	6	0	0
Part B	Treatment during the second year	61	100	0	0	5	8	49	80	4	7	3	5	0	0
		65	101	1	2	7	11	52	80	2	3	2	3	1	2
Part C	Cavitation status at the end of the first year	42	99	1	2	5	12	30	71	2	5	3	7	1	2
		84	100	0	0	7	8	71	85	4	5	2	2	0	0
Part D	All patients	126	101	1	1	12	10	101	80	6	5	5	4	1	1

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

Procedures

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 was obtained. At two years, two overnight sputum specimens and a pair of laryngeal swabs were examined routinely. The standard procedure was, therefore, to obtain 14 bacteriological specimens from each patient during the second year. Occasionally, extra monthly specimens were examined, especially if a positive result had recently been obtained. Sometimes scheduled bacteriological examinations were missed, and a small proportion of the cultures was contaminated. The sputum specimens were examined by smear and culture, the laryngeal swabs by culture, and tests of sensitivity to isoniazid and to PAS were performed on positive cultures. The techniques have been described in an earlier report (Tuberculosis Chemotherapy Centre, 1959).

Intensity of culture examinations

Table 5 sets out the numbers of culture investigations in the second year. It will be seen from Part A that the majority of patients in both series—namely, 62% of the former home and 77 % of the former sanatorium patients—had 11 to 14 culture results during the year; 27% of the home and 18% of the sanatorium patients had more than 14 culture results. Although there were differences in the distributions for the two series, the average number of culture results was similar, being 13.2 for the home and 13.6 for the sanatorium series.

Culture results

The results of the culture examinations for tubercle bacilli during the second year are given in Table 6, Part A. Fifty-two (91%) of the 57 home and 61 (88%) of the 69 sanatorium patients yielded only negative cultures throughout the second year. Three (5%) home and two (3%) sanatorium patients yielded a single positive culture. One of the home patients died towards the end of the seventeenth month, having produced an isolated positive culture at 15 months following 12 months of bacteriological negativity; the other home patients had isolated cultures at 13 months and 16 months, respectively. The two sanatorium patients yielded isolated positive cultures at 14 and 24 months, respectively. Two home and six sanatorium patients

TABLE 4
CHANGES IN CAVITATION IN THE SECOND YEAR IN PATIENTS WITH
RESIDUAL CAVITATION AT THE END OF ONE YEAR*

Patient series	Total patients	Disappearance of cavitation	Cavities smaller or fewer	No change	Cavities larger or more numerous
Home	19	2	12	1	4
Sanatorium	19	4	4	8	3
Calcium	18	2	7	5	4
Isoniazid	20	4	9	4	3
All patients • *	38	6	16	9	7

* Assessment on standard radiographs and tomographic series at one and at two years.

**Excluding three patients (one home, calcium; two sanatorium, isoniazid) who had their treatment changed on account of a radiographic deterioration associated with a bacteriological relapse and one patient (home, isoniazid) who died.

yielded more than one positive culture during the second year. One of the home and four of the sanatorium patients also deteriorated radiographically and their treatment was changed (page 515). The second home patient produced four positive cultures during the year (at 16, 21 and 24 months), three of the cultures being a solitary colony. Of the remaining two sanatorium patients, one yielded a positive culture at 14, 15 and 16 months, but all the nine cultures between then and the end of the second year

were negative. The other yielded nine positive cultures at eight monthly examinations, the number of colonies being between one and seven in eight of these and 1-plus growth (20-100 colonies) in the ninth. In summary, the majority of patients, whether originally treated at home or in sanatorium, yielded only negative cultures. Isolated positive cultures were uncommon; multiple positive cultures occurred in eight patients and were associated with radiographic deterioration in five of these.

TABLE 5
INTENSITY OF CULTURE EXAMINATIONS DURING THE SECOND YEAR

Total number of culture examinations during the second year	Part A				Part B				Part C				Part D	
	Place of treatment during the first year				Treatment during the second year				Cavitation status at the end of the first year				All patients	
	home		sanatorium		calcium		isoniazid		cavitated		non-cavitated			
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
10 or less	6	11	3	5	3	5	6	10	3	8	6	7	9	8
11-14	34	62	50	77	41	71	43	69	25	66	59	72	84	70
15-20	5	27	12	18	14	24	13	21	10	26	17	21	27	22
Total patients •	55	100	65	100	58	100	62	100	38	100	82	100	120	100
Average number of culture examinations	13.2		13.6		13.4		13.4		13.3		13.4		13.4	

* Excluding five patients (one home, four sanatorium: three calcium, two isoniazid; three cavitated, two non-cavitated) who had their treatment changed on account of a bacteriological relapse with a radiographic deterioration and one patient (home, isoniazid, cavitated) who died.

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	
	Place of treatment during the first year				Treatment during the second year				Cavitation status at the end of the first year				All patients	
	home		sanatorium		calcium		isoniazid		cavitated		non-cavitated			
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
All cultures negative	52	91	61	88	54	89	59	91	37	88	76	90	113	90
One culture positive	3*	5	2	3	2	3	3*	5	1**	2	4	5	5*	4
More than one culture positive	2	4	6	9	5	8	3	5	4	10	4	5	8	6
Total patients	57	100	69	100	61	100	65	101	42	100	84	100	126	100

* Including one patient who died.

** This patient died.

TABLE 7

CLASSIFICATION OF DISEASE AT THE END OF TWO YEARS AS QUIESCENT, PRESUMED QUIESCENT OR RELAPSED, ON THE BASIS OF THE CULTURE RESULTS DURING THE SECOND YEAR

Status at the end of two years	Part A				Part B				Part C				Part D	
	Place of treatment during the first year				Treatment during the second year				Cavitation status at the end of the first year				All patients	
	home		sanatorium		calcium		isoniazid		cavitated		non-cavitated			
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
<i>Patients with bacteriologically quiescent disease:</i> that is, patients all of whose cultures at the last six monthly examinations were negative	54	95	63*	91	56*	92	61	94	37	88	80*	95	117	93
<i>Patients with presumed bacteriologically quiescent disease :</i> that is, patients who produced a solitary positive culture at one of the last six monthly examinations	0	0	1	1	1	2	0	0	0	0	1	1	1	1
<i>Patients with bacteriologically relapsed disease:</i> that is, (a) patients who had more than one positive culture during the last six monthly examinations but no radiographic deterioration or (b) patients who had more than one positive culture at any time in the second year, associated with a radiographic deterioration necessitating a change of treatment	1	2	1	1	1	2	1	2	1	2	1	1	2	2
	1	2	4	6	3	5	2	3	3	7	2	2	5	4
Deaths	1	2	0	0	0	0	1	2	1	2	0	0	1	1
Total patients . . .	57	101	69	99	61	101	65	101	42	99	84	99	126	101

*I Including one patient who produced positive cultures at 14, 15 and 16 months.

Sensitivity test results

The results of the sensitivity tests are of particular interest in relation to whether the patient received calcium gluconate or isoniazid in and are discussed in section III (see page 522).

Bacteriological status at two years

In Table 7 the disease is classified bacteriologically at the end of two years as quiescent, presumed quiescent or relapsed, on the basis of the culture results during the second year. Patients who yielded only negative cultures at the last six monthly examinations were considered to have quiescent disease and the disease in the patient who yielded a single positive culture in this period had been classified as presumed bacteriologically quiescent. Patients who had more than one positive culture in the last six months were regarded as having bacteriologically relapsed disease, as were patients who had more than one positive culture associated with a radiographic deterioration at any time in the second year.

It will be seen from Table 7, Part A, that 54 (95%) of 57 home patients had bacteriologically quiescent disease at two years compared with 63 (91%) of 69 sanatorium patients, and that the disease in one sanatorium patient was presumed quiescent. In all, two (4%) of the home and five (7%) of the sanatorium patients had disease classified as bacteriologically relapsed, one of the home and four of the sanatorium patients having radiographic deteriorations also. Thus, there was little difference between the two series, the great majority of patients in both remaining consistently bacteriologically negative.

Working capacity at two years

The five patients (one home, four sanatorium) who had their treatment changed and the one (home) who died apart, 53 (96%) of 55 home and 63 (97%) of 65 sanatorium patients were undertaking unrestricted activity at two years. The majority of these patients had done so for all or most of the second year. The remaining two home and two sanatorium patients were liked to part-time activity at two years.

II. COMPARISON OF THE CALCIUM GLUCONATE AND ISONIAZID SERIES

In this section the progress of the 61 patients who received calcium gluconate in the second year (the calcium, series) is compared with that of the 65 patients who received isoniazid (the isoniazid series). Before considering the progress in the second year, the clinical and radiographic condition of the patients in the two series at the end of the first year are compared, since the random allocation of the second-year treatment was made at that time.

AGE AND SEX

The distributions of estimated age (not tabulated here) were very similar, 34% of the 61 isoniazid patients being under the age of 25 years; 18% of the calcium and 17% of the isoniazid series were 45 years of age or more. Of the calcium series 57% and of the isoniazid series 65% were males.

CLINICAL AND RADIOGRAPHIC CONDITION AT THE END OF THE FIRST YEAR

The assessment of the clinical and radiographic condition at one year are given for the calcium and isoniazid series in Table 2, Part B. There were rather fewer patients weighing 80-89 lb. in the calcium series than in the isoniazid series-namely,

11% compared with 36%; conversely, there were rather more patients weighing 100-109 lb. in the calcium than in the isoniazid series-namely, 31% compared with 22%. Of the patients in the calcium series, 38 (62%) had an ESR of 21 mm or more compared with 27 (42%) in the isoniazid series, a statistically significant difference. The distributions of the number of lung zones involved in disease and the proportions with bilateral disease were very similar for the two series. There were similar proportions of patients in the two series with residual cavitation at the end of the first year, but six (9%) patients in the isoniazid series had extensive residual cavitation, compared with none in the calcium series. To summarize, the two series were similar at the start of the second year except that rather more patients in the calcium series had a high ESR and the isoniazid series was possibly at a minor disadvantage in respect of the extent of cavitation.

CLINICAL RESULTS IN THE SECOND YEAR

Deaths

The one death among the 126 patients occurred in a male who received isoniazid in the second year. His case is summarized on page 515.

Bacteriological relapse with radiographic deterioration

Of the five patients who had their treatment changed on account of a bacteriological relapse with radiographic deterioration (page 515), three were in the calcium and two in the isoniazid series.

Changes in weight

Of the 58 patients in the calcium series and the 62 in the isoniazid series who followed the allocated regimen uninterruptedly in the second year, 69% and 60%, respectively, lost weight, the calcium series losing, on the average, 2.9 lb. (1.32 kg) and the isoniazid series 2.8 lb. (1.27 kg) and the isoniazid series 2.8 lb. (1.27 kg). In the calcium series the greater part of the loss-2.4 lb. (1.09 kg)-occurred in the first six months of the second year, but in the isoniazid series the loss was distributed evenly over the two 6-month periods.

Changes in the ESR

At the beginning of the second year 19% of 57 calcium patients with observations available had a normal ESR (10mm or less) compared with 34% of 62 isoniazid patients. A difference persisted at the end of two years, 25% of the patients in the calcium series compared with 36% of the isoniazid series having normal ESRs at that time.

Changes in radiographic appearances

In each series (Table 3, Part B) 80% of patients showed no change in the radiographic appearances in the second year; five patients in the calcium series and eight in the isoniazid series showed radiographic improvement. Seven (11%) of the calcium and four (6%) of the isoniazid series showed radiographic deterioration, treatment being changed in three of the calcium and two of the isoniazid patients. There is a suggestion that the isoniazid series had fared better, but the differences are trivial.

Changes in cavitation

Of the 42 calcium and 42 isoniazid patients who were assessed as having no cavitation at one year, two of the calcium patients had slight cavitation at two years (two more patients on calcium had had their treatment changed). There were 18 calcium and 20 isoniazid patients with residual cavitation at one year who received the allocated treatment for the whole of the second year. At two years two calcium and four isoniazid patients had no cavitation and seven of the former and nine of the latter had less cavitation (Table 4). The over-all findings were slightly in favour of the isoniazid series.

BACTERIOLOGY IN THE SECOND YEAR

Intensity of culture examinations

Table 5, Part B, sets out the distributions for the number of culture examinations during the second year for the two series. The distributions were very similar, the average number of cultures being 13.4 for both series.

Culture results

During the second year, 3% of the calcium and 5% of the isoniazid patients yielded isolated positive cultures, and 8% of the calcium and 5% of the isoniazid series yielded two or more positive cultures (Table 6, Part B).

Sensitivity test results

Sensitivity test results were available in the second year for four of the five patients who yielded isolated positive cultures. (None of the four had had residual cavitation at one year). Two (one home, one sanatorium) of the four were in the calcium series; one (home) yielded organisms sensitive to both drugs and the other a strain that was resistant to both drugs and the other a strain that was resistant to isoniazid and sensitive to PAS. The remaining two patients (one home, one sanatorium) had received isoniazid; the strains from both were sensitive to isoniazid and to PAS.

Of three patients who yielded multiple positive cultures and who did not deteriorate radiographically, two (one home, one sanatorium; both noncavitated) were in the calcium series. One (sanatorium) had organisms resistant to isoniazid but sensitive to PAS. The other yielded strains that were sensitive to both drugs at 16 months, sensitive to isoniazid but resistant to PAS. The other yielded strains that were sensitive to both drugs at 16 months, sensitive to isoniazid but resistant to PAS at 21 months, and resistant to both drugs at two years. The third patient (sanatorium, cavitated) received isoniazid; all his strains were resistant to isoniazid but sensitive to PAS.

Of five patients who relapsed bacteriologically with a radiographic deterioration, three (one home, cavitated; two sanatorium, non-cavitated) were in the calcium series. The strains in these three cases were sensitive to both drugs. The remaining two patients (sanatorium, cavitated) received isoniazid. One, who took her medication irregularly, relapsed with a strain sensitive to both drugs; the other relapsed with a strain resistant to isoniazid but sensitive to PAS.

In summary, 12 patients had results of sensitivity tests. The first positive culture in the second year was sensitive to PAS in all 12 patients. Of seven patients in the calcium series the first culture was sensitive to isoniazid in five and resistant in two, and of five patients who received isoniazid the first culture was sensitive to isoniazid in three and resistant in two.

Bacteriological status at two years

Four patients on calcium and three on isoniazid had relapsed bacteriologically, three of the former and two of the latter with radiographic deterioration

(Table 7). One patient on isoniazid died. Apart from one calcium patient with presumed quiescent disease, the remaining 92% of the calcium patients and the 94% of the isoniazid series had bacteriologically quiescent disease. It may be concluded that the bacteriological status of the second year.

Working capacity at two years

Considering the patients who continued on the allocated treatment for the whole of the second year, 97% of the patients in each series had unrestricted activity at two years, and the remainder were on part-time activity.

IV. COMPARISON OF THE CAVITATED AND ON-CAVITATED SERIES

In this section the progress in the second year of the 42 patients with residual cavitation at one year is compared with that of the 84 patients who had no definite evidence of residual cavitation. Before considering the progress in the second year, the clinical and other radiographic features at one year are compared to see whether the cavitated and non-cavitated series differed in other respects also.

AGE AND SEX

There was a major difference in the distributions of estimated age for the two series; 14% of the 42 patients in the cavitated series were under 25 years of age, compared with 40% of the 84 in the non-cavitated series. At the other extreme, 29% of the patients in the cavitated series were aged 45 years or more, compared with 12% of the non-cavitated series. The sex distribution was similar, 57% of the cavitated and 63% of the non-cavitated series being male.

CLINICAL AND RADIOGRAPHIC CONDITION AT THE END OF THE FIRST YEAR

The assessments of the clinical and radiographic condition at one year are given for the cavitated and non-cavitated series in Table 2, Part C. The weight distributions were similar. There was a striking difference between the two series in the distributions of the ESRs, 7% of the cavitated series having a normal ESR (10mm or less) compared with 36% of the non-cavitated series ($P < 0.01$). The cavitated series had more extensive residual lesions, as indicated by the number of lung zones involved in disease, for only 75 had less than two lung zones involved compared with 25% of the non-cavitated lesions. Correspondingly, 86% of the cavitated

compared with 64% of the non-cavitated lesions were bilateral. In summary, the cavitated series had higher ESRs and more extensive radiographic lesions than the non-cavitated series.

CLINICAL RESULTS IN THE SECOND YEAR

Deaths

The one death among the 126 patients occurred in a male who received isoniazid in the second year. His case is summarized on page 515.

Bacteriological relapse with radiographic deterioration

Of the five patients who had their treatment changed on account of a bacteriological relapse with radiographic deterioration (page 515), three were in cavitated and two in the non-cavitated series.

Changes in weight

Of the 38 patients in the cavitated series and the 82 in the non-cavitated series who followed the allocated regimen uninterruptedly for the second year, 68% and 62% respectively, lost weight. The average loss of weight in the second year was 2.6 lb. (1.18 kg) for the cavitated series and 3.0 lb. (1.36 kg) for the non-cavitated series, the loss of weight between one year and 18 months being 1.6 lb. (0.73 kg) and 2.1 lb. (0.95 kg), respectively.

Changes in the ESR

The distribution of the ESRs for the two series at one year and two years is shown in Table 8. It will be seen that there was a tendency for the ESR to fall in both series, but that this was greater in the cavitated series. Thus, 41% of the cavitated series had an ESR of 20 mm or less at one year compared

TABLE 8
DISTRIBUTIONS OF THE ERYTHROCYTE
SEDIMENTATION RATE AT ONE YEAR AND AT TWO
YEARS ACCORDING TO THE CAVITATION STATUS AT
THE END OF THE FIRST YEAR

ESR (mm in 1 hour)	At one year				At two years			
	cavitated		non-cavitated		cavitated		non-cavitated	
	No.	%	No.	%	No.	%	No.	%
0 -10	3	8	29	35	8	22	8	34
11 - 20	12	32	15	18	15	41	24	29
21 - 50	18	49	26	32	10	27	25	30
51 - 100	4	11	12	15	4	11	5	6
Total Patients assessed*	37	100	82	100	37	101	82	99

*Excluding five patients (three cavitated, two non-cavitated) who had their treatment changed on account of bacteriological relapse with a radiographic deterioration, one patient (cavitated) who died and one patient (cavitated) for whom one observation is missing.

with 62% at two years. In the non-cavitated series the corresponding proportions were 54% at one year compared with 63% at two years.

Changes in radiographic appearances

The majority of the patients (71% in the cavitated and 85% in the non-cavitated series) showed no radiographi change in the second year (Table 3, Part C). In the cavitated series there were five radiographic deteriorations (three leading to changes of chemotherapy) and one death, compared with six deteriorations (two leading to changes of chemotherapy) in the non- cavitated series. There was thus little difference in the radiographic progress of the two series in the second year.

Changes in cavitation

Of 84 patients assessed as having no residual cavitation at one year, two had cavitation at two years and two had a bacteriological relapse with a radiographic deterioration necessitating a change of treatment. Of 42 patients with cavitated lesions, one died and three had their treatment changed. Cavitation disappeared in six patients (Table 4) and was less in 16 others. It may be concluded that the great majority of patients without residual cavitation during the second year and that there was a tendency to further improvement in the cavitated series.

BACTERIOLOGY IN THE SECOND YEAR

Intensity of culture examinations

The intensity of culture examination is set out in Table 5, Part C. The distributions were very

similar for the two series; the average number of culture examinations was 13.3 for the cavitated and 13.4 for the non- cavitated series.

Culture results

One patient (2%) with residual cavitation at one year had a single positive culture compared with four (5%) in the non- cavitated series (Table 6, Part C). Four (10%) of the cavitated and four (5%) of the non- cavitated series yielded more than one positive culture. It may be concluded that there was, at most, a slight disadvantage to the cavitated series.

Sensitivity tests results

In four patients with residual cavitation (see page 522), the first positive culture in the second year was sensitive to isoniazid in two cases and resistant to isoniazid in two, compared with six sensitive and two resistant strains in eight patients without residual cavitation. All 12 strains were sensitive to PAS.

Bacteriological status at two years

The great majority of patients in both series had bacteriologically quiescent disease at two years (Table 7) -namely, 37 (88%) of the 42 patients in the cavitated series and 80 (95%) of the 84 in the non- cavitated series, the disease in one (1%) more of the latter being presumed bacteriologically quiescent. Four (10%) patients in the cavitated series had relapsed bacteriologically, three (7%) with a radiographic deterioration, compared with three (4%) in the non- cavitated series, two (2%) with a radiographic deterioration. One patient in the cavitated series died. There was thus a suggestion that the patients with residual cavitation at one year fared slightly less well than the patients without residual cavitation.

In view of this finding, a sub-analysis was undertaken of the bacteriological status at two years in the patients with cavitated lesions, according to whether they received calcium gluconate or isoniazid in the second year. Of 19 patients who were allocated to the calcium series, 18 had bacteriologically quiescent disease and one had relapsed bacteriologically with a radiographic deterioration, compared with 19 patients with bacteriologically quiescent disease, one bacteriologically relapsed, two relapsed bacteriologically with a radiographic deterioration and one death in 23 patients allocated to isoniazid. It may be concluded that the patients with cavitated lesions who continued treatment in the calcium

series for the second year were not at a disadvantage compared with those receiving isoniazid.

Working capacity at two years

Considering the patients who continued on the allocated treatment for the whole of the second year,

92% of 38 patients in the cavitated series had unrestricted activity at two years compared with 99% of 82 patients in the non-cavitated series. The remaining patients were on part-time activity.

V. RESULTS IN THE EIGHT SUB-GROUPS OF THE THREE MAIN COMPARISONS AND IN PATIENTS NOT ALLOCATED TO TREATMENT AT RANDOM.

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

The 126 patients with bacteriologically quiescent disease who were allocated at random to calcium gluconate or to isoniazid may be classified in eight sub-groups according to three factors (Table 9). The number of patients with bacteriologically quiescent disease at the end of two years in each sub-group is given in the table. Although the figures are small they do not suggest that there is any important difference between any of the sub-groups contributing to the three main comparisons already presented.

AMALGAMATED RESULTS TO THE EIGHT SUB-GROUPS

In view of the finding that there was comparatively little difference in the response of the patients in the eight sub-groups contributing to the three main comparisons (Table 9), it is legitimate to amalgamate the findings for all 126 patients whether they were treated at home or in sanatorium in the first year, whether they received calcium gluconate or isoniazid in the second year and whether or not they had residual cavitation at one year. The findings are readily summarized as follows:

Radiographic changes

Of the 126 patients, 80% showed no change in the radiographic appearances during the second year; 5% had slight deterioration, 4% had had a change of treatment following a bacteriological relapse with radiographic deterioration and one patient had died (Table 3, Part D).

Culture results

Of the 126 patients, 90% yielded only negative cultures, 4% had one positive culture and the

remaining 6% had more than one positive culture (Table 6, Part D).

Bacteriological status at two years

In all, 93% of the patients had bacteriologically quiescent disease at two years and the disease in one more patient (1%) was presumed bacteriologically quiescent; 2% of the patients had had a bacteriological relapse without a radiographic deterioration and 4% had had a bacteriological relapse with a radiographic deterioration (Table 7, Part D).

In summary, the over-all findings in the second year for the patients who had bacteriologically quiescent disease at one year were very satisfactory, the relapse rate being 6%.

TABLE 9
NUMBERS OF PATIENTS IN THE EIGHT SUB-GROUPS WITH BACTERIOLOGICALLY QUIESCENT DISEASE AT THE END OF TWO YEARS

Place of treatment during the first year	Cavitation status at the end of the first year	Treatment during the second year	Number of patients	Patients with bacteriologically quiescent disease at the end of two years	
				No.	%
Home	Cavitated	Calcium	11	10	91
		Isoniazid	10	9	90
	Non-cavitated	Calcium	18	17	94
		Isoniazid	18	18	100
Home	Cavitated	Calcium	8	8	100
		Isoniazid	13	10	77
	Non-cavitated	Calcium	24	21	88
		Isoniazid	24	24	100
Total . . .			126	117	93

RESULTS IN THE FOUR PATIENTS NOT ALLOCATED TO TREATMENT AT RANDOM

There were four eligible patients who were not included in the random allocation. One male patient (home, cavitated) had a carcinoma of the oesophagus and died in the fifteenth month. Two female patients (one home, one sanatorium; both non-cavitated) were considered unlikely to co-operate in the second year; they received no antituberculosis chemotherapy, and at two years they still had quiescent disease. One male patient (home) with residual cavitation,

whose lesion had been misclassified as active at the end of the first year, continued on isoniazid plus PAS. He produced positive cultures at 15, 19, 23 and 24 months, resistant to isoniazid and sensitive to PAS, and had a radiographic deterioration, and his treatment was changed (at the twenty-fifth monthly examination). It will be appreciated that if he had been allocated at random to treatment in the second year he would probably have appeared as a case of bacteriological relapse in the home series, and in the cavitated series.

VI. REGULARITY OF SELF-ADMINISTRATION OF THE MEDICINE

The emphasis laid on the importance of taking the medicaments regularly and the procedures for checking on the co-operation of the patients have been reported earlier (Fox, 1958; Gangadharam et al., 1958; Tuberculosis Chemotherapy Centre, 1959). The two methods that were used to check the regularity were counts of the pill stocks at surprise visits to the home for all the patients, and, only for the patients receiving isoniazid, tests for the drug in specimens of urine obtained at routine visits to the Centre and at surprise visits to the home.

A urine specimen was tested for isoniazid each time a patient receiving this drug visited the Centre (except in the case of females who were menstruating). The results of these routine tests permit valid comparisons of the regularity of medicine-taking during the second year between the patients treated at home and those treated in sanatorium in the first year, and also between males and females. The results of the corresponding tests on specimens obtained at surprise visits to the home, on the other hand, may be subject to bias, since during the second year many patients, especially the males, were not at home when visits were made. Occasionally, also, a doctor would order an extra surprise visit because a patient had recently yielded a negative result. Pill counting is subject to the same sources of bias, but was the only method available in this study for checking the regularity with which the patients took the placebo, calcium gluconate.

PILL COUNTS

Table 10 sets out the findings of the counts of the patients' stocks of pills at surprise visits to the

homes. An average of 6.9 counts was made during the course of the second year for patients in the home series, compared with an average of 6.2 for the former sanatorium patients. Of a total of 381 counts in the home series, 22.0% disclosed incorrect stocks compared with 17.8% of 400 counts in the sanatorium series, a difference which does not attain statistical significance. More than 80% of the

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

	Place of treatment during the first year		Treatment during the second year	
	home	sanatorium	calcium	isoniazid
Number of patients*	55	65	58	62
Total number of occasions on which pills were counted	381	400	354	427
Average number of pill counts per patient	6.9	6.2	6.1	6.9
Number of occasions on which incorrect pill stocks were found	84	71	68	87
Percentage of occasions on which incorrect pill stocks were found	22.0	17.8	19.2	20.4

* Excluding five patients (one home, four sanatorium, three calcium, two isoniazid) who had their treatment changed on account of a bacteriological relapse with a radiographic deterioration and one patient (home, isoniazid) who died.

inaccuracies were surpluses, and the rest were deficits.

Comparing the patients in the calcium and isoniazid series, the average number of counts was 6.1 for the former and 6.9 for the latter. The proportions of incorrect stocks were very similar, being 19.2% for the calcium and 20.4% for the isoniazid series.

To summarize, there is a slight suggestion from the pill counts that the original home series was rather less regular than the original sanatorium series in taking medicine at home in the second year, but there is no evidence of a difference between the patients on calcium gluconate and those on isoniazid. The frequency of incorrect stocks was of the order of 20%.

URINE TESTS

For the patients in the isoniazid series only, urine specimens were obtained at all the routine visits made by the patients to the Centre and surprise visits of the staff to the homes. The naphthoquinone-mercuric chloride test (Short & Case, 1957) was performed on these specimens and, if a negative result was obtained, a hydrolysis test was carried out (Gangadharam et al., 1958)

Table 11 sets out the number of months in which one or more negative test results were obtained. The majority of patients—namely, 70% of the 27 in the home and 77% of the 35 in the sanatorium series—had negative results in from one to six months. Three patients (all home) had negative results in 10 or more months. There was no difference between the sexes, unlike the experience in the first year (Tuberculosis Chemotherapy Centre, 1959).

Table 12 sets out the information on the total number of tests performed on urine specimens, and on the portions that gave negative results. The findings for the tests performed on specimens obtained at routine visits of the patients to the centre and those on the specimens obtained at the surprise visits to the homes are given separately.

Considering first the specimens obtained at the routine visits to the Centre, 23.2% of the results for the home series were negative compared with 20.8% for the sanatorium series. There was also little difference between the sexes; 22.4% of the results in the male patients were negative compared with 20.9% in the female patients.

TABLE 11
NUMBER OF MONTHS DURING WHICH IRREGULARITY IN THE SELF-ADMINISTRATION OF ISONIAZID OCCURRED DURING THE SECOND YEAR (AS ASSESSED BY THE NAPHTHOQUINONE-MERCURIC CHLORIDE TEST ON URINE SPECIMENS)

Number of months with at least one negative test result	Place of treatment during the first year				Sex			
	home		sanatorium		male		female	
	No.	%	No.	%	No.	%	No.	%
0	3	11	4	11	5	12	2	10
1 - 3	11	41	14	40	17	41	8	38
4 - 6	8	30	13	37	14	34	7	33
7 - 9	2	7	4	11	3	7	3	14
10 - 12	3	11	0	0	2	5	1	5
Total patients*	27	100	35	99	41	99	21	100

*Excluding five patients (three cavitated, two non-cavitated) who had their treatment changed on account of bacteriological relapse with a radiographic deterioration, one patient (cavitated) who died and one patient (cavitated) for whom one observation is missing.

For surprise specimens 33.1% of the results in the home series were negative compared with 27.7% in the sanatorium series, a difference which does not attain statistical significance. However, the difference between the sexes - namely, 25.7% in the males and 35.5% in the females - attains statistical significance at the 5% level. The differences in both these comparisons arose from the females treated at home in the first year, 43.8% of the tests on surprise specimens obtained from them being negative. The corresponding percentage for the sanatorium females was 29.0, for the home males 25.3 and for the sanatorium males 26.2. These findings suggest that some patients, especially the home females, were taking medicine on the days when they attended the Centre in order to produce a positive results in the test.

To summarize, a noteworthy number of all the results were negative, the proportion being significantly lower for tests on specimens at routine visits than for test on specimens at surprise visits. This difference reflected mainly the high proportion of negative test results on specimens obtained from home females at surprise visits.

disease at two years, although tubercle bacilli reappeared in the sputum of one between one year and 18 months.

COMPARISON OF CAVITATED AND NON-CAVITATED LESIONS

Four patients had cavitated lesions at one year. These included the patient who relapsed bacteriologically and had a radiographic deterioration and the patient who relapsed bacteriologically only but attained quiescence at the end of the second year. All five patients without residual cavitation remained bacteriologically

negative throughout the second year.

In summary, only one patient had a bacteriological relapse with a radiographic deterioration in the second year. It may be concluded that a single positive culture in the last three months of the first year of treatment, for this group of patients under intensive bacteriological investigation (an average of three cultures a month), did not carry a bad prognosis in the second year. The two patients who relapsed bacteriologically had not, in fact, yielded isolated positive cultures. Their relapse had commenced in the last month of the first year.

VIII. DISCUSSION

Although there have been a few controlled studies of the relative value of bed rest and ambulation in the treatment of pulmonary tuberculosis (Weir et al., 1956, 1957a, 1957b; Tyrrell, 1956; Research Committee of the Tuberculosis Society of Scotland, 1957, 1960), none was undertaken in such unfavourable domiciliary conditions as those in the present study and the longest period of treatment was eight months (Weir et al., 1957a, 1957b). Further, a number of reports favouring long-term chemotherapy have been published (Hoyle et al., 1955; Ross & Kay, 1956; Ross et al., 1958; Ross, 1959); these have not been based on random allocation of patients to different durations of chemotherapy. Also, in most studies surgery has been used as an adjunct. The present comparison of one year and two years of chemotherapy based on random allocation in a group of patients who had bacteriologically quiescent disease at one year, none of whom underwent collapse therapy or resection, is believed to be the first of its kind to be reported.

There is a steadily increasing volume of literature on residual cavitation in quiescent disease, the so-called "open negative" syndrome (Russell et al., 1955; Auerbach & Small, 1957; Corpe & Blalock, 1958). A particularly valuable contribution has been that of Raleigh (1957), who studied the progress both of "open negative" and of "closed negative" cases. He reported a relapse rate of 8% after one year of follow-up in the "closed negative" group and of 23% in the "open negative" group. These figures, however, do not readily lend themselves to comparison with ours because of differences in the chemotherapeutic regimes and their duration, the use of surgery in a proportion of Raleigh's cases, and differences in the criteria used for assessing relapse.

The present report is mainly concerned with the assessment of the progress during the second year of all the 130 patients who had been treated in a controlled comparison of combined chemotherapy at home and in sanatorium for one year and whose disease was bacteriologically quiescent at the end of the period. The patients had been drawn from the lower income groups or the unemployed in Madras City, which has the largest urban community in South India. The living conditions were poor, the majority of the families being overcrowded, and the dietary standards low (Tuberculosis Chemotherapy Centre, 1959). At the end of the first year 126 of the patients were allocated at random to treatment with isoniazid alone or to a placebo, calcium gluconate, the patients being treated at home in the second year and the great majority following their usual occupations.

Of the 126 patients, 117 (93%) had quiescent disease at two years. The difference at the end of the second year between the progress of patients who had been treated at home in the first year and the progress of those treated in sanatorium was small so that, in the event, bacteriological quiescence attained at home has proved to be at least as stable in the second year as quiescence achieved in sanatorium. The home series showed, in fact, a slight benefit in the second year, which, at least in part, redresses the slight over-all advantage to the sanatorium series at the end of the first year of treatment (Tuberculosis Chemotherapy Centre, 1959).

The study provides no evidence that continuing chemotherapy in quiescent cases, albeit with isoniazid alone, for a second year gives better results than those obtained by discontinuing antituberculosis chemotherapy at the end of a year of treatment.

The decision to use isoniazid alone rather than combined chemotherapy was taken because the patients had quiescent disease, because the drug was cheaper, less bulky and possibly more acceptable for self-administration than isoniazid plus PAS and since there is no prospect in the foreseeable future that combined chemotherapy will be available for wide spread use in the under-developed countries for a single year, let alone two. It is possible that two years of *combined* chemotherapy might give a more satisfactory over-all result than one year. On the other hand, it will be appreciated that the relapse rate (7%) was relatively low in the patients who had only one year of chemotherapy (that is, who received calcium gluconate) so that there was, in any case, only restricted scope for further chemotherapy, no matter how potent, to demonstrate a clear-cut benefit.

Although the patients with bacteriologically quiescent disease and residual cavitation at one year, the open negative syndrome, did not fare quite as well as those without residual cavitation, there was no evidence that chemotherapy with isoniazid alone in the second year was capable of preventing relapse in the patients with cavitated lesions. (More information on the open negative syndrome is being accumulated from current studies and will be reported later).

In the earlier study 10 patients (6.1% of the 163 who contributed to the major analyses) had disease classified as being bacteriologically of doubtful status at the end of one year's treatment (Tuberculosis Chemotherapy Centre, 1959). These were the patients who had produced solitary positive results amongst seven to nine cultures examined at 10, 11, and 12 months. At the end of two years one of the 10 had a bacteriological relapse with a radiographic deterioration. The positive culture at 12 months in this patient proved, in the event, to be the commencement of the relapse. The other nine patients had quiescent disease. Thus, isolated positive cultures in this series did not carry a poor prognosis, a finding in keeping with that of Raleigh (1957).

The problems associated with the long-term self-administration of oral therapy in the form of cachets, as studied in the Madras patients, have already been reported (Fox, 1958; Tuberculosis Chemotherapy Centre, 1959). During the second year two further aspects were studied: first, the regularity with which patients took one pill a day either of the placebo or of isoniazid; secondly, whether there was any

difference between the regularity of patients whose medicine-taking had been supervised in sanatorium for a full year and the regularity of those who had self-administered medicine throughout the whole two years. During the second year, except for the females treated at home in the first year, who were particularly irregular, there was little difference between the patients who had been treated at home and those who had been treated in sanatorium or between those receiving isoniazid and those receiving the placebo. It seems likely that at least a quarter of the doses were not being taken. These findings support the views of Fox (1958) that the difficulty experienced in ensuring regular self-administration of medicine is, in fact, a socio-psychological problem and not simply attributable to side-effects or to the physical bulk or taste of the medicine, as a number of workers have concluded from studies on the self-administration of PAS. Further, supervision in sanatorium, even for a year, did not develop the habit of regularity in those patients in the second year.

In conclusion, studies from this Centre have shown that the domiciliary treatment for a year of tuberculous patients, drawn from an undernourished section of the community living in poor conditions, gives results which closely approach those achieved in sanatorium (Tuberculosis Chemotherapy Centre, 1959). It has also been shown in a year's follow-up of the close family contacts (Andrews et al., 1960¹) It has also been shown that the relapse rates in the second year for patients treated at home and for those treated in sanatorium are both small and similar, and that a second year of chemotherapy with isoniazid alone does not, apparently, confer further benefit. It has thus been established that a year of domiciliary treatment with isoniazid plus PAS has proved most successful both in the results achieved in the patients in a two-year period and in the absence of special risk to the contacts in the first year of follow-up.

The study is continuing and the patients are being followed up to investigate the relapse rates in the third year. As part of this study chemotherapy for a third year is also being evaluated. Longer-term information on the contacts is also ensured, since a high degree of co-operation of the families is still being maintained.

¹ See article on page 463 of this issue.

IX. SUMMARY

1. In the main analysis of a year's study of combined chemotherapy with isoniazid plus PAS at home or in sanatorium, it was reported that 130 patients attained bacteriological quiescence at one year (Tuberculosis Chemotherapy Centre, 1959). Of these, 126 (57 home, 69 sanatorium) were allocated at random to treatment at home for a second year 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.

2. Three main comparisons have been made for the 126 patients for the second year—namely, between (a) the 57 home and 69 sanatorium patients, (b) the 61 calcium and 65 isoniazid patients, and (c) the 42 patients with residual cavitation and the 84 patients with non-cavitated lesions at one year.

3. In addition, the progress of 10 patients with disease whose bacteriological status at one year was in doubt has been studied.

4. One patient (home, isoniazid and cavitated series) died, the cause of death being unestablished.

5. At the start of the first year, 82% of the home and 72% of the sanatorium patients had bilateral disease: 84% of the former and 93% of the latter had cavitated lesions. All the patients had tubercle bacilli in their sputum. At the end of the first year, the home patients had gained less weight, had higher ESRs and had rather more extensive residual radiographic lesions than the sanatorium patients. At the end of the second year, there was little to choose between the progress of the two series, 95% of the 57 home patients having bacteriologically quiescent disease, compared with 91% of the 69 sanatorium patients. The disease in one other sanatorium patient was presumed bacteriologically quiescent. One home and four sanatorium patients had their treatment changed on account of a bacteriological relapse with a radiographic deterioration.

6. There were no important differences at the beginning of the second year, when the random allocation was made, between the patients receiving calcium gluconate and those receiving isoniazid. At the end of two years, 92% of the 61 calcium patients and 94% of the 65 isoniazid patients had bacteriologically quiescent disease. Four calcium

and three isoniazid patients had relapsed bacteriologically, and these, three calcium and two isoniazid patients had radiographic deterioration also.

7. Comparing the cavitated and non-cavitated series, at one year the cavitated series contained a higher proportion of older patients (29% of 42 patients being 45 years of age or more compared with 12% of 84 in the non-cavitated series), and had fewer normal ESRs (7% of the cavitated and 36% of the non-cavitated series), and the over-all radiographic residual lesions, quite apart from the cavitation, were more extensive. At the end of two years, 88% of the cavitated series and 95% of the non-cavitated series had bacteriologically quiescent disease. Four patients in the cavitated series had relapsed bacteriologically (one calcium, three isoniazid) and three in the non-cavitated series (all calcium), three of the cavitated and two of the non-cavitated cases showing radiographic deterioration also.

8. Twelve patients had sensitivity test results in the second year. The only or first positive culture in this period was sensitive of PAS in all 12 patients and was sensitive to isoniazid in eight and resistant in four.

9. The regularity of self-administration of the medicine was checked by counting the stock of pills and by urine tests for isoniazid. Pill counting at surprise visits to the home revealed incorrect stocks in approximately 20% of the counts, there being hardly any difference between the home and the sanatorium series or between the males and the females. Urine specimens were obtained at planned visits to the Centre; 23% of the results were negative in the home series and 21% in the sanatorium series; for the male patients 22% of the tests were negative compared with 21% for the female patients.

10. Of the 10 patients whose bacteriological status at one year was in doubt, nine had quiescent disease at two years.

11. It is concluded that in the second year there was very little difference between the patients whose disease attained bacteriological quiescence following a year of domiciliary treatment and those whose disease attained quiescence following a year's treatment with the same combination of drugs in sanatorium. Secondly, there was no evidence that a

second year of treatment with isoniazid alone conferred any benefit. Thirdly, the patients with residual cavitation at one year fared slightly less well in the second year than the patients without obvious residual cavitation; isoniazid therapy for the second year did not, however, reduce the likelihood of relapse.

12. This study of the progress in the second year of patients with quiescent disease consolidates further the conclusions reached at the end of one year's treatment that "the results of domiciliary chemotherapy, as carried out in this study, approach

sufficiently closely the results of sanatorium treatment to suggest that it is appropriate to treat the majority of patients at home" (Tuberculosis Chemotherapy Centre, 1959). It has also been shown (Andrews et al., 1960¹) that there is, in all probability, no special risk to family contacts in the first year if the patients are treated at home with effective chemotherapy. Considered together, these studies have now firmly established the value of domiciliary chemotherapy.

¹ See article on page 463 of this issue.

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health visitors and clinic nurses, whose efforts have largely been responsible for the completeness of the data.

RESUME

Dans une première étude, les chercheurs du Centre de chimiothérapie de la tuberculose, à Madras, Inde, avaient montré que le traitement des tuberculeux pendant une année au moyen de l'isoniazide et de l'acide paraminosalicylique (PAS) donnait des résultats analogues, que les malades soient traités à domicile ou en sanatorium.

Les malades de ces deux groupes qui, au bout de l'année, avaient atteint le stade de quiescence bacillaire ont été soignés et suivis pendant une année encore. Le but de l'étude qui fait l'objet de cet article était de préciser: a) si le taux des rechutes au cours de la deuxième année était plus élevé chez les malades qui, à l'origine, avaient été traités à domicile que chez ceux qui avaient bénéficié des soins en sanatorium; b) si une deuxième année de traitement par l'isoniazide seule influençait la fréquence des rechutes; c) quelle était l'influence éventuelle de la présence, à la fin de la première année, de cavernes résiduelles. Tous les malades suivis ont vécu

à domicile pendant cette deuxième année, prenant eux-mêmes leurs médicaments - les uns de l'isoniazide, les autres un placebo, le gluconate de calcium.

Pendant cette deuxième année on a constaté que le taux des rechutes différait très peu entre les groupes traités antérieurement à la maison ou en sanatorium, qu'il n'était pas influencé par la poursuite du traitement à l'isoniazide, et que l'état des malades avec des cavernes résiduelles était légèrement moins bon que celui des sujets qui n'en présentaient pas.

En conclusion générale de ces études, les auteurs estiment que les résultats de la première année ont été confirmés après la deuxième année, et que le traitement domiciliaire des malades atteints de tuberculose est adéquat et peut convenir à la majorité des patients. Il n'y a pas, vraisemblablement, de risques particuliers pour les contacts, si la chimiothérapie est régulièrement appliquée aux malades.

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