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## Progress in the Second and Third Years 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 controlled comparison by the Tuberculosis Chemotherapy Centre, Madras, of the merits of home as compared with sanatorium treatment for pulmonary tuberculosis showed that, at the end of a year of chemotherapy with isoniazid plus p-aminosalicylic acid (PAS), the response of the home patients closely approached that of the sanatorium patients. The present report reviews the progress of those patients in the controlled comparison whose disease had attained bacteriological quiescence by the end of the year of combined chemotherapy. During the second year, half of the patients received further chemotherapy, with isoniazid alone, and half received a placebo, calcium gluconate. During the third year, half of those who were treated with isoniazid in the second year and whose disease remained quiescent continued to receive that drug and all the remaining patients with quiescent disease received the placebo. In the second and third years all the patients were treated at home and administered the medicaments to themselves.*

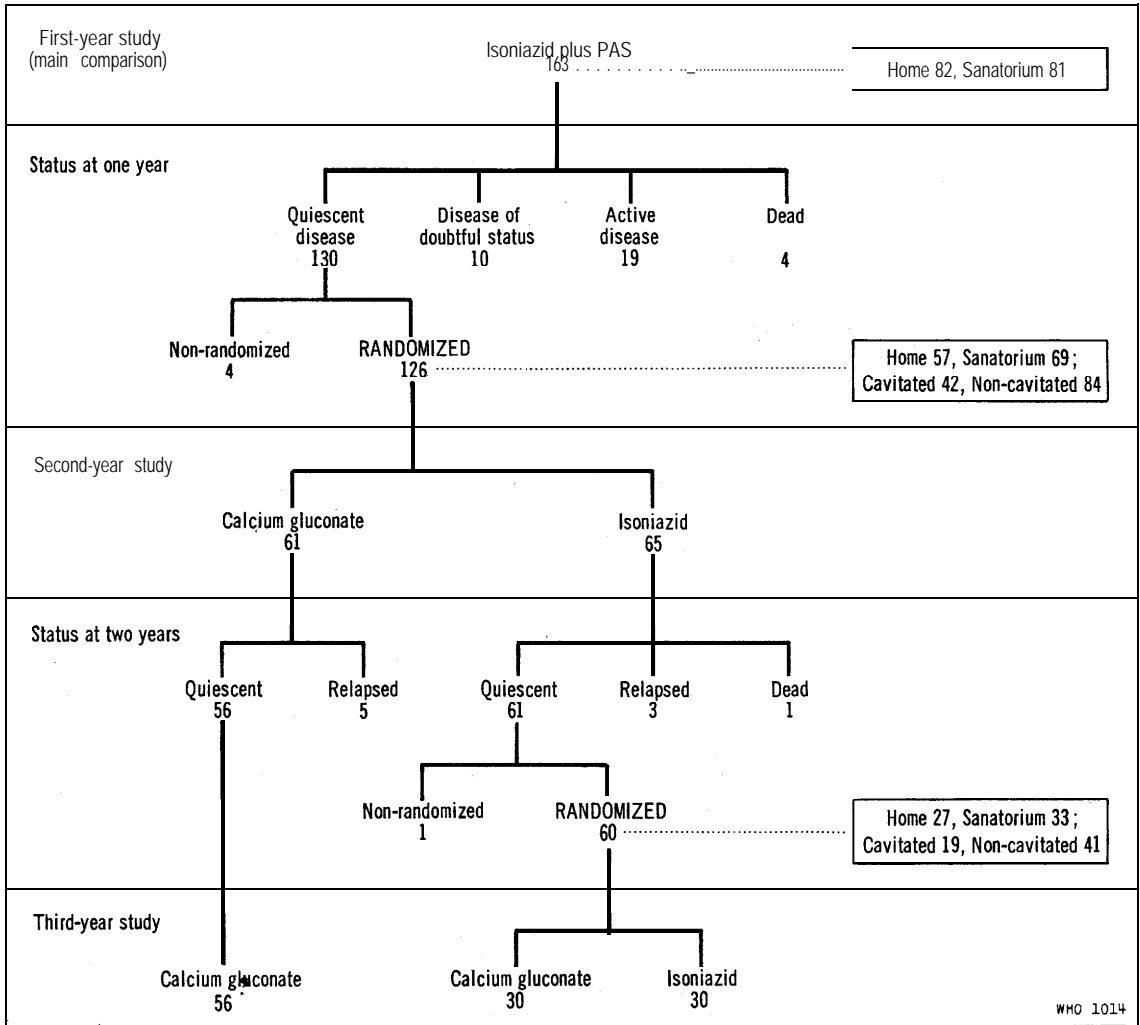
*It has been concluded from this follow-up study that in the second and third years there was relatively little difference between the progress of the patients whose disease attained quiescence following a year of domiciliary treatment with isoniazid plus PAS and that of those whose disease attained quiescence following a year's treatment with the same drugs in sanatorium ; that a second or third year of further treatment with isoniazid alone gave no better results than a year of combined chemotherapy, followed by careful observation of the patient and further chemotherapy if relapse occurred: and that the relapse rate among the patients with residual cavitation at the end of the year of combined chemotherapy was slightly higher than that among the patients with no residual cavitation at the end of the first year.*

An earlier report from the Tuberculosis Chemotherapy Centre, Madras, gave the findings of a controlled comparison of home and sanatorium treatment of pulmonary tuberculosis for a year, all patients receiving isoniazid plus p-aminosalicylic acid (PAS) (Tuberculosis Chemotherapy Centre, 1959). It was found that the response of the domiciliary patients closely approached the results in the patients treated in sanatorium. At the end of the first year the patients with bacteriologically quies-

cent disease were allocated, at random, to treatment with isoniazid alone for the second year, or to a placebo. In a subsequent report (Velu et al., 1960b) it was concluded, first, 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

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DIAGRAMMATIC REPRESENTATION OF THE NUMBERS OF PATIENTS IN THE STUDY, THEIR DISEASE STATUS AND TREATMENT



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." These same patients have now completed three years and the present report describes their progress in the second and third years. The numbers of patients in the various categories and their treatment in the second and third years are shown in the accompanying chart. The present report includes (a) a comparison of the patients whose chemotherapy was stopped at the end of one year with those who received chemotherapy, with isoniazid

alone, for a second and in some cases for a third year, (b) a comparison of the progress of the patients in the home and sanatorium series, (c) the influence of residual cavitation at one year, the so-called "open negative" syndrome, on the progress in the second and third years and (d) a comparison of the patients whose chemotherapy was stopped at the end of two years with those who received isoniazid alone for a third year. In addition, the progress in the second and third years is reported for 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 (see chart).

The organization of the Centre, which 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, has been described in detail in an earlier report (Tuberculosis Chemotherapy Centre, 1959).

## I. GENERAL PLAN AND CONDUCT OF THE STUDY

Contrary to expert opinion, both in India and in Europe, it proved possible to keep the co-operation of the patients during their year of combined chemotherapy in the home and sanatorium comparison. As a consequence it was decided that the patients whose disease was bacteriologically quiescent (as defined on page 152) at the end of the year, whether treated at home or in sanatorium, should be allocated at random to treatment for a second year with daily isoniazid or with a daily placebo, calcium gluconate (see chart). The patients continued to be co-operative in the second year, and it was therefore decided to make a comparison of two years and three years of chemotherapy; the patients who had been allocated to isoniazid in the second year and who still had quiescent disease at the end of two years were therefore allocated again at random to treatment for a third year with daily isoniazid or with daily calcium gluconate. (The patients who had been allocated the placebo in the second year received it in the third year also, unless their disease was no longer quiescent at the end of two years.) All the patients were to be treated at home in the second and third years. The plan of the study, therefore, evolved with experience of the co-operation which could be obtained from the patients.

### SOURCE OF CASES

The patients were drawn from the poorest sections of the population of Madras City. All had presented themselves at local chest clinics because of symptoms. Mass radiography was not used as a source of cases.

### NUMBERS OF PATIENTS IN THE STUDY

A total of 130 patients in the main analysis of the first report (Tuberculosis Chemotherapy Centre, 1959) were classified as having bacteriologically quiescent disease at the end of the first year (see chart above). Of these, 126 patients (57 home, 69 sanatorium) were allocated at random to calcium gluconate (61 patients) or to isoniazid (65 patients)

for the second year, 42 having definite residual cavitation and 84 showing no evidence of residual cavitation. These 126 patients may be divided according to these criteria into eight subgroups (Table 1.) The remaining four patients (three home, one sanatorium), although kept under observation, were not included in the random allocation for reasons reported by Velu et al. (1960b).

In the second year five patients in the calcium series and three in the isoniazid series relapsed bacteriologically and one (isoniazid) died. At two years, therefore, 56 patients who had received calcium gluconate and 61 who had received isoniazid still had quiescent disease. The former continued on calcium gluconate, and 60 of the latter were allocated at random to calcium gluconate (30 patients) or to isoniazid (30 patients) for the third year. Of the 60 patients 27 had been treated at home in the first year and 33 in sanatorium, 19 having had

TABLE 1  
NUMBERS OF PATIENTS IN THE EIGHT SUBGROUPS  
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
Sanatorium	Cavitated	Calcium	8
		Isoniazid	13
	Non-cavitated	Calcium	24
		Isoniazid	24
Total . . .			126

residual cavitation at one year and 41 no residual cavitation. One patient was not included in the random allocation for the third year because he was going to Bombay and it was uncertain whether he would continue to co-operate in treatment. He was prescribed calcium gluconate.

A further 10 patients (seven home, three sanatorium), whose disease at one year was of doubtful bacteriological status (Tuberculosis Chemotherapy Centre, 1959), are the subject of a subsidiary analysis in this report (see page 170).

#### CHEMOTHERAPY DURING THE FIRST YEAR

All the patients studied in the present report had received isoniazid plus PAS (sodium salt) in two doses daily for the first 12 months, those weighing 100 lb. or more having been prescribed 200 mg and 10 g daily, respectively, those weighing 80-99 lb., 175 mg and 8.75 g, and those weighing less than 80 lb., 150 mg and 7.5 g daily.

#### 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 (one of the present authors—J. H. A.—in the first week that he joined the Centre's staff) on the basis of the postero-anterior radiographs and a tomographic series at one year (Velu et al., 1960b).

#### DEFINITION OF BACTERIOLOGICAL QUIESCENCE AT ONE YEAR

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

#### DEFINITION OF BACTERIOLOGICAL QUIESCENCE AT TWO YEARS

A patient's disease was classified as bacteriologically quiescent at the end of the second year if all the cultures for at least the last six monthly examinations had been negative. The patients had usually had eight negative cultures during this period.

#### TREATMENT IN THE SECOND AND THIRD YEARS

*All the patients were treated at home in the second and third years. The dosages of the two regimens were:*

##### *Isoniazid :*

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

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

150 mg daily, for patients weighing less than 80 lb.

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 decreased.

##### *Calcium :*

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

#### ALLOCATION OF TREATMENT

Each patient who completed the first year of treatment, whether at home or in sanatorium, and had quiescent disease on the evidence of the then available bacteriological data (the culture results of the eleventh and twelfth months were not usually available at that time), was allocated to treatment for the second year within a week of the completion of the first year's chemotherapy. The allocation of calcium gluconate or isoniazid 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 Centre'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.

Each patient who completed the second year of treatment with isoniazid and had quiescent disease (on the evidence of the then available bacteriological data) was allocated at random to treatment with calcium gluconate or isoniazid for the third year within a week of the completion of the second year's therapy. The allocation was again made by the Centre's statistical staff from two series of sealed envelopes, one for patients with residual cavitation and the other for patients without residual cavitation at the end of one year.

The patients had originally been admitted to treatment in the period 24 September 1956 to 24 September 1957.

#### GENERAL MANAGEMENT

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 by a health visitor, one visit being made to deliver a bottle for a sputum specimen and the other, a surprise visit, being made 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.

In the third year the patients attended the Centre every month for a month's supply of their medicine and had a routine examination every three months. A surprise visit to the home was usually made once a month to count the stock of pills and, if the patient was receiving isoniazid, to collect a specimen of urine to test for the drug. Once every three months an extra visit was paid to deliver a sputum bottle to the home.

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 considered in this report had any form of collapse therapy or resection during the three years.

#### CLINICAL INVESTIGATIONS

Examinations and assessments were undertaken monthly in the second year and 3-monthly in the third year 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

In the second year 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 instead. At the end of the second year, two overnight sputum specimens and a pair of laryngeal swabs from each patient were examined. At 27, 30 and 33 months, the patients brought an overnight sputum specimen, and a pair of laryngeal swabs was also taken in the Centre. At the end of the third year, two overnight sputum specimens and a pair of laryngeal swabs were examined. The standard procedure was therefore to obtain 14 bacteriological specimens from each patient during the second year and nine during the third 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. If the patient deteriorated radiographically also, the routine was to change treatment and to examine three specimens each month thereafter.) The sputum specimens were examined by smear and culture, the laryngeal swabs by culture only. Tests of sensitivity to isoniazid and to PAS were performed on one positive culture each month. The techniques have been described in an earlier report (Tuberculosis Chemotherapy Centre, 1959). Because of the difficulty experienced in interpreting the results of the PAS-sensitivity tests (Tuberculosis Chemotherapy Centre, 1960; Selkon et al., 1960), no further reference is made to these results in this report.

#### DEFINITION OF BACTERIOLOGICAL RELAPSE

Patients who yielded two or more positive cultures in a period of six months have been considered to have relapsed bacteriologically. In the second year this meant two or more positive cultures in seven consecutive monthly examinations. In the third year, when examinations were performed every three months, this meant two or more positive cultures in three consecutive examinations—for example, at 30, 33 and 36 months. (The definition of bacteriological relapse in the second year is more stringent than that used in the report of Velu et al. (1960).)

#### INDEPENDENT ASSESSMENT OF THE RADIOGRAPHS

All the radiographic series for the second year were shown to an independent assessor (one of the present authors—J. H. A.—in the first week that he joined the Centre's staff) who was unaware of

the treatment allocated to any patient in the first or in the second year. Apart from the cavitation assessments, for which tomographic series were also used, all the assessments 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, and (e) 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 at two years.

For the assessments in the third year all the radiographic series were shown to another independent assessor (Dr Raj Narain) who was unaware of the treatment allocated to any patient in the first, second or third year. This assessor classified (a) the extent of residual disease at two years, on the basis of the lung-zone involvement, (b) the lesions at two years, as unilateral or bilateral, (c) the radiographic changes in the third year, viewing the postero-anterior radiographs at two and at three years, and (d) the cavitation at three years in relation to the cavitation at the end of the second year, viewing the postero-anterior radiographs at two and at three years. He was also shown, when he so desired, the radiographs which had been taken at monthly intervals in the first and second years and at 3-monthly intervals in the third year, as well as the tomographic series at one and at 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.* Comparison of the progress of the 61 patients who received one year of chemotherapy with that of the 65 patients who received two or three years of chemotherapy.

*Section III.* Comparison of the progress of the 57 patients who were treated at home for the first year with that of the 69 patients who were treated in sanatorium for the first year.

*Section IV.* Comparison of the progress of the 42 patients with definite residual cavitation at one year with that of the 84 patients without residual cavitation at one year.

*Section V.* Comparison of the progress of the 30 patients who received two years of chemotherapy with that of the 30 patients who received three years of chemotherapy (all the patients had bacteriologically quiescent disease at two years).

*Section VI.* (a) Results in the eight subgroups in the three comparisons in sections II, III and IV; (b) results for all the 126 patients in the eight subgroups combined.

*Section VII.* (a) Results for the four patients not allocated at random to treatment for the second year; (b) disease status at three years of all the 130 patients-i.e., the 126 allocated at random and the four not allocated at random.

*Section VIII.* Regularity of self-administration of the medicaments.

*Section IX.* Progress in the second and third years of the 10 patients whose bacteriological status at one year was in doubt (Tuberculosis Chemotherapy Centre, 1959).

## II. COMPARISON OF ONE YEAR OF CHEMOTHERAPY WITH TWO OR THREE YEARS OF CHEMOTHERAPY

This section compares the progress in the second and third years of the 61 patients who received one year of chemotherapy with that of the 65 patients who received two or three years of chemotherapy. The former are termed the calcium series, and the latter the isoniazid series.

#### CLINICAL AND RADIOGRAPHIC CONDITION AT THE START OF THE FIRST YEAR

It was shown in an earlier report (Tuberculosis Chemotherapy Centre, 1959) that a large proportion

of the patients had serious disease on their admission to the first year of treatment. Most of the 126 patients whose disease attained bacteriological quiescence at one year, and who were then allocated at random to calcium gluconate or isoniazid for the second year, also had severe disease on admission to treatment. Thus, at the start of the first year, 77 % of the 126 patients had bilateral disease and 89% had cavitated lesions, the cavitation being moderate or extensive in 70%. All the patients had tubercle bacilli in their sputum on admission. Con-

sidering the results of a single overnight specimen, 87% of the patients had a positive result on direct smear examination, 41% having a 3-plus (heavy) positive result.

#### CLINICAL AND RADIOGRAPHIC FEATURES AT THE END OF THE FIRST YEAR

Before considering the results, the clinical and radiographic features at the end of the first year are compared, since the random allocation to treatment in the second year was made at that time.

##### *Age and sex*

The distributions of estimated age (not tabulated here) were very similar, 34% of the 61 calcium patients and 29% of the 65 isoniazid patients being under the age of 25 years; 18% of the calcium and 17% of the isoniazid series were aged 45 years or more. As to the sex distribution, 57% of the patients in the calcium series and 65% in the isoniazid series were male.

##### *Clinical and radiographic condition*

The assessments of the clinical and radiographic condition at the end of the first year are given for the calcium and isoniazid series in Table 2, Part A. There were rather fewer patients weighing 80-89 lb. in the calcium series than in the isoniazid series—namely, 11% as compared with 26%; however, there were rather more patients weighing 100-109 lb. in the calcium than in the isoniazid series—namely, 31% as 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, an unexpectedly large difference ( $P(0.05)$ ). 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, as compared with none in the calcium series. In summary, 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 that the isoniazid series was possibly at a disadvantage in respect of the extent of cavitation.

#### CLINICAL RESULTS IN THE SECOND AND THIRD YEARS

##### *Deaths*

There was one death among the 126 patients. This occurred in a 48-year-old male patient (isoniazid,

home, cavitated). An isolated positive culture was obtained at 15 months, this being 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 possibility that the patient died as a result of a 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 given.

##### *Bacteriological relapses*

Nine patients had a bacteriological relapse (as defined on page 153), three (two calcium, one isoniazid) without a radiographic deterioration and six (four calcium, two isoniazid) with a radiographic deterioration, confirmed by an independent assessor (Dr K. S. Sanjivi), necessitating a change of treatment (Table 7, Part A). One of the latter (isoniazid) also had an haemoptysis.

Considering, first, the three patients who relapsed bacteriologically without a radiographic deterioration, one (calcium, home, non-cavitated), a female aged 22 years, yielded a single colony at 16 months and another single colony at 21 months. At 24 months a positive culture with 1-plus growth (20-100 colonies) was obtained. Further positive cultures, each of two colonies, were isolated at 28 and 30 months, respectively. Sensitivity test results were available for four of these five cultures; all were sensitive to isoniazid. The five cultures thereafter to the end of the third year were negative although the patient continued to receive calcium gluconate. The second patient (calcium, home, non-cavitated), a male aged 23 years, yielded two positive cultures of 10 and 15 colonies, respectively, in the twenty-seventh month, the strain tested being highly resistant to isoniazid. All 15 cultures, 10 of sputum and five of laryngeal swabs, from then until the end of the third year were negative even though the patient continued to receive calcium gluconate. A smear-positive, culture-negative result was obtained at 31 months, and another at 32 months. The third patient (isoniazid, sanatorium, cavitated), a male aged 53 years, produced nine positive cultures at eight monthly examinations in the second year, the number of colonies being between one and seven in eight of the cultures and 1-plus growth in the ninth;

TABLE 2  
CONDITION OF PATIENTS AT THE END OF THE FIRST YEAR

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

<sup>a</sup> 1 lb = 0.45 kg.



all eight strains tested were highly resistant to isoniazid. Despite the fact that he had no radiographic deterioration, chemotherapy was changed in the twenty-sixth month and all the 20 cultures from then to the end of the third year were negative.

Considering, next, the four calcium patients who had a bacteriological relapse with a radiographic deterioration, treatment was changed in the second year for three and in the third year for one. Of these patients, one (sanatorium, non-cavitated), a male aged 18 years, had positive sputum findings at 14, 15, 16 and 17 months; the organisms were sensitive to isoniazid. His treatment was changed in the seventeenth month, when there was a radiographic deterioration. Following the start of a new chemotherapeutic combination this patient yielded only negative cultures from 26 months onwards, and 23 consecutive negative cultures had been obtained by the end of the third year. The second patient (also sanatorium, non-cavitated), a male aged 35 years, had a positive sputum specimen at 17 months, and treatment was changed at the end of 22 months, when a radiographic deterioration was confirmed; the organisms remained sensitive to isoniazid. The patient's subsequent treatment was complicated by an amoebic lung abscess, but during treatment with a new combination of drugs all the cultures from 32 months onwards were negative, 14 consecutive cultures having been examined by the end of the third year. The third patient (home, cavitated), a female aged 25 years, remained bacteriologically negative until 22 months, when a relapse occurred with organisms sensitive to isoniazid. The lesion showed radiographic deterioration and treatment was changed at 24 months. From 25 months onwards all the cultures were negative; 34 consecutive negative cultures had been obtained by the end of the third year. Another female patient (sanatorium, non-cavitated), aged 20 years, yielded positive cultures at 14, 15 and 16 months, the two strains tested being isoniazid-resistant. Nine consecutive negative cultures were then obtained up to 24 months, but at 25 months the patient produced four colonies on culture, sensitive to isoniazid. Six more consecutive negative cultures were obtained but at 28 months she had a bacteriological relapse (six positive cultures were obtained in a period of 12 days); one of these strains was tested and found resistant to isoniazid. There was also a radiographic deterioration and treatment was changed. All the cultures from 31 months onwards were negative,

16 having been examined by the end of the third year.

Considering the two isoniazid patients whose chemotherapy was changed, one (sanatorium, cavitated), a female aged 25 years, developed a positive sputum at 15 months, the organisms being resistant to isoniazid. She had a radiographic deterioration and an haemoptysis and her chemotherapy was changed in the seventeenth month. All the 50 consecutive cultures obtained from 18 months to the end of three years were negative. The second patient (sanatorium, cavitated), a female aged 20 years, developed a positive sputum at 18 months with organisms sensitive to isoniazid. She moved more than seven miles away from the Centre and refused to co-operate in a change of treatment until the twenty-fourth month, when, being eight months pregnant, she agreed to be admitted to sanatorium; she discharged herself, however, soon after delivery and discontinued her chemotherapy. In the thirty-second month she reattended the Centre with very far advanced disease, but was still uncooperative. She eventually agreed to readmission to sanatorium in the thirty-fourth month. At 36 months she was bacteriologically positive and had advanced bilateral disease.

It is not within the scope of this report to detail the subsequent chemotherapy for patients who relapsed. The standard procedure was to prescribe streptomycin plus pyrazinamide (Velu et al., 1960a, 1961).

#### *Isoniazid-sensitivity test results in the patients with a bacteriological relapse*

Of the six patients who had a bacteriological relapse in the calcium series, four did so with isoniazid-sensitive organisms and two with highly isoniazid-resistant organisms (growth on 50 µg/ml). Of the three patients with a bacteriological relapse in the isoniazid series, one—namely, the uncooperative patient described above—relapsed with isoniazid-sensitive organisms (there was evidence from urine tests that she had been irregular in taking her isoniazid) and two with resistant organisms (growth on 1 µg/ml and on 50 µg/ml, respectively).

#### *Patients who yielded isolated positive cultures*

Five patients (two calcium, three isoniazid) yielded isolated positive cultures (Table 7, Part A). Considering the calcium patients first, one (home, non-cavitated) yielded an isolated positive culture at 16 months and the other (sanatorium, non-cavitated) at 24 months. Of the three patients in the isoniazid series who yielded an isolated positive culture, one

(home, non-cavitated) had an isolated positive culture at 13 months. The other two patients (both sanatorium, non-cavitated) yielded an isolated positive culture at 14 and at 36 months, respectively. In addition, one patient (isoniazid, home, cavitated) yielded a positive culture in the fifteenth month and died in the seventeenth month. A sensitivity test was not available for this patient. Four of the other five isolated positive cultures were sensitive to isoniazid: the culture obtained at 24 months from a calcium patient was resistant to isoniazid (growth on 1 µg/ml).

#### Changes in the ESR

At one year nine (16%) of 56 patients in the calcium series with observations available had had a normal ESR (10 mm or less) as compared with 19 (32%) of 59 isoniazid patients (Table 3). At three years the numbers had increased to 11 (20%) and 21 (36%), respectively. It will be observed that many patients in both series retained high ESRs, the numbers with ESRs of 51 or more being seven and nine, respectively, at one year and eight and six, respectively, at three years. Indeed, at three years 23 (41%) of the calcium and 27 (46%) of the isoniazid series still had ESRs of 21 or more.

#### Radiographic progress

The considerable majority of patients—namely, 49 (82%) of 60 in the calcium series and 52 (80%) of 65 in the isoniazid series—showed no radiographic change in the second year, only five of the calcium and eight of the isoniazid patients showing some radiographic improvement (Table 4). In the third year 51 (89%) of 57 calcium and 54 (87%) of 62 isoniazid patients showed no change, while two and five patients, respectively, showed slight improvement. Since so few changes occurred in either year, no separate assessment for the whole 2-year period was undertaken.

#### Changes in cavitation status

Considering the patients with residual cavitation at the end of the first year (Table 5), cavitation had disappeared by the end of the second year in four of 19 patients in the calcium series as compared with four of 23 in the isoniazid series and was less in five and nine patients, respectively. Of a total of 16 patients with residual cavitation at two years in the calcium series, cavitation had disappeared in one by the end of the third year and was less in two, as compared with one and three, respectively, of 16 patients in the isoniazid series.

TABLE 3  
DISTRIBUTIONS OF THE ERYTHROCYTE SEDIMENTATION RATE AT ONE YEAR AND AT THREE YEARS

ESR (mm in 1 hour)	At one year		At three years		At one year		At three years			
	calcium	isoniazid	calcium	isoniazid	home	sanatorium	cavitated	non-cavitated		
									home	sanatorium
0-10	9	19	11	21	7	21	2	26	8	24
11-20	11	16	22	13	14	13	12	15	10	23
21-50	29	15	15	19	25	19	18	26	12	24
51-100	7	9	7	7	9	4	4	12	5	6
101 or more	0	0	1	0	0	0	0	0	1	2
Total patients assessed <sup>a</sup>	56	59	56	60	55	60	36	79	36	79

<sup>a</sup> Excluding seven patients (four calcium, three isoniazid; one home, six sanatorium; four cavitated, three non-cavitated) who had their chemotherapy changed on account of a bacteriological relapse with or without a radiographic deterioration, one patient (isoniazid, home, cavitated) who died and three patients (one calcium, two isoniazid; all sanatorium; one cavitated, two non-cavitated) for whom one observation is missing.

TABLE 4  
CHANGES IN RADIOGRAPHIC APPEARANCES DURING THE SECOND AND THE THIRD YEAR

Year	Patient series	Total patients <sup>a</sup>	Improvement		No change	Deterioration		Change of treatment <sup>b</sup>	Death
			moderate	slight		slight	moderate		
Second	Calcium	60	0	5	49	3	0	3	0
	Isoniazid	65	1	7	52	2	0	2	1
Third	Calcium	57	0	2	51	1	2	1	0
	Isoniazid	62	0	5	54	2	0	1	0
Second	Home	56	1	4	46	3	0	1	1
	Sanatorium	69	0	8	55	2	0	4	0
Third	Home	54	0	3	48	2	1	0	0
	Sanatorium	65	0	4	57	1	1	2	0
Second	Cavitated	42	1	5	30	2	0	3	1
	Non-cavitated	83	0	7	71	3	0	2	0
Third	Cavitated	38	0	5	28	2	2	1	0
	Non-cavitated	81	0	2	77	1	0	1	0
Second	All patients	125	1	12	101	5	0	5	1
Third	All patients	119	0	7	105	3	2	2	0

<sup>a</sup>Excluding throughout one patient (calcium, home, non-cavitated) who had cancer of the lung.

<sup>b</sup>On account of a bacteriological relapse with or without a radiographic deterioration.

Of 41 patients in the calcium series without cavitation at one year, two showed cavitation at two years as compared with none of 42 in the isoniazid series. At two years, 41 patients in the calcium series had no cavitation; one of these showed cavitation at three years as compared with none of 46 in the isoniazid series.

#### Number of culture results

Table 6, Part A, sets out the number of culture results during the second and third years. The majority of patients in both series—namely, 71% of the calcium and 70% of the isoniazid series—had 11 to 14 culture results in the second year, the average number of results being 13.3 for each series (the planned total was 14).

In the third year the intensity of investigation was less and the majority of patients—namely, 64% of the calcium and 66% of the isoniazid series—had seven to nine culture results, the average number of

results for the former series being 8.9 and for the latter 8.4 (the planned total was nine).

#### Disease status

Of the calcium series 53 (87%) patients and of the isoniazid series 58 (89%) yielded only negative cultures in the second and third years (Table 7, Part A); two (3%) of the former series and three (5%) of the latter yielded an isolated positive culture. If these isolated positive findings are regarded as unimportant, the proportion of patients with bacteriologically quiescent disease throughout the period was 90% for the calcium and 94% for the isoniazid series.

Bacteriological relapse occurred in six (10%) of the calcium and three (5%) of the isoniazid series in the second and third years, four of the former and two of the latter being associated with a radiographic deterioration, so that a change of treatment was necessary (one of these patients had an haemoptysis also). One isoniazid patient who showed no radio-

TABLE 5. CHANGES IN CAVITATION STATUS IN THE SECOND AND IN THE THIRD YEAR <sup>a</sup>

Year	Patient series	Total patients with cavitation	Dis-appearance of cavitation	Cavities smaller or fewer	No change	Cavities larger or more numerous	Change of treatment, <sup>b</sup> or death	Total patients without cavitation	Ap-pearance of cavitation	Change of treatment <sup>b</sup>
Second	Calcium	19	4	5	5	4	1	41 <sup>c</sup>	2	2
	Isoniazid	23	4	9	4	3	3	42	0	0
	<b>Home Sanatorium</b>	21 21	4 4	10 4	1 8	4 3	2 2	35 <sup>c</sup> 48	1 1	0 2
	<b>All patients</b>	42	8	14	9	7	4	83 <sup>c</sup>	2	2
Third	Calcium	16	1	2	9	3	1	41	1	0
	Isoniazid	16	1	3	7	5	0	46	0	1
	<b>Home Sanatorium</b>	16 16	2 0	2 3	9 7	3 5	0 1	38 49	0 1	0 1
	<b>All patients</b>	32	2	5	16	8	1	87	1	1

<sup>a</sup>Assessments on standard radiographs and tomographic series for the second year and on standard radiographs for the third year.

<sup>b</sup>On account of a bacteriological relapse with or without a radiographic deterioration.

<sup>c</sup>Excluding one patient who developed cancer of the lung.

TABLE 6. NUMBER OF CULTURE RESULTS DURING THE SECOND AND THE THIRD YEAR

Year	Total number of culture results <sup>a</sup>	Part A				Part B				Part C				Part D	
		Treatment during the second year				Place of treatment during the first year				Cavitation status at the end of the first year				All patients	
		calcium		isoniazid		home		sanatorium		cavitated		non-cavitated			
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Second	10 or less	3	5	6	10	6	11	3	5	3	8	6	8	9	7.7
	11-14	40	71	43	70	34	63	49	78	25	68	58	72	83	70.9
	15-18	13	23	12	20	14	26	11	17	9	24	16	20	25	21.4
	Total patients	56	99	61	100	54	100	63	100	37	100	80	100	117	100.0
	Average number of culture results	13.3		13.3		13.1		13.5		13.2		13.4		13.3	
Third	6 or less	4	7	6	10	4	8	6	10	3	8	7	9	10	8.6
	7-9	35	64	40	66	37	70	38	60	26	70	49	62	75	64.7
	10-16	16	29	15	25	12	23	19	30	8	22	23	29	31	26.7
	Total patients <sup>b</sup>	55	100	61	101	53	101	63	100	37	100	79	100	116	100.0
	Average number of culture results	8.9		8.4		8.6		8.7		8.8		8.6		8.7	

<sup>a</sup>Excluding throughout eight patients (five calcium, three isoniazid; two home, six sanatorium; four cavitated, four non-cavitated) who relapsed bacteriologically in the second year and one patient (isoniazid, home, cavitated) who died.

<sup>b</sup>Excluding one patient (calcium, home, non-cavitated) who relapsed bacteriologically in the third year.

TABLE 7  
DISEASE STATUS IN THE SECOND AND THIRD YEARS

Year	Finding	Part A		Part B		Part C				Part D					
		Treatment during the second year				Place of treatment during the first year				Cavitation status at the end of the first year				AH patients	
		calcium		isoniazid		home		sanatorium		cavitated		non-cavitated			
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%		
Second and third	<i>Quiescent disease</i>														
	All cultures negative	53	87	58	89	51	89	60	87	37	88	74	88	111	88.1
	Isolated positive culture	2	3	3	5	2	4	3	4	0	0	5	6	5	4.0
	<i>Relapsed disease</i>														
	Bacteriological relapse (two or more positive cultures) without radiographic deterioration	2	3	1 <sup>a</sup>	2	2	4	1 <sup>a</sup>	1	1 <sup>a</sup>	2	2	2	3	2.4
	Bacteriological relapse with radiographic deterioration necessitating a change of treatment	4	7	2	3	1	2	5	7	3	7	3	4	6	4.8
<i>Death</i>	0	0	1 <sup>b</sup>	2	1 <sup>b</sup>	2	0	0	1 <sup>b</sup>	2	0	0	1	0.8	
Second	<i>Quiescent disease</i>														
	All cultures negative	54	89	59	91	52	91	61	88	37	88	76	90	113	89.7
	Isolated positive culture	2	3	2	3	2	4	2	3	0	0	4	5	4	3.2
	<i>Relapsed disease</i>														
	Bacteriological relapse (two or more positive cultures) without radiographic deterioration	2 <sup>c</sup>	3	1	2	1	2	2 <sup>c</sup>	3	1	2	2 <sup>c</sup>	2	3	2.4
	Bacteriological relapse with radiographic deterioration necessitating a change of treatment	3	5	2	3	1	2	4	6	3	7	2	2	5	4.0
<i>Death</i>	0	0	1 <sup>b</sup>	2	1 <sup>b</sup>	2	0	0	1 <sup>b</sup>	2	0	0	1	0.8	
<b>Total patients . . . . .</b>		<b>61</b>	<b>100</b>	<b>65</b>	<b>100</b>	<b>57</b>	<b>100</b>	<b>69</b>	<b>100</b>	<b>42</b>	<b>100</b>	<b>84</b>	<b>100</b>	<b>126</b>	<b>100.0</b>

<sup>a</sup>This patient had a bacteriological relapse in the second year and treatment was changed in the third year because the patient remained persistently bacteriologically positive.

<sup>b</sup>This patient produced an isolated positive culture in the fifteenth month and died in the seventeenth month (see text, page 155).

<sup>c</sup>Including one patient who continued on calcium and yielded only negative cultures from the seventeenth month up to the end of the second year (see text, page 157).

graphic deterioration had chemotherapy changed because positive cultures were obtained persistently.

The lower half of Table 7 gives the corresponding findings for the second year only. It will be seen that there was very little difference between the findings in the second year and those in the second and third years combined. In fact, the only changes in the third year were that one isoniazid patient yielded an

isolated positive culture; one calcium patient, who had had a bacteriological relapse in the second year, had a radiographic deterioration necessitating a change of treatment in the third year; and another patient in the calcium series had a bacteriological relapse. In summary, the great majority of patients in both series retained quiescent disease throughout the period and all except one of the relapses occurred in the second year

### III. COMPARISON OF THE HOME AND SANATORIUM SERIES

This section compares the 57 home and 69 sanatorium patients with bacteriologically quiescent disease at one year who were allocated at random to treatment in the second year.

#### 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 is given for the home and sanatorium patients in Table 2, Part B. It will be seen that the home patients, who had had an inferior diet (Tuberculosis Chemotherapy Centre, 1959; Ramakrishnan et al., 1961b) weighed less than the sanatorium patients; 15 (26%) of the former as compared with 44 (64%) of the latter weighed 100 lb. or more. In addition, 38 % of the sanatorium patients had normal ESRs (10 mm or less) as compared with 12 % in the home 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; and 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 AND THIRD YEARS

##### *Deaths*

The one death among the 126 patients occurred in a male in the home series. His case is summarized on page 155.

##### *Changes in the ESR*

At one year 13 % of 55 home and 35 % of 60 sanatorium patients had normal ESRs (Table 3). At three years the corresponding proportions were 25 % and 30 %, respectively; 47 % of the home and 40 % of the sanatorium patients still had ESRs of 21 mm or more.

##### *Radiographic progress*

The majority of patients in both series—namely, 46 (82%) of the home and 55 (80%) of the sanatorium series—showed no change in the radiographic appearances in the second year (Table 4), and five

home and eight sanatorium patients improved radiographically. In the third year 48 (89 %) of the home and 57 (88%) of the sanatorium patients showed no change and three patients in the home and four in the sanatorium series improved radiographically.

##### *Changes in cavitation status*

Considering the patients with residual cavitation at the end of the first year (Table 5), cavitation disappeared in four of 21 home patients as compared with four of the same number of sanatorium patients in the second year and was less in 10 and four patients, respectively. In the third year it disappeared in two of 16 home and none of 16 sanatorium patients, and was less in two and three patients, respectively.

Of 35 home patients who had no residual cavitation at one year, one showed cavitation at two years as did one of 48 patients in the sanatorium series. Of 38 home patients without cavitation at two years, none showed cavitation at the end of the third year as compared with one of 49 patients in the sanatorium series.

##### *Number of culture results*

Table 6 sets out the number of culture results during the second and third years. The majority of patients in both series—namely, 63% of the home and 78 % of the sanatorium series—had 11 to 14 culture results in the second year, the average number of results being 13.1 for the home series and 13.5 for the sanatorium series. In the third year the intensity of bacteriological investigation was less and the majority of patients—namely, 70% of the home and 60% of the sanatorium series—had seven to nine culture results, the average number of cultures for the former series being 8.6 and for the latter 8.7.

##### *Disease status*

Considering both the second and third years together (Table 7, Part B), 51(89 %) of the home and 60 (87%) of the sanatorium patients yielded only negative cultures. Two (4%) of the home and three (4%) of the sanatorium patients yielded an isolated positive culture. The proportion of patients with bacteriologically quiescent disease was 93 % for the home and 91% for the sanatorium series.

Bacteriological relapse occurred in three (5%) of the home and six (9%) of the sanatorium patients, one of the home and five of the sanatorium patients

having a radiographic deterioration also, necessitating a change of treatment. The sixth sanatorium patient had treatment changed because of persistent positive cultures. (Details of the individual patients who relapsed bacteriologically have already been given (see page 155 et seq.).) The position showed very little change from that in the second year (lower

half of Table 7). The only changes that occurred in the third year were that one sanatorium patient yielded an isolated positive culture, one home patient had a bacteriological relapse without a radiographic deterioration and another sanatorium patient, who had already had a bacteriological relapse in the second year, had a radiographic deterioration.

#### IV. COMPARISON OF THE CAVITATED AND NON-CAVITATED SERIES

In this section the progress in the second and third years of the 42 patients with residual cavitation at the end of the first year is compared with that of the 84 patients who had no definite evidence of residual cavitation. Before considering the progress in the second and third years, the clinical and other radiographic features at the end of the first 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 distribution of estimated age for the two series; 14% of the 42 patients in the cavitated series were under 25 years of age, as 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, as compared with 12% of the non-cavitated series. The sex distribution was similar in the two series, 57% of the cavitated and 63 % of the non-cavitated series being males.

##### 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 (10 mm or less) as 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 7% had less than two lung zones involved as compared with 25 % of the patients in the non-cavitated series. Correspondingly, 86% of the patients in the cavitated series as compared with 64 % in the non-cavitated series had bilateral disease.

In summary, the cavitated series had higher ESRs and more extensive residual radiographic lesions than the non-cavitated series.

##### CLINICAL RESULTS IN THE SECOND AND THIRD YEARS

###### *Deaths*

The one death among the 126 patients occurred in a male in the cavitated series. His case is summarized on page 155.

###### *Changes in the ESR*

Two (6%) of 36 patients in the cavitated series had had a normal ESR at one year compared with 26 (33 %) of 79 in the non-cavitated series. At three years the corresponding proportions were 22% and 30 %, respectively. At three years 50 % of the cavitated series and 41 % of the non-cavitated series still had an ESR of 21 mm or more.

###### *Radiographic progress*

In the second year (Table 4) 30 (71%) of 42 patients with cavitated lesions showed no change and six (14 %) showed radiographic improvement, as compared with 71 (86 %) and seven (8 %), respectively, of 83 patients assessed in the non-cavitated series. In the third year, the majority of patients in both series—namely, 28 (74%) of 38 patients in the cavitated series and 77 (95%), of 81 in the non-cavitated series—showed no change. Again the numbers who improved were small—namely, five (13 %) of the cavitated series and two (2%) of the non-cavitated series. In summary, a majority of patients in both series showed no change in the second year and no change in the third year.

###### *Changes in cavitation status*

Considering the 42 patients with residual cavitation at one year (Table 5), cavitation had disappeared

in eight and was less in 14 by the end of the second year. There were 32 patients with residual cavitation at the beginning of the third year; in two of these patients cavitation had disappeared by the end of the third year and in five of them it was less.

Of the 83 patients assessed as having no cavitation at one year (Table 5), two showed cavitation at the end of the second year. At the beginning of the third year there were 87 patients assessed as having no cavitation; cavitation was apparent in one of these at the end of the third year.

In summary, there was little change in the 2-year period in the patients with no cavitation, but in the patients with cavitation there was more evidence of improvement in the second than in the third year.

#### *Number of culture results*

Table 6 sets out the number of culture results during the second and third years. The majority of patients in both series—namely, 68 % of the cavitated and 72% of the non-cavitated series—had 11 to 14 culture results in the second year, the average number of results being 13.2 for the cavitated series and 13.4 for the non-cavitated series. In the third year the intensity of investigation was less and the majority of patients—namely, 70% of the cavitated and 62% of the non-cavitated series—had seven to

nine culture results, the average number of cultures being 8.8 and 8.6, respectively.

#### *Disease status*

Considering the second and third years together, 37 (88%) of the patients in the cavitated and 74 (88%) of those in the non-cavitated series yielded only negative cultures (Table 7, Part C). A further five (6%) in the non-cavitated series yielded an isolated positive culture so that the proportion of patients with quiescent disease in the two series was 88 % for the cavitated and 94 % for the non-cavitated series. Three (7%) patients in the cavitated series relapsed bacteriologically with a radiographic deterioration necessitating a change of treatment, as did three (4%) in the non-cavitated series. There was very little change in the third year. One patient (non-cavitated) produced an isolated positive culture. Another patient (non-cavitated) relapsed bacteriologically and a third patient, also in the non-cavitated series, who had relapsed bacteriologically in the second year, had treatment changed in the third year after a radiographic deterioration. It may be concluded that the great majority of patients in both series retained quiescent disease throughout the period and there was only a little evidence that the cavitated series fared less well than the non-cavitated series.

## V. COMPARISON OF THE PATIENTS ALLOCATED AT RANDOM TO CALCIUM OR TO ISONIAZID FOR THE THIRD YEAR

This section compares the progress in the *third* year of the 60 patients who received one year of isoniazid plus PAS, either at home or in sanatorium, followed by one year of isoniazid at home, and who were then allocated at random to a third year of treatment at home, either with calcium gluconate, the "2-year series" (30 patients), or with isoniazid, the "3-year series" (30 patients). All the patients had bacteriologically quiescent disease at the end of the first and at the end of the second year. One patient in the isoniazid series voluntarily stopped his chemotherapy at 27 months. He was followed up and had quiescent disease at three years. He has been included in the analysis.

Before considering the results of treatment in the third year, the clinical and radiographic condition of the patients on admission to treatment, at the end of the first year and at the end of the second

year are compared to see if the two series were similar.

#### CLINICAL AND RADIOGRAPHIC CONDITION

Most of the patients in both series were ill and had extensive lesions when they were *originally admitted* to treatment. Thus, at that time, 22 of the 30 patients in the 2-year series and 20 of the 30 in the 3-year series had moderate or extensive cavitation; 22 patients in each series had bilateral disease and 21 in each series had four, five or six lung zones involved. The ESR was 51 mm or more in 26 patients in the 2-year series and 20 in the 3-year series. Of the patients in the 2-year series, 15 were originally treated at home as compared with 12 in the 3-year series.

At the *end of the first year* there was very little difference between the two series. In the 2-year



series 11 patients and in the 3-year series eight patients had residual cavitation at one year.

The clinical and radiographic features at the *end of the second year*, when the random allocation to treatment for the third year was made, are given in Table 8. It will be seen that there were no important differences between the two series in respect of the factors tabulated.

In summary, the differences between the two series at the start of treatment, at the end of the first year and at the end of the second year were small. In the 2-year series there were more patients who had received the first year's treatment at home, and more who had had residual cavitation, the "open-negative" syndrome, at one year than there were in the 3-year series.

#### CLINICAL RESULTS IN THE THIRD YEAR

##### *Changes in radiographic appearances*

Of the 30 patients in the 2-year series, three showed slight radiographic improvement in the third year, 26 showed no change and one showed slight deterioration, as compared with two, 27 and one, respectively, of the 30 patients in the 3-year series.

##### *Changes in cavitation*

Eight patients in each series had residual cavitation at two years. In the 2-year series it had disappeared by the end of the third year in one patient, was less in two, was unchanged in four and was more in one patient. In the 3-year series, the cavitation was less at the end of the third year in one patient, unchanged in three and more in four. In each series 22 patients had no cavitation at the end of the second year; none of these had cavitation at the end of the third year.

##### *Number of culture results*

The average number of culture results in the third year was 8.5 for each series.

##### *Culture and sensitivity test results*

All the cultures examined in both series throughout the third year were negative, except one, sensitive to isoniazid, from a patient (sanatorium, cavitated) in the 3-year series. He produced an isolated positive laryngeal swab culture at 36 months with a growth of 16 colonies. Two overnight sputum specimens and another pair of laryngeal swabs which were also examined at 36 months were negative.

TABLE 8  
CONDITION AT THE END OF THE SECOND YEAR  
OF THE PATIENTS ALLOCATED AT RANDOM TO  
CALCIUM IN THE THIRD YEAR (THE P-YEAR SERIES) OR  
TO ISONIAZID (THE 3-YEAR SERIES)

	2-year series	3-year series
<i>Weight (lb.):</i>		
60-69	1	0
70-79	5	4
80-89	9	9
90-99	5	11
100-109	7	2
110 or more	3	4
<i>ESR (mm in 1 hour):</i>		
0-10	7	13
11-20	14	10
21-50	9	5
51-100	0	2
101 or more	0	0
<i>Number of lung zones involved in disease:</i>		
0	1	4
1	6	8
2	18	12
3	5	5
4	0	1
5	0	0
6	0	0
<i>Extent of radiographic lesion:</i>		
Nil	1	4
Unilateral	11	11
Bilateral	18	15
<i>Extent of cavitation:</i>		
Nil	22	22
Slight	3	2
Moderate	3	4
Extensive	2	2
Total patients	30	30

\* 1 lb. = 0.45 kg.

*Disease status at three years*

All the patients in both series had bacteriologically quiescent disease throughout the third year. The

patient in the 3-year series who yielded an isolated positive culture was also presumed to have quiescent disease.

## VI. RESULTS IN THE EIGHT SUBGROUPS OF THE THREE MAIN COMPARISONS AND PROGRESS OF ALL THE 126 PATIENTS WITH QUIESCENT DISEASE AT ONE YEAR

### RESULTS IN THE EIGHT SUBGROUPS OF THE THREE MAIN COMPARISONS

The 126 patients with bacteriologically quiescent disease at one year who were allocated at random to treatment with calcium gluconate or isoniazid in the second year may be classified in eight subgroups. The number of patients in each subgroup who had bacteriologically quiescent disease throughout the second and third years is given in Table 9. Although the figures are small they do not suggest that there is any important difference between the subgroups contributing to the comparisons already presented.

### PROGRESS OF ALL THE 126 PATIENTS WITH QUIESCENT DISEASE AT ONE YEAR

In view of the finding that there was comparatively little difference in the response of the patients in the eight subgroups, it is legitimate to amalgamate the findings for all the patients. This subsection therefore studies the progress of all the 126 patients who had bacteriologically quiescent disease at one year.

*Radiographic progress*

The great majority of the patients—namely, 81% of those assessed in the second year and 88% of those assessed in the third year—showed no radiographic change (Table 4); 10% and 6%, respectively, showed radiographic improvement.

*Changes in cavitation*

Considering the 42 patients with cavitation at the end of the first year, cavitation had disappeared by the end of the second year in eight and was less in 14 (Table 5). Considering the 32 patients who had residual cavitation at the end of the second year, cavitation had disappeared by the end of the third year in two and was less in five. Of the 83 patients with no residual cavitation at the end of the first year, two showed cavitation at the end of the second year. There were 87 patients who had no cavitation at the end of the second year; of these,

one showed cavitation at the end of the third year.

*Number of culture results*

In the second year 70.9% of the patients had 11 to 14 culture results, the average number of results being 13.3 (Table 6, Part D). In the third year the majority of patients—namely, 64.7%—had seven to nine culture results; the average number was 8.7.

*Disease status*

In the second and third years, five (4.0%) of the 126 patients yielded an isolated positive culture (Table 7, Part D). Three (2.4%) had a bacteriological relapse without a radiographic deterioration and six (4.8%) more patients had a bacteriological relapse

TABLE 9  
NUMBER OF PATIENTS IN THE EIGHT SUBGROUPS WITH BACTERIOLOGICALLY QUIESCENT DISEASE THROUGHOUT THE SECOND AND THIRD YEARS

Place of treatment during the first year	Cavitation status at the end of the first year	Treatment during second year	Number of patients	Patients with bacteriologically quiescent disease throughout the second and third years	
				No.	%
Home	Cavitated	Calcium	11	10	91
		Isoniazid	10	9	90
	Non-cavitated	Calcium	18	16	89
		Isoniazid	18	18	100
Sanatorium	Cavitated	Calcium	8	8	100
		Isoniazid	13	10	77
	Non-cavitated	Calcium	24	21	88
		Isoniazid	24	24	100
Total . . .			126	116	92

with a radiographic deterioration necessitating a change of treatment. In all, therefore, nine (7.1%) of the patients had had a bacteriological relapse. The corresponding figure for the second year was eight (6.3 %); in other words, all except one of the bacteriological relapses occurred in the second year.

#### *Prognostic factors*

An analysis (not tabulated here) was undertaken to investigate whether there were any factors of prognostic importance in the nine patients whose disease relapsed in the second or the third year. There was only a slight suggestion that these patients had more extensive lesions on their original admission to treatment than those whose disease continued to remain quiescent. Thus, *on admission*, six (67%) of the nine had five or six lung zones involved in disease as compared with 43 (37%) of the 117 with persisting quiescent disease. All nine had bilateral disease as compared with 88 (75%) of the 117; six (67%) of the former had a 3-plus (heavy) direct

smear on sputum examination as compared with 46 (39%) of the latter. Initial cavitation was not a factor of prognostic importance, neither was the ESR nor the age. Four (44%) of the nine patients whose disease relapsed were males, as compared with 73 (62%) of those with persisting quiescent disease.

There was little difference in the month of the original sputum conversion; seven (78 %) of the nine who relapsed had converted their sputum to negativity within the first three months as compared with 77 (66%) of those with quiescent disease throughout the second and third years.

Considering the condition of the patients at *one year*, there was no difference between those who relapsed and those who did not in terms of the ESR, but four (44%) of the former and 22 (19%) of the latter had four or more lung zones involved in disease, all the former and 81 (69%) of the latter having bilateral disease. Four (44%) of the nine and 38 (32%) of the 117 had residual cavitation.

## VII. RESULTS IN PATIENTS NOT ALLOCATED TO TREATMENT AT RANDOM AND DISEASE STATUS AT THREE YEARS OF ALL PATIENTS WITH QUIESCENT DISEASE AT ONE YEAR

### RESULTS IN THE FOUR PATIENTS NOT ALLOCATED AT RANDOM TO TREATMENT IN THE SECOND YEAR

Of the four eligible patients with quiescent disease at one year who were not included in the random allocation to treatment in the second year, one patient (home, cavitated) died of a carcinoma of the oesophagus in the fifteenth month. Two patients (one home, one sanatorium; both non-cavitated), who received the placebo in the second and third years, yielded only negative cultures. The fourth patient (home, cavitated), who continued on isoniazid plus PAS, yielded positive cultures, resistant to isoniazid, at 15, 19, 23 and 24 months, had a radiographic deterioration and had his treatment changed at 25 months.

### DISEASE STATUS AT THREE YEARS OF THE 130 PATIENTS WITH QUIESCENT DISEASE AT ONE YEAR

The above four patients were included in an analysis of the disease status at three years of *all*

the 130 patients with quiescent disease at one year. Patients have been classified as bacteriologically quiescent at three years if all their cultures were negative in the last six months of the period, irrespective of whether they had continued on the prescribed treatment or had had their treatment changed owing to a relapse. Of the 130 patients, two had died, one of carcinoma of the oesophagus and the other from a cause which could not be established (see page 155); 126 patients had quiescent disease and only two patients still had active disease. Of these, one patient, who had persistently been uncooperative and had interrupted her chemotherapy on two occasions, still had a positive sputum and advanced disease; the other was under treatment and, although having active disease by the above stringent definition, had yielded only negative cultures in the last five months of the period.

## VIII. REGULARITY OF SELF-ADMINISTRATION OF THE MEDICINE

Much emphasis was laid on the importance of taking the medicaments regularly. 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 who received isoniazid, tests for the presence of the drug

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

Year		Treatment		Place of treatment during the first year		Sex	
		calcium	isoniazid	home	sanatorium	male	female
Second	Number of patients with one or more pill counts <sup>a</sup>	55	61	53	63	70	46
	Total number of occasions on which pills were counted	355	427	331	401	432	350
	Average number of pill counts per patient	6.5	7.0	7.2	6.4	6.2	7.6
	Number of occasions on which incorrect pill stocks were found	68	87	84	71	93	62
	Percentage of occasions on which incorrect pill stocks were found	19.2	20.4	22.0	17.7	21.5	17.7
Third	Number of patients with one or more pill counts	83	26	52	57	67	42
	Total number of occasions on which pills were counted	684	210	456	438	497	397
	Average number of pill counts per patient	8.2	8.1	8.8	7.7	7.4	9.5
	Number of occasions on which incorrect pill stocks were found	172	44	122	94	109	107
	Percentage of occasions on which incorrect pill stocks were found	25.1	21.0	26.8	21.5	21.9	27.0

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

<sup>b</sup>Excluding one patient (isoniazid, home, male) who discharged himself after having received the allocated treatment for three months and two patients (one calcium, one isoniazid; both sanatorium; one cavitated, one non-cavitated) who had their treatment changed on account of a bacteriological relapse with or without a radiographic deterioration.

in specimens of urine obtained at the 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. 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 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 for the counts of the patients' stocks of pills at surprise visits to the

homes for the second and third years separately. The average number of counts in the second year was 6.5 for the patients in the calcium series and 7.0 for those in the isoniazid series. Of a total of 355 counts in the calcium series, 19.2% disclosed incorrect stocks as compared with 20.4% of 427 counts in the isoniazid series. Comparing the patients treated at home in the first year with those treated in sanatorium, inaccuracies in the stock of pills were found in the second year in 22.0% of the former and 17.7% of the latter. The male patients had inaccurate stocks at 21.5% of the counts and the females at 17.7%.

As a result of the random allocation procedure at two years, the number of patients receiving calcium gluconate in the third year whose pill stocks were checked increased to 83, whereas the corresponding number of those receiving isoniazid fell to 26. The average number of pill counts per patient in the third year was 8.2 for the calcium series and 8.1 for the isoniazid series. Of a total of 684 counts in the

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

Year		Specimens at planned visits to the Centre				Specimens at surprise visits to the home			
		place of treatment during the first year		sex		place of treatment during the first year		sex	
		home	sanatorium	male	female	home	sanatorium	male	female
Second	Number of patients with one or more test results <sup>a</sup>	27	35	41	21	25	30	35	20
	Total number of test results	393	466	581	278	172	173	179	166
	Average number of test results per patient	14.6	13.3	14.2	13.2	6.9	5.8	5.1	8.3
	Number of test results which were negative	91	97	130	58	57	48	46	59
	Percentage of test results which were negative	23.2	20.8	22.4	20.9	33.1	27.7	25.7	35.5
Third	Number of patients with one or more test results <sup>a</sup>	11	18	22	7	11	16	21	6
	Total number of test results	107	159	213	53	56	92	88	60
	Average number of test results per patient	9.7	8.8	9.7	7.6	5.0	5.8	4.2	10.0
	Number of test results which were negative	24	30	40	14	20	27	22	25
	Percentage of test results which were negative	22.4	18.9	18.8	26.4	35.7	29.3	25.0	41.7

<sup>a</sup>Excluding one patient (home, male) who died and two patients (both sanatorium, female) who had their treatment changed on account of a bacteriological relapse with a radiographic deterioration.

<sup>b</sup>Excluding one patient (home, male) who discharged himself after having received the allocated treatment for three months.

calcium series, 25.1% revealed inaccurate stocks, as compared with 21.0% of 210 counts in the isoniazid series. The general order of the irregularities was slightly higher in the third than in the second year. Comparing the patients treated at home in the first year with those treated in sanatorium, inaccuracies in the stocks in the third year were found in 26.8 % of the former and 21.5 % of the latter. The findings for the males and females were 21.9 % and 27.0%, respectively.

#### URINE TESTS

For the patients in the isoniazid series only, urine specimens were obtained at all the routine visits to the Centre and at surprise visits of the staff to the home. 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 total number of

tests performed on urine specimens and the numbers 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 surprise visits to the home are presented separately for each year. Considering first the specimens obtained at the routine visits to the Centre, in the second year 23.2% of the results for the patients initially treated at home were negative, as compared with 20.8 % for the patients who were initially treated in sanatorium. Considering the male patients, 22.4% of the tests were negative, as compared with 20.9% of the tests for the female patients. For surprise specimens the corresponding four proportions were 33.1%, 27.7 %, 25.7 % and 35.5 %. Thus, the surprise visits revealed a somewhat greater degree of irregularity, and it is likely that some of the patients were more regular in taking their isoniazid on the days of their visits to the Centre than on other days. It will be noted that the female patients were more irregular than the males.

The greater irregularity amongst the patients treated at home was due to this fact, for further analysis (not tabulated here) showed that the home males yielded negative results in 25.3% of surprise tests and the home females in 43.8%; the finding in the sanatorium males was 26.2 % and in the sanatorium females 29.0 %.

In the third year, the findings are based on smaller numbers, but the proportions of tests with negative

results were 22.4% for the patients treated at home in the first year and 18.9 % for those treated in sanatorium, and 18.8 % for the males and 26.4 % for the females. The tests at surprise visits again yielded evidence of greater irregularity, the corresponding proportions being 35.7%, 29.3 %, 25.0% and 41.7%, respectively. It may be concluded that the general order of irregularity was the same for both the second and the third year.

#### IX. PATIENTS WITH DISEASE OF DOUBTFUL BACTERIOLOGICAL STATUS AT ONE YEAR

As reported earlier (Tuberculosis Chemotherapy Centre, 1959), 10 patients (seven home, three sanatorium) 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—i.e., at 10, 11 or 12 months". These 10 patients represented 6.1% of the total of 163 patients in the main analysis. Their progress during the second year has already been reported (Velu et al., 1960b). This section summarizes their progress during the second and third years.

Of the seven home patients, one had erroneously been regarded at the time as having had active disease at one year (Velu et al., 1960b) and, for this reason, continued on the originally prescribed isoniazid plus PAS in the second and third years. She produced another positive culture at 13 months, but all the 12 cultures between then and the end of the second year were negative and at two years her disease was bacteriologically quiescent. At 27 months the patient produced two positive cultures, which were followed by a radiographic deterioration, and her chemotherapy was changed at 30 months. The remaining six home patients were allocated at random to treatment with isoniazid or the placebo in the second year. Of these, four (two calcium, non-cavitated; one calcium, cavitated; one isoniazid, cavitated) yielded only negative cultures in the second and third years. One patient (calcium, non-cavitated) yielded growth of a single colony at 33 months, sensitive to isoniazid. The sixth home patient (cavitated), who had isoniazid throughout the second and third years, yielded positive cultures at 13, 15, 16 and 18 months. The sputum then became

negative and nine consecutive negative cultures were obtained. At 27 months she yielded a positive culture with growth of six colonies and at 30 months another with growth of two colonies. She then became bacteriologically negative again. At 36 months she yielded another positive culture with 1-plus growth. All the eight strains were resistant to isoniazid.

Considering the three sanatorium patients, also allocated at random to treatment with isoniazid or the placebo for the second year, two (calcium, non-cavitated) yielded only negative cultures throughout the second and third years. The third, who had yielded a positive culture at 12 months, also yielded positive cultures at 13, 14, 15 and 16 months. He had a radiographic deterioration and his treatment was changed in the seventeenth month. (This patient's organisms alternated between being sensitive to isoniazid and resistant at a low level (growth on 0.2 µg/ml but not on 1 µg/ml, repeated at a second test on the same strain).)

In summary, the three patients who had a bacteriological relapse had all had positive cultures at 12 and 13 months, i.e., the positive culture at 12 months, in the event, proved to be the commencement of the relapse.

The disease status at three years was assessed for all 10 patients irrespective of whether or not the chemotherapy had been changed owing to a relapse. Eight had quiescent disease at three years, that is, had yielded no positive cultures in the last six months of the period. One patient was presumed to have quiescent disease; he had yielded a single colony at 33 months. The tenth patient, who had received isoniazid in the second and third years, had active disease at the end of the period.

## X. DISCUSSION

The present report is mainly concerned with the progress during the second and third years of *all* the 130 patients whose pulmonary tuberculosis had attained bacteriological quiescence at the end of a year of the prescribed chemotherapy in a comparison of home and sanatorium treatment in a total of 163 patients. The patients, most of whom had very extensive lesions on admission to treatment, had been drawn from the lower income groups or the unemployed in Madras City, which is 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; Ramakrishnan et al., 1961b).

In the second year 126 of the patients were allocated at random to treatment either with isoniazid alone (65 patients) or with a placebo, calcium gluconate (61 patients). Of the former, 61 still had quiescent disease at two years, and 60 of these were allocated at random to treatment for a third year either with isoniazid alone (30 patients) or with calcium gluconate (30 patients). The patients who had been allocated the placebo in the second year continued on it for the third year, unless their disease was no longer quiescent at the end of two years. Of the 126 patients, eight (6.3%) had a bacteriological relapse in the second year. One more patient had a relapse in the third year, giving a total of nine (7.1%) for the 2-year period. The relapse rate compares favourably with the findings of other workers. For example, Raleigh (1957) reported a cumulative relapse rate of 14% at one year and 21% at three years following quiescence after six to eight months of chemotherapy. His figures include both bacteriological and radiographic relapses. Ross et al. (1958) reported a relapse rate of 7% in a two to three year period of follow-up. Low (1959) reported a relapse rate of 6% in a 2-year follow-up of patients who had six or more months of multiple drug therapy which included isoniazid.

The findings for the main subdivisions of the 126 patients are readily summarized. Six (10%) of the 61 patients who had had only one year of chemotherapy relapsed bacteriologically during the second and third years, as compared with three (5%) of 65 who had had two or three years of chemotherapy. In the second and third years, three (5%) of the 57 patients who had been treated at home in the

first year relapsed as compared with six (9%) of 69 who had been treated in sanatorium. Four (10%) of 42 patients with residual cavitation at one year, the "open negative" syndrome, relapsed in the second or third year, as compared with five (6%) of 84 without residual cavitation at one year. It may be concluded that it made comparatively little difference to the progress of the patients whether they were treated for one year or for two or more years, whether they had been originally treated at home or in sanatorium, and whether they had had the "open negative" syndrome or no cavitation at the end of the first year. There was some evidence that a second year of isoniazid may have prevented relapse in patients with non-cavitated lesions at one year, for none of 42 patients who received isoniazid relapsed, as compared with five of 42 who received the placebo—a statistically significant difference. However, only one of 19 patients with cavitated lesions, who received the placebo, had a bacteriological relapse (as compared with three of 23 who received isoniazid) so that the finding of five relapses in 42 patients may not be representative of the true relapse rate in non-cavitated lesions. Further data on the role of isoniazid in the prevention of relapse during the second year will shortly be available in another series (see Tuberculosis Chemotherapy Centre, 1960) of patients whose disease had attained bacteriological quiescence at the end of a year of chemotherapy at home. These additional results should clarify the position further.

The comparison in the third year of patients who received either two or three years of chemotherapy, based on the random allocation of 60 patients, is of interest. No patient in either series had a bacteriological relapse. Even though the comparison is based on small numbers, this observation underlines the importance of control groups in interpreting the findings of long-term chemotherapy studies. In the absence of a control group it would have been tempting but erroneous to conclude that the excellent results in the group who received chemotherapy for the third year were due to this continuation of chemotherapy.

In evaluating these findings it must be borne in mind that all the patients had originally attended routine chest clinics on their own initiative because of symptoms and that the great majority were clinically ill and had far advanced bilateral cavitated disease. The good results were obtained even though

the patients were drawn from a poverty-stricken, malnourished, overcrowded community in the tropics and despite the fact that the patients treated at home had comparatively little rest, even in the early stages of treatment. The findings have particular reliability in view of the high intensity of bacteriological investigation of the patients. Thus, the patients had, on the average, 13.3 cultures examined in the second year and 8.7 in the third year, so that the assessment of bacteriological quiescence is based on much more extensive bacteriological data than are usually available in relapse studies.

Considerable evidence is accumulating that it is difficult to persuade tuberculous patients to co-operate in the long-term self-administration of drugs, whatever the nature of those drugs. This has been shown principally with combinations containing PAS (Wynn-Williams & Arris, 1958; Luntz & Austin, 1960) and some workers attribute the difficulty specifically to that drug (Poole & Stradling, 1960). Evidence has, however, been reported that smaller tablets containing isoniazid alone are no more acceptable for self-administration than a similar number of large PAS-containing cachets (Tuberculosis Chemotherapy Centre, 1960). It has also been shown in a study in this Centre that irregularities also occur with a single daily tablet of isoniazid alone, and even with a daily placebo (Velu et al., 1960b); the present study has confirmed these findings. Irregularities, and in some patients serious omissions of medicaments, thus represent a major problem of long-term chemotherapy in tuberculosis.

There is much controversy concerning the place of surgery in the treatment of the "open negative" syndrome, that is, bacteriologically quiescent disease with residual cavitation (Raleigh, 1957; Bloch et al., 1958; Corpe & Blalock, 1958; Mitchell & Auerbach, 1959). In the present series, patients with the "open negative" syndrome at the end of one year of chemotherapy fared slightly less well than patients without cavitation at that time, but further chemotherapy with isoniazid alone did not influence the relapse rate. The patients with residual cavitation who relapsed responded to further courses of chemotherapy and their end results may well prove to be as satisfactory in the long-term follow-up as the results in patients without residual cavitation. Many developing countries do not have the resources to treat the "open negative" syndrome surgically, but even for the technically advanced countries the question arises whether surgery is justified, especially in view of the operative mortality and post-operative com-

plications (Mitchell & Auerbach, 1959). There is clearly an urgent need for more information on the management of the "open negative" syndrome (Ross et al., 1958; American Trudeau Society, 1959). Further findings will be reported later from this and other studies in this Centre.

Finally, it is of interest to consider the factors which may be used to assess the progress of patients with bacteriologically quiescent disease. In this community, it has emerged that the ESR is often elevated in patients who have had quiescent disease for two years or even longer. It is therefore an unsatisfactory measure of progress, a finding in keeping with that in East African patients (Courdurier & Brygoo, 1947; McGregor & Deegan, 1954; Hutton et al., 1956). Considering the radiographic assessments, most patients showed no radiographic improvement in the second or third year. Indeed, the majority of the patients showed no change in the second six months of the first year either (Tuberculosis Chemotherapy Centre, 1959). Thus, even with advanced lesions, the maximum radiographic improvement usually occurs early and the lesions then become stabilized. Further radiography confirms the stability of the lesions but does not usually demonstrate continuing radiographic improvement, although calcification may become apparent at a later stage (Fox, Sutherland & Daniels, 1954; Fox & Sutherland, 1956, 1959).

In the present study, an independent assessor often recorded a radiographic improvement or deterioration because there was a change in the size of residual cavitation. The majority of such changes, however, occurred in patients who had a persistently negative sputum, the assessor being unaware of this fact. It is open to question how much importance should be attached to fluctuations in the size of cavities in patients who have a persistently negative sputum. The changes are almost certainly mechanical in origin and it is very unlikely in the present study that they represented activity of the tuberculous disease, for they did not usually presage relapse. These findings are in keeping with the recommendations of the American Trudeau Society (1959) that unfavourable radiographic changes with negative bacteriological findings should not be regarded as a relapse.

Although in the present study, in agreement with Raleigh's (1957) findings, an isolated positive culture in patients undergoing frequent examinations seems of little importance, the occurrence of two or more positive cultures in a patient with previously quiescent disease bacteriologically, was, in the majority



of cases, followed by a radiographic spread so that the instability of the lesions in patients in whom tubercle bacilli reappear in two or more specimens cannot be doubted. It is clear that the bacteriological assessments are the most valuable method of following the patient's progress.

It seems reasonable to conclude from the evidence presented in this report that, in general, at the present time, the developing countries with their limited resources need not aim at administering courses of effective chemotherapy of more than a year's duration. This conclusion is strengthened because it was possible, in the present study, to treat successfully those patients whose disease relapsed. Thus, at the end of three years, seven of the nine patients who had had a relapse had bacteriologically quiescent disease again (that is, six or more consecutive months of culture negativity) and in one more the disease was approaching quiescence (five consecutive months of culture negativity). The only patient who had active disease and a positive sputum at three years had refused to co-operate in further chemotherapy and so cannot be regarded as a failure of chemotherapy. There is no evidence in this study that a year of combined chemotherapy, followed by careful supervision, and further chemotherapy if relapse occurred, gave results in any way inferior to those which might

have been obtained by uninterrupted chemotherapy for the whole 3-year period.

This study of the progress in the second and third years of patients with bacteriologically quiescent disease at one year firmly consolidates 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., 1960; Ramakrishnan et al., 1961 a<sup>1</sup>) that there is no special risk to family contacts in a 2-year period if the patients are treated at home with isoniazid plus PAS. Considered together, these studies have established the value of properly planned domiciliary chemotherapy, even in most adverse environmental, economic and dietary circumstances.

The observation of both the patients and the contacts is continuing and there is every prospect that a successful 5-year follow-up will be obtained; further findings for both will be reported later. The long-term findings for patients and contacts in other domiciliary studies from this Centre will also be reported in due course.

## XI. 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 of 163 South Indian patients with pulmonary tuberculosis had attained bacteriological quiescence at one year (Tuberculosis Chemotherapy Centre, 1959). Of these, 126 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. The daily dosage of calcium gluconate was 500 mg.

2. At two years, 60 of the 61 patients in the isoniazid series who still had bacteriologically quiescent disease were allocated at random for a third year to isoniazid in the same dosage (30 patients) or to the placebo (30 patients).

3. The patients in the calcium series continued on calcium gluconate in the third year unless their disease was no longer bacteriologically quiescent at two years.

4. The main comparisons for the second and third years are between (a) 61 calcium and 65 isoniazid patients; (b) 57 home and 69 sanatorium patients; (c) 42 patients with residual cavitation at one year and 84 patients without cavitation at one year. A comparison for the third year is made between 30 patients who received two years of chemotherapy and 30 who received it for three years.

5. One patient (home, cavitated) who received isoniazid in the second year died in the seventeenth month, the cause of death being unestablished.

6. At the end of the third year there was relatively little difference between the progress of patients in the various subgroups; six (10%) of 61 patients who

<sup>1</sup>See article on page 129 of this issue.

received one year of chemotherapy relapsed bacteriologically, as compared with three (5%) of 65 who received two or three years of chemotherapy; three (5%) of 57 patients treated at home in the first year relapsed as compared with six (9%) of 69 treated in sanatorium; four (10%) of 42 patients with the "open negative" syndrome at one year relapsed, as compared with five (6%) of 84 in the non-cavitated series. In all, nine (7.1%) of the 126 patients relapsed in the second or third year, eight (6.3%) of these having relapsed in the second year.

7. None of the 60 patients in the comparison of two years and three years of chemotherapy, based on random allocation, relapsed (although one in the 3-year series produced an isolated positive culture at 36 months).

8. The regularity of self-administration of medicine was checked by counting the stocks of pills and by urine tests for isoniazid. Pill counting at surprise visits to the home revealed inaccuracies of the order of 20%, there being no major differences between the patients originally treated at home and in sanatorium or between the males and the females. Urine specimens were obtained at planned visits to the Centre for the patients receiving isoniazid. They yielded negative results in approximately 20% of tests.

9. In addition, the progress in the second and third years of the 10 patients with disease whose bacteriological status at one year was in doubt has been studied. Of these 10 patients, three had a bacteriological relapse; in each instance an apparently isolated positive culture at 12 months proved to be the beginning of the relapse.

10. It is concluded that in the second and third years there was relatively little difference between the patients whose disease attained quiescence following a year of domiciliary chemotherapy 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 or third year of treatment with isoniazid alone gave better results than a year of chemotherapy followed by careful observation of the patient and further chemotherapy if a relapse occurred. Thirdly, patients with residual cavitation at one year had slightly higher relapse rates than those without residual cavitation.

11. Taken in conjunction with earlier studies, the present study confirms the value of properly planned domiciliary chemotherapy for one year even in the most adverse environmental and dietary circumstances.

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

#### RÉSUMÉ

Poursuivant la comparaison des résultats à brève et longue échéance du traitement chimiothérapique de la tuberculose à domicile et en sanatorium parmi la population pauvre et mal nourrie de certains quartiers de Madras, les auteurs de cet article ont suivi 130 malades chez lesquels la maladie avait atteint un stade de quiescence à la fin de la première année de traitement par l'isoniazide et le PAS.

Dès la fin de cette première année, les malades suivis continuèrent tous leur traitement – réel ou fictif – à domicile. Durant la deuxième année, c'est-à-dire celle qui a suivi le traitement combiné, la moitié environ de ces patients a continué à être soumis au traitement à l'isoniazide, mais sans adjonction de PAS. L'autre moitié, servant de témoins, recevait un placebo, en l'occurrence du gluconate de calcium. Sur 126 malades, répartis

arbitrairement en groupes de traitement, 8 eurent des rechutes au cours de la deuxième année et un au cours de la troisième année, ce qui porte à 9 cas, soit 6,3%, la proportion des rechutes, chiffre qui supporte avantageusement la comparaison avec ceux qu'ont trouvés d'autres auteurs dans d'autres séries. Durant la troisième année, 50% des patients qui avaient reçu l'isoniazide seul poursuivirent ce traitement, l'autre moitié rejoignant le groupe recevant le gluconate.

Les résultats montrèrent que durant la deuxième et la troisième année, il n'y avait que peu de différence entre les sujets qui, au cours de la première année, avaient été traités à domicile d'une part, en sanatorium d'autre part.

Une deuxième ou une troisième année de traitement, par l'isoniazide seul, n'a pas amélioré les résultats obtenus la première année par le traitement combiné.

étant bien entendu que les patients ont été attentivement surveillés et les rechutes traitées dès leur apparition.

L'état général des malades présentant des lésions cavitaires résiduelles à la fin de la première année était peut-être un peu moins bon que celui des malades exempts de ces lésions, sans pour autant que la proportion des rechutes dans l'un et l'autre groupe accuse des différences significatives.

D'une façon générale, on peut conclure que les pays en voie de développement, dont les ressources sont res-

treintes, peuvent envisager de limiter à une année le traitement chimiothérapeutique des tuberculeux. Cela implique évidemment que les rechutes soient dépistées et immédiatement traitées. Dans la présente étude, 7 des 9 cas de rechutes avaient retrouvé leur état quiescent à la fin de la troisième année. Il faut relever d'autre part la difficulté d'obtenir des malades qu'ils prennent régulièrement leur médicament. Cette irrégularité est un écueil dans l'organisation d'un traitement à long terme à domicile.

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