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The Prevention and Treatment of Isoniazid Toxicity in the Therapy of Pulmonary Tuberculosis

1. An Assessment of Two Vitamin B Preparations and Glutamic Acid*

TUBERCULOSIS CHEMOTHERAPY CENTRE, MADRAS [1]

This paper from the Tuberculosis Chemotherapy Centre, Madras, presents the results of a study designed primarily (a) *to assess the efficacy of two preparations—Tab. Aneurin. Co. (a vitamin B compound not containing pyridoxine) and glutamic acid—in preventing the development of peripheral neuropathy during high-dosage (12.5-15.2 mg/kg) isoniazid therapy for pulmonary tuberculosis, and* (b) *to compare the therapeutic efficacy, once isoniazid neuropathy has developed, of Tab. Aneurin. Co., administered at twice the prophylactic dosage, and a vitamin-B-complex preparation containing a small amount of pyridoxine (amounting to 6 mg daily).*

Tab. Aneurin. Co. was found to be ineffective in preventing peripheral neuropathy, which occurred in five of the 18 patients receiving this preparation, as compared with six of the 18 who received a placebo, calcium gluconate. Glutamic acid appeared to have some prophylactic effect, since only two of the 19 patients receiving it developed the neuropathy, but the difference between the frequency in the glutamic series and that in the placebo series did not attain statistical significance.

As to the therapeutic efficacy of the two vitamin B preparations, Tab. Aneurin. Co., at twice the prophylactic dosage, did not prevent the progression of the neuropathy in five out of seven patients, whereas improvement occurred in eight of the nine patients who received the vitamin-B-complex preparation containing the small amount of pyridoxine.

This study has confirmed that the frequency of peripheral neuropathy is significantly higher among slow than among rapid inactivators of isoniazid and has indicated that the therapeutic response of the tuberculosis is not materially affected by increasing the dosage of isoniazid from 7.8-9.6 mg/kg (the dosage used in a previous study) to 12.5-15.2 mg/kg.

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* This paper will also be published, in Spanish, in the *Boletín de la Oficina Sanitaria Panamericana.*

[1] The Centre is under the joint auspices of the Indian Council of Medical Research (ICMR), the Madras State Government, the World Health Organization (WHO) and the Medical Research Council of Great Britain (MRC). The members of the scientific staff of the Centre with major responsibility for the work reported here are: Dr Wallace Fox (WHO), Senior Medical Officer, succeeded by Dr Hugh Stott in November 1960; Dr C. V. Ramakrishnan (ICMR) and Dr S. Velu (Madras Government), Medical Officers; Dr S. Devadatta (ICMR), Assistant Medical Officer; Dr J. H. Angel (WHO), Medical Officer, succeeded by Dr J. J. Y. Dawson; Dr A. L. Bhatia (ICMR) and Dr J. B. Selkon (WHO), Bacteriologists; Dr P. R. J. Gangadharam (ICMR), Assistant Bacteriologist; Mr D. V. Krishnamurthy (ICMR), Biochemist; Mr C. Narayanan Nair (ICMR) and Mr T. V. Subbaiah (ICMR), Laboratory Research Assistants; Mr K. L. Thomas (WHO), Laboratory Technician; Mr S. Radhakrishna (Madras Government), Senior Statistician; Mr K. Ramachandran (ICMR) and Mr P. R. Somasundaram (ICMR), Statisticians; and Mr B. Janardhanam (ICMR), Senior Assistant Statistician.

The research of the Centre is guided by a Project Committee consisting of three ICMR representatives (Dr P. V. Benjamin, Convener, Dr J. Frimodt-Møller and Dr K. S. Sanjivi), the Director of the ICMR (Dr C. G. Pandit), the Director of Medical Services, Madras State (Dr V. R. Thayumanaswamy, succeeded by Dr A. B. Marikar), a WHO representative (appointed for each meeting), an MRC representative (appointed for each meeting) and the Senior Medical Officer of the Centre. The joint secretaries were Mrs K. Daniels and Mr B. S. Verma, succeeded by Mr D. Chakravarti and Mr V. S. Talwar. The MRC, through its Tuberculosis Research Unit, is responsible for the scientific direction of the research in accordance with plans prepared by the Project Committee.

The patients in the present study were referred to the Centre from the Government Tuberculosis Institute, Madras (Director: Dr M. A. Hamid) and the Corporation Tuberculosis Clinic, Pulianthope (Medical Officer in Charge: Dr V. S. Selvapathy).

I. INTRODUCTION

A previous report from the Tuberculosis Chemotherapy Centre, Madras, showed that isoniazid given by itself in moderate dosage (7.8-9.6 mg/kg body-weight) once daily was more effective than the same daily dosage given in two doses, but was less effective than a standard combination of isoniazid plus PAS (Tuberculosis Chemotherapy Centre, 1960). It was therefore considered important to investigate whether an even larger single daily dose of isoniazid could approach the efficacy of the combined regimen. Unfortunately, peripheral neuropathy occurred in 18% of 74 patients receiving isoniazid in the moderate dosage (7.8-9.6 mg/kg) when this was given once daily. A still larger dosage of isoniazid would therefore be unsuitable unless some means of preventing toxicity could be found.

Various substances have been tried in the prophylaxis of isoniazid neuropathy. Pyridoxine has been used successfully by Biehl & Vilter (1954) and Tchertkoff et al. (1956), but it has been suggested that in high dosage it might interfere with the antituberculous properties of the isoniazid (East African/British Medical Research Council Isoniazid Investigation, 1960). It was for this reason, and also because the prophylactic use of pyridoxine, in the usual dosage of 100 mg daily or more, greatly increases the cost of treatment with isoniazid, that other possible prophylactics have been investigated.

It has been reported that glutamic acid prevents the development of neuropathy (Schettino, 1953; Almeida et al., 1960). Turner (1961) [1] found that a vitamin-B-complex preparation not containing pyridoxine was successful in the *treatment* of peripheral neuropathy due to a high dosage of isoniazid even when the latter was continued.

In this study glutamic acid and a vitamin-B-complex preparation not containing pyridoxine (Tab. Aneurin. Co.), similar to that found to be effective therapeutically by Turner, have been tested for their prophylactic efficacy. In addition, the therapeutic effect, once isoniazid neuropathy has developed, of Tab. Aneurin. Co. and of a vitamin-B-complex preparation containing pyridoxine, shown earlier at the Centre to have a beneficial effect on peripheral neuropathy (Devadatta et al., 1960), has been tested.

OBJECTS OF THE STUDY

1. (*a*) To assess the efficacy of two preparations —namely, glutamic acid and Tab. Aneurin. Co. —in the *prevention* of toxicity due to high-dosage isoniazid therapy.

   (*b*) to investigate in patients with peripheral neuropathy the *therapeutic* effectiveness of two supplements—namely, an increased dosage of Tab. Aneurin. Co. and a vitamin-B-complex preparation containing a small amount of pyridoxine.

2. To assess the frequency of isoniazid peripheral neuropathy in slow and rapid inactivators of isoniazid.

3. To obtain preliminary information on the therapeutic effectiveness of high-dosage isoniazid in patients with pulmonary tuberculosis.

II. PLAN AND CONDUCT OF THE STUDY

The study was designed to compare the frequency of isoniazid neuropathy among patients receiving Tab. Aneurin. Co. or glutamic acid with that among patients receiving a placebo (calcium gluconate) and to test the therapeutic effect on the neuropathy of Tab. Aneurin. Co. as well as a more comprehensive B-complex preparation. In order to eliminate the possibility of bias in the diagnosis of peripheral neuropathy and the assessment of its progress, the investigation was conducted by the " double-blind " method. In this way it was ensured that although the clinicians knew that isoniazid was being given they did not know the dosage or rhythm in which it was being administered, and neither they nor the health visitors knew the number of the supplements or their nature or were aware of any subsequent change in them.

PATIENTS

Patients were drawn from the same defined area in Madras City as in a previous investigation (Tuberculosis Chemotherapy Centre, 1960). As before,

[1] Information originally reported by Turner in 1958 in a personal communication to the Centre.

nearly all came from the poorest sections of the population, and were referred to the Centre from local tuberculosis clinics where they had attended with symptoms. In a few instances they were contacts of patients already under treatment at the Centre.

All patients had bacteriologically confirmed pulmonary tuberculosis. They were admitted to the study on the same criteria as those which applied in previous studies undertaken at the Centre (Tuberculosis Chemotherapy Centre, 1959, 1960); in particular, the patients were aged 12 years or more, had no clinical evidence of leprosy or diabetes, and had either received no previous antituberculosis chemotherapy or had had it for a maximum of two weeks. In addition, no patient with any evidence of peripheral neuropathy was admitted to treatment.

The patients were examined clinically with special attention to the nervous system. Among other pretreatment investigations were:

1. A full-plate postero-anterior chest radiograph.

2. The examination by direct smear and culture of a minimum of four sputum specimens; three were collected overnight in the home (collection specimens) and one was expectorated on demand at the Centre (spot specimen).

3. Tests of sensitivity to isoniazid and streptomycin on two cultures.

4. The determination of the rate of inactivation of isoniazid.

REGIMENS

Chemotherapy

All the patients were prescribed high-dosage isoniazid (12.5-15.2 mg/kg body-weight—see Table 1) to be taken once daily. The mean daily dosage of isoniazid at the start of chemotherapy was 13.8 mg/kg. If the patient gained weight at a monthly examination and moved into a higher weight category, the dosage was increased; if, however, he lost weight the dosage was not reduced.

Allocation of prophylactic supplements

Each patient was allocated at random to one of three supplementary regimens, two being tested for their prophylactic effect and one being a placebo. The allocation was made by the statisticians from a list which was based on random sampling numbers and which had been incorporated in a series of numbered sealed envelopes before the start of the study. The first allocation was made on 26 December 1959 and the last on 9 June 1960. During this period 56 patients were admitted to the study.

Supplements

The three supplement series were:

(*a*) Tab. Aneurin. Co. (*British National Formulary*), prescribed as three tablets of 0.2 g twice daily. Each tablet contained 1 mg of aneurine hydrochloride, 1 mg of riboflavine and 15 mg of nicotinamide (Aneurin. Co. series).

TABLE 1
DAILY DOSAGE OF ISONIAZID IN RELATION TO BODY-WEIGHT

Body-weight [a]		Amount of isoniazid given daily (mg)	Daily dosage (mg/kg body-weight)	Number of patients (on admission to treatment)
lb.	kg			
40-49	18.0-22.4	300	16.7-13.4	1
50-59	22.5-26.9	350	15.6-13.0	2
60-69	27.0-31.5	400	14.8-12.7	7
70-79	31.6-36.0	450	14.2-12.5	17
80-89	36.1-40.6	550	15.2-13.5	13
90-99	40.7-45.1	600	14.7-13.3	11
100-109	45.2-49.6	650	14.4-13.1	1
110-119	49.7-54.2	700	14.1-12.9	2

[a] The weight was recorded to the nearest lb.

(*b*) *l*-glutamic acid in a dosage of 5 g, prescribed as five tablets of 0.5 g twice daily (glutamic series).

(*c*) Calcium gluconate (the placebo), prescribed as five tablets of 0.5 g twice daily (calcium series).

Method of dispensing the isoniazid and supplements

The morning dose, consisting of isoniazid and supplement, was dispensed in a sealed pink packet and the evening dose, consisting of supplement only, in a sealed white packet. The patients received a week's supply of packets at each weekly visit to the Centre.

Prescribed duration of treatment

Both the isoniazid and the supplements were provisionally prescribed for a period of 12 months.

General management

The patients were treated at home and attended the Centre each week for supplies of medicine. A surprise visit was paid to the home twice weekly by a health visitor to check the patient's stock of drugs and to collect a specimen of urine. A few patients who were very ill had their medicine delivered to the home in the early weeks. All patients were advised to stop work initially and the majority did so; only patients feeling really ill took the advice to rest and most patients were ambulant for much of the time and were frequently not at home when surprise visits were paid. Patients were encouraged to return to work when they were medically fit, but a number returned to work even before being recommended to do so.

Regularity of drug taking

Regularity of drug taking was supervised in two ways. The stock of sealed packets remaining in the patient's possession was counted at the surprise visits paid to the home by the health visitors and specimens of urine collected at home and at each clinic attendance were tested for isoniazid by the combined naphthoquinone-mercuric chloride (N-M) test (Gangadharam et al., 1958).

ASSESSMENT AND MANAGEMENT OF PERIPHERAL NEUROPATHY

Assessment

Any *spontaneous* complaint suggestive of peripheral neuropathy was recorded, but patients were not questioned to elicit symptoms. If symptoms were reported on more than one occasion a full neurological examination was carried out and this was repeated at intervals depending on the severity of the symptoms. When two of the Centre's doctors agreed that one or more physical signs of peripheral neuropathy were present, the patient was examined by an independent assessor (Dr J. Chandy, Dr S. Janaki, Dr C. E. Klontz or Dr K. V. Mathai of the Christian Medical College, Vellore). When the assessor confirmed the diagnosis of peripheral neuropathy a change of supplement was made, but the dosage of isoniazid remained the same and the patient was re-examined neurologically at the Centre at intervals of two weeks. If there was an increase in the severity of symptoms and the development of fresh physical signs, confirmed by at least two of the Centre's physicians, the peripheral neuropathy was deemed to have progressed and the supplement was changed again without recourse to an outside assessor. The same dosage of isoniazid was, however, continued.

Therapeutic supplements for isoniazid neuropathy

Supplements were changed for patients who developed peripheral neuropathy as shown in Fig. 1.

(*a*) Patients receiving Tab. Aneurin. Co. (Aneurin. Co. series) were given a vitamin-B-complex supplement that had previously been found, by Devadatta et al. (1960), to be effective, prescribed as three tablets of 0.3 g twice daily; each tablet contained 10 mg of aneurine hydrochloride, 5 mg of riboflavine, 50 mg of nicotinamide, 1 mg of pyridoxine, 3 mg of panthenol and 1 μg of cyanocobalamin (an average of 10% of riboflavine, pyridoxine and panthenol, 33% of aneurine hydrochloride and 50% of cyanocobalamin had been added by the manufacturers).

(*b*) Patients receiving glutamic acid (glutamic series) or calcium gluconate (calcium series) had their supplements changed to Tab. Aneurin. Co., four tablets three times daily, that is, twice the prophylactic dosage. The extra dose was dispensed in green packets to be taken at mid-day. If, in spite of this change of supplement, the neuropathy advanced, a further change was made and three tablets twice daily of the vitamin B complex containing pyridoxine referred to above were given.

(*c*) If the neuropathy progressed on the vitamin-B-complex supplement, the patients in all three series were eligible for 300 mg of pyridoxine daily, and 1 g of streptomycin sulfate daily plus 5 g of PAS sodium twice daily instead of the isoniazid.

MANAGEMENT OF PULMONARY TUBERCULOSIS

Routine assessments during treatment

Assessments made at monthly intervals after the start of chemotherapy included (*a*) measurement of the weight, (*b*) a postero-anterior chest radiograph, (*c*) the examination of two overnight collection specimens of sputum by smear and culture (in addition, from three months onwards, a pair of laryngeal swabs by culture), and (*d*) tests of sensitivity to isoniazid on one positive culture.

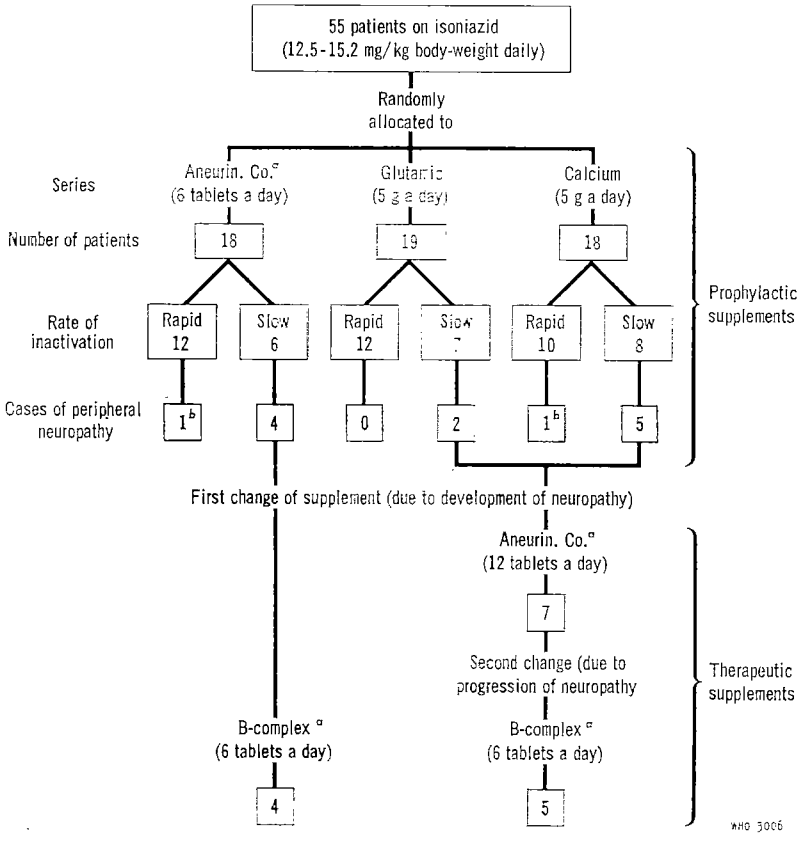
Tomograms were taken at the end of one year and the rate of inactivation of isoniazid was determined again.

Radiographic or clinical deterioration warranting a change of chemotherapy

Radiographic deterioration was assessed as described previously (Tuberculosis Chemotherapy Centre, 1960). In brief, the full radiographic series of any sputum-positive patient who was considered by the Centre's medical staff to have a definite radiographic extension of the tuberculous lesion at any examination subsequent to the first monthly examination was shown to an independent assessor, Dr K. S. Sanjivi, who was unaware of the treatment the patient was receiving. He decided whether or not the new lesion warranted a change of chemotherapy.

FIG. 1

DIAGRAMMATIC REPRESENTATION OF THE FREQUENCY OF PERIPHERAL NEUROPATHY AND THE SEQUENCE OF CHANGE OF PROPHYLACTIC AND THERAPEUTIC SUPPLEMENTS



[a] For the full constituents of Aneurin. Co. and B-complex, see pages 457 and 458.

[b] The two cases of peripheral neuropathy among the rapid inactivators (Aneurin. Co. and calcium series) were not confirmed by the assessor until the 12th month and so the supplement was not changed.

Serious clinical deterioration was regarded as a ground for changing the chemotherapy without recourse to the independent assessor.

Change of chemotherapy

If the pulmonary tuberculosis progressed to an extent which warranted a change of chemotherapy, the isoniazid and supplements were continued unchanged, and in addition 1 g of streptomycin daily, intramuscularly, for six days a week and 1-1.5 g of pyrazinamide daily by mouth (approximately 30 mg/kg body-weight) were given.

III. BACTERIOLOGICAL AND ASSAY PROCEDURES

EXAMINATION OF SPUTUM SPECIMENS AND LARYNGEAL SWABS; SENSITIVITY TESTS

The methods used to examine sputum specimens and laryngeal swabs and to determine the sensitivity of cultures to isoniazid and streptomycin have been described in detail elsewhere (Tuberculosis Chemotherapy Centre, 1959). In brief, the smears were examined by fluorescence microscopy and were graded as 3-plus, 2-plus, 1-plus and negative. Sputum specimens were cultured, after treatment with 4% NaOH, on Löwenstein-Jensen medium which did not contain potato starch (Jensen, 1955). Tests of sensitivity to isoniazid were performed by inoculating a suspension of growth on to slopes of Löwenstein-Jensen medium containing 0.2, 1, 5, and 50 μg/ml of isoniazid and on to a control slope containing no isoniazid. The standard sensitive strain H37Rv was also set up with each batch of tests as a control.

DEFINITIONS OF BACTERIAL RESISTANCE TO ISONIAZID

In the following definitions of isoniazid resistance growth has been defined as 20 or more colonies.

Pretreatment tests

Resistance was defined as:

(*a*) growth on 1 μg/ml or a higher concentration even if the result of a test on a second culture was sensitive; or

(*b*) growth on 0.2 μg/ml, followed by growth on the same or a higher concentration at a repeat test on the same culture, even if the result of a test on a second culture was sensitive; or

(*c*) growth on 0.2 μg/ml for two separate cultures, irrespective of the results of any repeat test.

Tests during treatment

Cultures isolated during treatment were regarded as resistant if growth occurred on 0.2 μg/ml or a higher concentration of isoniazid, irrespective of the results of repeat tests.

SERUM ISONIAZID ASSAY

The rate of inactivation of isoniazid was determined for each patient before treatment, and again in the last month of treatment, after withdrawal of all drugs for two days prior to the test. A test dose of isoniazid (nominally 3 mg/kg body-weight) [1] was given intramuscularly, and four-and-a-half hours later a sample of blood was taken and the concentration of isoniazid in the serum was measured by microbiological assay (Gangadharam et al., 1961).

If the mean serum concentration of the two tests (or, in five patients, the result of the only test performed) was 0.69 μg/ml or greater the patient was classified as a slow inactivator; if it was less than 0.49 μg/ml the patient was classified as a rapid inactivator. No patient had a mean serum concentration between these levels.

IV. PATIENTS ADMITTED TO THE STUDY

Fifty-six patients were admitted to the study; 50 were allocated at random to one of the three supplements (Tab. Aneurin. Co., glutamic acid, and calcium gluconate). The remaining six were contacts of six of these patients and were prescribed the same high dosage of isoniazid and the same supplements as their index cases. There were 21 (38%) slow and 35 (62%) rapid inactivators of isoniazid.

[1] An assay of the isoniazid content of the solution contained in a sample of ampoules taken from the batch in use showed this to be about 15% less than that stated on the labels. Making allowance for this reduction in dosage did not affect the classification of any patient.

V. ISONIAZID TOXICITY

This section describes the toxic effects of high-dosage isoniazid. One patient (rapid inactivator) has been excluded because he had previously received isoniazid plus PAS for eight months; his progress is described on page 462. Of the remaining 55 patients 13 developed peripheral neuropathy during the year; three of these also had cerebral symptoms—convulsions in two and a toxic psychosis in the third. Another patient had convulsions without evidence of peripheral neuropathy.

There was no history of exposure to neurotoxic substances other than isoniazid in any of these patients except one, who developed peripheral neuropathy and a toxic psychosis and who was known to have a supply of methyl alcohol (see below). There was no evidence of consumption of alcohol (prohibited by law in Madras State since 1948) by any other patient in this series.

PERIPHERAL NEUROPATHY

Age and sex

Of the 15 patients aged 35 or more, five (33%) developed peripheral neuropathy, as compared with eight (20%) of the 40 patients under 35 years of age. Peripheral neuropathy occurred in 24% of 29 males and 23% of 26 females.

Rate of inactivation of isoniazid

Eleven (52%) of the 21 slow inactivators of isoniazid, as compared with only two (6%) of the 34 rapid inactivators, developed peripheral neuropathy—a highly significant difference ($P < 0.001$). This difference was present in each of the three series (see Fig. 1).

Time of onset

Of the 13 patients six first complained of symptoms suggestive of neuropathy in the second month, two in the third, four in the fourth and one in the fifth. (The two rapid inactivators first developed their symptoms in the fourth and fifth months, respectively.)

Clinical features

The clinical features were similar in the three series and closely resembled those observed previously at the Centre and described by Devadatta et al. (1960). The earliest symptoms were variously described as burning, pricking pain, numbness or tingling of the feet; in a few patients the hands were also affected. The earliest signs elicited were usually loss of vibration sense in the toes and loss of ankle jerks. Both these signs were present in 11 of the 13 patients at the time of diagnosis.

OTHER TOXIC EFFECTS

Psychosis

One patient (calcium, slow inactivator) developed peripheral neuropathy in the second month and his supplement was therefore changed to Tab. Aneurin. Co. Despite this he deteriorated mentally in the third month and became listless and withdrawn. His supplement was changed again, from Tab. Aneurin. Co. to vitamin B complex, and the isoniazid was continued; he became mentally normal in about two months. This patient was found on several occasions by the health visitor to have methyl alcohol in his home; however, isoniazid was probably the exciting cause of the neurotoxic changes since the onset of the symptoms occurred soon after the start of treatment with isoniazid.

Convulsions

Three patients, none of whom gave a history of previous epilepsy, had epileptiform seizures probably attributable to isoniazid toxicity. They complained of a feeling of giddiness for a period of about one hour before the seizures, which occurred between five and 12 hours after taking a dose of isoniazid. One patient (Aneurin. Co., slow inactivator) had a number of attacks in the first three months of treatment. Another patient (Aneurin. Co., rapid inactivator) had one attack two days after the start of chemotherapy and another in the eleventh month. The third patient (calcium, rapid inactivator) had a single seizure in the sixth month of treatment. The first two patients also developed peripheral neuropathy, the symptoms first occurring in the second and fourth months, respectively.

The first patient had no more seizures when his supplement was changed from Tab. Aneurin. Co. to vitamin B complex even though the isoniazid was continued. The supplements were not changed in the other two patients as they had only isolated attacks.

VI. PREVENTION AND TREATMENT OF PERIPHERAL NEUROPATHY

Of the 56 patients 18 were given Tab. Aneurin. Co. (Aneurin Co. series), 19 glutamic acid (glutamic series), and 19 calcium gluconate (calcium series). One patient (calcium) was excluded from the analysis below because he had previously been treated with isoniazid.

PRETREATMENT COMPARISON OF THE THREE SUPPLEMENT SERIES

In order to assess the effectiveness of the supplements in preventing isoniazid toxicity, it is necessary to verify that the three series were similar at the start of treatment. The distributions of estimated age were closely similar, the proportion of patients over 35 years of age being 28% in the Aneurin. Co. series, 27% in the glutamic series and 28% in the calcium series. The distributions of sex, general condition and weight were also similar. Further, the proportions of slow and rapid inactivators of isoniazid were similar: six (33%) of the Aneurin. Co. series, seven (37%) of the glutamic series and eight (44%) of the calcium series were slow inactivators.

EFFECT OF THE SUPPLEMENTS

Prophylactic effect

Peripheral neuropathy occurred in five (28%) of the 18 patients in the Aneurin. Co. series, two (11%) of the 19 patients in the glutamic series and six (33%) of the 18 patients in the calcium series who were included in the analysis (Fig. 1). Although these differences are not statistically significant, there is some evidence that glutamic acid may have reduced the frequency of peripheral neuropathy but there is no evidence that Tab. Aneurin. Co. did so.

Therapeutic effect

According to the plan of the study the 13 patients who developed peripheral neuropathy were all eligible for a change of supplement, but in two the diagnosis was confirmed by the assessor so late in the year that the supplement was changed in only 11. Seven patients (two glutamic, five calcium) had their original supplement changed to Tab. Aneurin. Co., in twice the prophylactic dosage; four patients (Aneurin. Co.) had their original supplement changed to vitamin B complex.

Tab. Aneurin. Co. Seven of the patients with peripheral neuropathy were given Tab. Aneurin. Co. therapeutically as the *first* change; five of these showed progression of the symptoms and signs of the neuropathy and their supplement was therefore changed again to vitamin B complex after intervals of 10, 19, 36, 37 and 66 days, respectively. The neuropathy did not progress in the remaining two patients, but in one of them the supplement was changed to vitamin B complex at 29 days because he developed a psychosis believed to have been due to isoniazid. The other patient improved symptomatically, but there was no change in the physical signs.

Tab. Aneurin. Co. was thus of little effect in preventing the progression of the peripheral neuropathy when given in twice the dosage used for prophylaxis.

Vitamin B complex. In all, nine patients were given vitamin B complex therapeutically, four as the *first* change of supplement when they had developed peripheral neuropathy while on Tab. Aneurin. Co. prophylactically and five (two glutamic, three calcium) as the *second* change of supplement because their neuropathy was progressing after the first change, which had been to Tab. Aneurin. Co. therapeutically (Fig. 1). In eight of the nine patients the symptoms improved, four showing regression of physical signs by the end of the year. The remaining patient, after three weeks on vitamin B complex, showed progression of the symptoms and signs; the isoniazid was therefore stopped and the patient received streptomycin and PAS, together with 300 mg of pyridoxine daily in addition to the vitamin-B-complex preparation.

It may be concluded that the vitamin-B-complex preparation was effective in the treatment of isoniazid neuropathy, even when the isoniazid was continued in high dosage.

The patient not included in the analysis of the effect of supplements

As mentioned earlier, one patient (calcium) was excluded from the analysis of the effect of supplements because it was found that he had had isoniazid plus PAS for eight months three years previously. There was therefore a remote possibility that this might have predisposed him to develop peripheral

neuropathy under further isoniazid treatment. This patient received isoniazid (alone, as prescribed) in the present study throughout the year. He developed peripheral neuropathy in the fifth month of treatment and was thereafter given Tab. Aneurin. Co. in the therapeutic dosage for the rest of the year; his symptoms improved, although his ankle jerks were subsequently lost.

In summary, there was no evidence that Tab. Aneurin. Co. had an effect either in preventing the development of peripheral neuropathy or in treating the condition once it had occurred. Glutamic acid may have had some effect in preventing peripheral neuropathy, but it was not marked. Vitamin B complex, on the other hand, was found to be effective therapeutically.

VII. PROGRESS OF PULMONARY TUBERCULOSIS TREATED WITH HIGH-DOSAGE ISONIAZID

Of the 56 patients admitted to the study two (both rapid inactivators) have been excluded from the analysis of the response of pulmonary tuberculosis to treatment with isoniazid; one patient, with an isoniazid-sensitive strain, was excluded because he had previously received isoniazid and PAS for eight months and the other because the infecting strain of *Mycobacterium tuberculosis* was found to be resistant to isoniazid. There are thus 54 patients with tubercle bacilli sensitive to isoniazid prior to admission to the study who were available for analysis.

The assessments of the radiographic and bacteriological condition of the patients on admission to treatment are given in Table 2. There were seven (13%) patients with extensive cavitation, 13 (24%) with gross or extensive disease, and 34 (63%) with more than three lung zones involved. The first or only collection specimen of sputum was positive on smear examination in 45 (83%) of the patients.

DEATHS

Three of the 54 patients died during the year. Death was due to pulmonary tuberculosis in one patient (glutamic), a female aged 27 years, who deteriorated clinically and radiographically in the second month. Her chemotherapy was changed but she died in the fourth month, two days after a spontaneous pneumothorax.

The other two patients died from non-tuberculous causes. The first (calcium), a male aged 25 years, died of intracranial bleeding following a mastoidectomy for a non-tuberculous infection; he had just completed two months' treatment and had shown favourable radiographic and bacteriological response. The second (Aneurin. Co.), a female aged 45 years, died in the eleventh month. The last radiograph showed considerable improvement of her initial small right apical lesion and all the cultures were negative from the first month. However, she became progressively weaker from the ninth month, but would not agree to enter hospital for further investigations. Her death was attributed to a non-

TABLE 2

RADIOGRAPHIC AND BACTERIOLOGICAL CONDITION ON ADMISSION

Assessment on admission to treatment	All patients	
	No.	%
Extent of cavitation:		
Nil	6	*11*
Slight	12	*22*
Moderate	29	*54*
Extensive	7	*13*
Total extent of disease:		
Trivial or slight	3	*6*
Limited or moderate	38	*70*
Extensive or gross	13	*24*
Number of lung zones involved in disease:		
1, 2 or 3	20	*37*
4, 5 or 6	34	*63*
Bacterial content of sputum: [a]		
Direct smear negative	9	*17*
Direct smear positive:		
1-plus (scanty)	9	*17*
2-plus (moderate)	28	*52*
3-plus (heavy)	8	*15*
Total patients	54	*100*

[a] First or only collection specimen.

tuberculous cause but its exact nature was not established. Permission for an autopsy was refused.

CHANGE OF CHEMOTHERAPY DUE TO RADIOGRAPHIC DETERIORATION

Three patients had a change of chemotherapy, in the eighth, ninth and tenth months, respectively, because of radiographic deterioration confirmed by an independent assessor. No patient had a change of chemotherapy on grounds of clinical deterioration alone.

CHANGE OF CHEMOTHERAPY DUE TO TOXICITY

One patient (Aneurin. Co. series), a slow inactivator, developed severe and rapidly progressive peripheral neuropathy in the third month (see page 462); the isoniazid was replaced by streptomycin and PAS.

PRESENTATION OF THE RESULTS FOR THE PATIENTS WHOSE CHEMOTHERAPY WAS CHANGED OR WHO DIED

As in a previous report (Tuberculosis Chemotherapy Centre, 1960) patients whose chemotherapy was changed on account of deterioration of their disease or who died of tuberculosis remain in the analyses for the rest of the year, whereas patients whose chemotherapy was changed on account of toxicity or who died from a non-tuberculous cause have been excluded from the tables thereafter.

RADIOGRAPHIC CHANGES

As in an earlier study (Tuberculosis Chemotherapy Centre, 1960), the radiographic changes were evaluated by an independent assessor, Dr Raj Narain, who was unaware of the treatment which any patient had received. In brief, the changes were assessed for the first six months and for the year, and four grades were used to classify improvement—namely, exceptional, considerable, moderate or slight. The findings are set out in Table 3. During the first six months of chemotherapy 33 (63%) of 52 patients showed moderate or greater improvement. Over the full 12 months 37 (73%) of 51 patients showed moderate or greater improvement, while two (4%) showed radiographic deterioration and four (8%) either had their treatment changed because of radiographic deterioration or died of tuberculosis.

The changes in cavitation for the 12-month period were also assessed by Dr Raj Narain; cavitation disappeared in 30 (67%) and was less in six (13%) of 45 patients with initial cavitation.

SMEAR AND CULTURE RESULTS

The smear and culture results of the first or only collection specimen of sputum at 3-monthly intervals are given in Table 4. There was a sharp decline in the proportion of patients with positive cultures during the early months of treatment; at three months 69% of 49 patients and at six months 75% of 51 patients had a negative culture. There was little

TABLE 3

CHANGES IN RADIOGRAPHIC APPEARANCES IN THE 12-MONTH PERIOD [a]

Period	Total patients [b]		Improvement								No change		Deterioration		Change of chemotherapy due to deterioration, or tuberculous death	
			Exceptional		Considerable		Moderate		Slight							
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
0-6 months	52	101	2	4	12	23	19	37	13	25	3	6	2	4	1	2
0-12 months	51 [c]	100	4	8	18	35	15	29	8	16	0	0	2	4	4	8

[a] Two separate assessments on standard radiographs.

[b] Excluding one patient who died in the third month of a non-tuberculous condition and one patient who had his chemotherapy changed in the third month on account of toxicity.

[c] Excluding one patient who died in the eleventh month of a non-tuberculous condition.

TABLE 4

PRESENCE OF TUBERCLE BACILLI IN SINGLE COLLECTION SPECIMENS OF SPUTUM TAKEN FROM PATIENTS AT 3-MONTHLY INTERVALS

Months after start of chemo-therapy	Total patients with culture results [a]	Tuberculous death	Change of chemo-therapy due to deterioration	Culture positive		Culture negative [b]	
				Smear positive	Smear negative	No.	%
0	54	—	—	45	5	4	7
3	49	0	0	10	5	34	69
6	51	1	0	8	4	38	75
9	51	1	2	7	4	37	73
12	50	1	3	6	3	37	74

[a] Patients who died of non-tuberculous conditions are excluded after their death and the patient who had his chemotherapy changed on account of toxicity is excluded after the change. Patients who died of tuberculosis or who had their chemotherapy changed owing to deterioration remain in the totals throughout.

[b] Even if the smear was positive.

change during the rest of the year and at 12 months the proportion of patients with a negative culture was 74%.

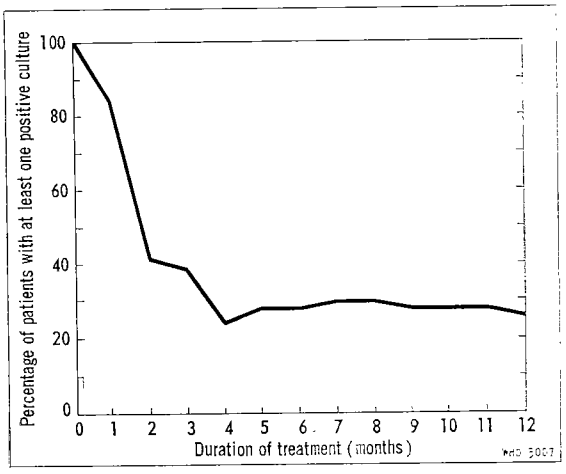
The average number of specimens examined for each patient monthly ranged from 2.6 to 2.9. The percentage of patients with at least one positive culture result at each month is shown in Fig. 2.

ISONIAZID SENSITIVITY

Tests of sensitivity to isoniazid were carried out each month on one positive culture from each patient. At one month four of 37 patients for whom sensitivity test results were available had a resistant culture; at three, six, nine and 12 months 16 of 19, all of 11, 10 of 11, and six of seven, respectively, had a resistant culture. The only patient with an isoniazid-sensitive culture at 12 months had had a bacteriological relapse with sensitive organisms at nine months. He had been exceedingly irregular in drug taking after the third month, 47 out of a total of 55 urine tests being negative for isoniazid.

FIG. 2

PERCENTAGE OF PATIENTS EACH MONTH WITH AT LEAST ONE POSITIVE CULTURE RESULT FROM MULTIPLE BACTERIOLOGICAL SPECIMENS



RESPONSE TO TREATMENT DURING THE 12 MONTHS

Table 5 presents a classification of all the patients at 12 months, based primarily on the bacteriological response to treatment. In all, 37 (73%) of 51 patients had bacteriologically quiescent disease; this includes two patients who had disease of bacteriologically doubtful status which previous studies have shown can be regarded as quiescent disease (Velu et al., 1960, 1961). Of the 35 patients with quiescent disease, 32 remained persistently culture-negative from the fourth month.

PATIENTS NOT INCLUDED IN THE ANALYSIS OF THE RESPONSE TO TREATMENT

As mentioned earlier, two patients were excluded from the analysis of the response to treatment. One had a primarily isoniazid-resistant infection of high degree (minimal inhibitory concentration greater than 50 μg/ml) and the other had received chemotherapy for more than two weeks before admission. Both patients had quiescent disease at one year.

VIII. RESPONSE TO TREATMENT RELATED TO VARIOUS FACTORS ON ADMISSION TO TREATMENT

With regard to the relation between pretreatment condition and response to treatment, four (57%) of seven patients with extensive cavitation showed an unfavourable response to treatment (bacteriologically relapsed or active disease, change of chemotherapy owing to deterioration, or death from tuberculosis), as compared with seven (25%) of 28 with moderate, one of 10 with slight and two of six with no cavitation. Five (42%) of 12 patients with disease graded as extensive or gross showed an unfavourable response, as compared with nine (23%) of 39 with less extensive disease. In respect of the number of lung zones involved in disease, 11 (34%) of 32 patients with four or more zones involved showed an unfavourable response, as compared with three (16%) of 19 with fewer zones involved. In respect of the bacterial content of the first or only collection specimen of sputum, 11 (31%) of 35 patients with 2-plus or 3-plus smears showed an unfavourable response, as compared with three (19%) of 16 with 1-plus or negative smears. It may be concluded that patients with more serious disease as measured by the radiographic extent of the lesion, cavitation, and the bacterial content of sputum more frequently showed an unfavourable response to treatment than patients with less serious disease.

Of the 51 patients, 20 (39%) were slow inactivators of isoniazid and 31 (61%) were rapid inactivators of isoniazid. There were no important differences between the slow and rapid inactivators in respect of the radiographic condition of their disease or the degree of sputum positivity on admission to treatment. An unfavourable response at 12 months occurred in four (20%) of the 20 slow inactivators and in 10 (32%) of the 31 rapid inactivators. This difference does not, however, attain statistical significance.

The response of the patients who developed peripheral neuropathy was similar to that of the patients who did not. Of the 13 patients who developed peripheral neuropathy, one was taken off isoniazid in the third month on account of severe toxicity (see page 462) and the response to isoniazid treatment of his pulmonary tuberculosis cannot be assessed. Of the remaining 12 patients, three (25%) had an unfavourable response to treatment, as compared with 11 (28%) of the 39 patients who did not develop peripheral neuropathy.

IX. COMPARISON OF RESPONSE WITH HIGH AND MODERATE DOSAGE OF ISONIAZID

The response to treatment of the 54 patients in the present study who received the high dosage of 12.5-15.2 mg/kg body-weight of isoniazid (650 mg for a 100-lb. patient) once daily may be compared with the results in 70 patients in a previous investigation (Tuberculosis Chemotherapy Centre, 1960), who received the moderate dosage of 7.8-9.6 mg/kg body-weight (400 mg for a 100-lb. patient) once daily (HI-1 series). Although the two series of patients were not treated concurrently, they were drawn from the same poor urban community and the same criteria of eligibility for admission to the studies were adopted. Moreover, all the radiographic assessments were made by the same independent assessor, and the same bacteriological procedures were followed. However, in order to see whether the comparison is valid it is essential to determine whether the condition of the patients before treatment in the two series was similar. Most of the patients were between 15 and 44 years of age (87% in the present series and 93% in the HI-1 series). An analysis of general condition and weight (not presented here) showed that there were no important differences between the two series. Table 6 shows a comparison of the pretreatment radiographic and bacteriological condition in the two series. Cavitation was graded as extensive in 13% of the 54 patients in the present series and in 10% of the 70 in the HI-1 series; however, 11% and 1%, respectively, had no cavitation. The distributions of the extent of radiographic disease and of the number of lung zones involved in disease were the same. The first or only collection specimen of sputum was negative on smear in 17% and 9%, respectively; 3-plus positive smears were obtained in 15% and 40%, respectively. In the present series 39% were slow inactivators, as compared with 53% of the HI-1 series.

In summary, the present series was at an advantage in respect of the extent of cavitation and the bacterial content of the sputum, but at a possible disadvantage in having fewer slow inactivators of isoniazid (Selkon et al., 1961).

TABLE 5

CLASSIFICATION OF ALL THE PATIENTS AT THE END OF 12 MONTHS ACCORDING TO THEIR RESPONSE TO TREATMENT

Classification at the end of 12 months		All patients	
		No.	%
Patients with bacteriologically quiescent disease:	First month of persisting culture negativity		
that is, patients whose cultures were all negative for at least the last three monthly examinations—i.e., at 10, 11 and 12 months	1	7	
	2	16	
	3	4	
	4	5	
	5	0	
	6	0	
	7	0	
	8	1	
	9	1	
	10	1	
Total patients with bacteriologically quiescent disease		35	*69*
Patients with disease of bacteriologically doubtful status:			
that is, 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		2	*4*
Patients with bacteriologically relapsed disease:			
that is, patients whose cultures were all negative at three or more consecutive monthly examinations, but who produced two or more positive cultures in the last three monthly examinations—i.e., at 10, 11 and 12 months		1	*2*
Patients with bacteriologically active disease:			
that is, (*a*) patients whose cultures were never all negative at three consecutive monthly examinations		9	*18*
or (*b*) patients who deteriorated and had their chemotherapy changed		3	*6*
Tuberculous death		1	*2*
Total patients with unfavourable response		14	*27*
Total		51	*100*
Patients who had their chemotherapy changed on account of toxicity		1	—
Non-tuberculous deaths		2	—
All patients		54	—

TABLE 6

RADIOGRAPHIC AND BACTERIOLOGICAL CONDITION ON ADMISSION TO TREATMENT OF PATIENTS IN THE PRESENT SERIES (12.5-15.2 mg/kg) AND IN THE HI-1 SERIES [a] (7.8-9.6 mg/kg)

Assessment on admission to treatment	Present series		HI-1 series	
	No.	%	No.	%
Extent of cavitation:				
Nil	6	*11*	1	*1*
Slight	12	*22*	26	*37*
Moderate	29	*54*	36	*51*
Extensive	7	*13*	7	*10*
Total extent of disease:				
Trivial or slight	3	*6*	4	*6*
Limited or moderate	38	*70*	49	*70*
Extensive or gross	13	*24*	17	*24*
Number of lung zones involved in disease:				
1, 2 or 3	20	*37*	26	*37*
4, 5 or 6	34	*63*	44	*63*
Bacterial content of sputum: [b]				
Direct smear negative	9	*17*	6	*9*
Direct smear positive:				
1-plus (scanty)	9	*17*	19	*27*
2-plus (moderate)	28	*52*	17	*24*
3-plus (heavy)	8	*15*	28	*40*
Total patients	54	*100*	70	*100*

[a] Tuberculosis Chemotherapy Centre (1960).
[b] First or only collection specimen.

RESULTS AT 12 MONTHS

Results at 12 months are available for 51 of the 54 patients in the present series (two non-tuberculous deaths and one change of chemotherapy on account of toxicity being excluded) and for 64 of the 70 patients in the HI-1 series (one non-tuberculous death and five changes of chemotherapy on account of toxicity being excluded).

Radiographic changes

Considering the radiographic changes during the 12 months (Table 7), 88% of the present series showed radiographic improvement, as compared with 86% of the HI-1 series.

TABLE 7

RADIOGRAPHIC AND BACTERIOLOGICAL RESPONSES IN THE PRESENT (12.5-15.2 mg/kg) AND IN THE HI-1 SERIES [a] (7.8-9.6 mg/kg)

Treatment series	Total patients	Radiographic response at 12 months								Bacteriological status at 12 months					
		Improvement		No change		Deterioration		Change of chemotherapy due to deterioration, or tuberculous death		Quiescent [b]		Relapsed or active		Change of chemotherapy due to deterioration, or tuberculous death	
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Present	51 [c]	45	88	0	0	2	4	4	8	37	73	10	20	4	8
HI-1	64 [d]	55	86	4	6	0	0	5	8	47	73	12	19	5	8

[a] Tuberculosis Chemotherapy Centre (1960).

[b] Including disease of bacteriologically doubtful status.

[c] Excluding two patients who died of non-tuberculous conditions and one patient who had his chemotherapy changed on account of toxicity.

[d] Excluding one patient who died of a non-tuberculous condition and five patients who had their chemotherapy changed on account of toxicity.

Cavitation changes

Cavitation disappeared in 30 (67%) of 45 patients in the present series and in 39 (62%) of 63 in the HI-1 series.

Bacteriologically quiescent disease

Table 7 shows that the proportions with bacteriologically quiescent disease at 12 months were the same—73% in each series. When statistical standardization for the pretreatment differences in the rate of inactivation of isoniazid, the extent of cavitation, and the bacterial content of sputum was undertaken, the standardized proportions of patients with quiescent disease were 73% for the present series and 72% for the HI-1 series.

In summary, there was little difference in the response to treatment with isoniazid in high and in moderate dosage.

X. SELF-ADMINISTRATION OF ISONIAZID AND THE SUPPLEMENTS

The importance of taking the tablets regularly was impressed on the patients both before and throughout the period of treatment. Two methods were used to assess the regularity with which they did so.

1. Specimens of urine were obtained from patients during their regular visits to the Centre and at surprise visits made to their homes. They were tested for isoniazid by the combined N-M test (Gangadharam et al., 1958).

2. The packets containing the tablets were counted at surprise visits to the patients' homes.

SENSITIVITY OF URINE TESTS

In order to evaluate the results of tests for isoniazid in the urine it was necessary to determine the period over which the test would remain positive. A series of 25 volunteers received isoniazid in a single supervised dose of 13-15 mg/kg body-weight. Specimens of urine were taken before the test dose and 28, 48 and 52 hours afterwards. The specimens were tested along with routine specimens in the laboratory, the laboratory staff being unaware that a special study was in progress.

Tests for isoniazid in the urine were positive in two of the 25 specimens taken before the test dose, in 20 of 24 specimens tested at 28 hours, in seven of 24 at 48 hours and in three of 23 at 52 hours. Thus a negative result for isoniazid in the urine indicated in a large proportion of patients that the drug had not been taken for at least 24 hours previously.

RELATION BETWEEN REGULARITY OF SELF-ADMINISTRATION OF ISONIAZID AND DEVELOPMENT OF PERIPHERAL NEUROPATHY

Variations in the self-administration of isoniazid could have affected the development of peripheral neuropathy in several important ways, namely:

(*a*) Peripheral neuropathy might have occurred only in those patients who took their isoniazid most regularly.

(*b*) If the irregularity was greater in one series than in others it might have affected the comparisons between the series.

(*c*) If patients with peripheral neuropathy took less isoniazid after the supplement was changed, the *therapeutic* supplement might give a false appearance of effectiveness.

These possibilities were examined on the basis of the results of tests on the urine specimens obtained at the Centre. The results of urine specimens collected from the homes of patients have not been considered for the reasons given in a previous report (Tuberculosis Chemotherapy Centre, 1960).

Comparison of regularity of self-administration of isoniazid in patients with and in patients without peripheral neuropathy

For the 13 patients with peripheral neuropathy, all of whom developed their first symptoms before six months, the results of urine tests on clinic specimens up to the time of onset of symptoms were compared with those in the first six months for the 42 patients without peripheral neuropathy. The proportions of negative results were very similar: 13.2% of 150 tests were negative in the former group, as compared with 14.7% of 1013 tests in the latter. (No relationship was found between irregularity in drug taking and the isoniazid inactivation state.)

Regularity of self-administration of isoniazid in the three supplement series

Comparing the three supplement series, the proportions of negative tests for isoniazid were 12.3% of 677 tests in the Aneurin. Co. series, 18.3% of 787 in the glutamic series and 21.6% of 611 in the calcium series. For the patients with peripheral neuropathy, only the clinic urine tests performed up to the time of the first change of supplement have been included. It is unlikely that these differences affected the frequency of peripheral neuropathy in the three series.

Regularity of self-administration of isoniazid after change of supplement

There was no evidence from the results of urine tests that the patients took their isoniazid less regularly after changing from their prophylactic to their therapeutic supplement.

In summary, there was no evidence that the degree of irregularity in taking isoniazid materially affected either the frequency of neuropathy in the three supplement series or its progression.

REGULARITY OF SELF-ADMINISTRATION OF THE SUPPLEMENTS

Variations in the self-administration of the supplements could also have affected the development of peripheral neuropathy. In this study, packet counts were the only means available for assessing the regularity with which the supplements were taken. The results of packet counts done up to the onset of symptoms for the patients who developed peripheral neuropathy were compared with those of the counts done in the first six months for the patients who did not develop peripheral neuropathy.

Prophylactic supplements

Surplus packets were found on 14.2% of 288 occasions on which counts were made at surprise visits to the homes of patients who developed peripheral neuropathy, as compared with 11.7% of 1980 occasions in the homes of patients who did not develop peripheral neuropathy. This difference is unlikely to have been of clinical importance.

Therapeutic supplements

There was no evidence from the packet counts of individual patients that there was any difference in the regularity with which the supplements were taken after the change from a prophylactic to a therapeutic supplement.

RELATION BETWEEN REGULARITY OF SELF-ADMINISTRATION OF ISONIAZID AND RESPONSE TO TREATMENT OF PULMONARY TUBERCULOSIS

Self-administration of isoniazid

The results of tests done on specimens of urine taken, during their visits to the clinic, from the 51 patients who completed one year of isoniazid therapy are given in Table 8. The average number of specimens collected per patient per month was 4.0 and was similar for males and females. The

TABLE 8

REGULARITY OF SELF-ADMINISTRATION OF ISONIAZID (AS ASSESSED BY TESTS ON URINE SPECIMENS OBTAINED AT ROUTINE VISITS TO THE CENTRE)

	Males	Females	All patients
Number of patients with test results [a]	27	24	51
Total number of tests	1 281	1 064	2 345
Average number of test results per patient per month	4.0	3.9	4.0
Number of test results which were negative	221	155	376
Percentage of test results which were negative	*17.3*	*14.6*	*16.0*

[a] Excluding two patients who died from non-tuberculous conditions and one who had his chemotherapy changed on account of toxicity.

TABLE 9

UNFAVOURABLE RESPONSE TO TREATMENT RELATED TO THE PROPORTION OF NEGATIVE TEST RESULTS ON URINE SPECIMENS OBTAINED AT ROUTINE VISITS TO THE CENTRE

Percentage of test results which were negative	Total patients [a]	Unfavourable response [b]	
		No.	%
0	7	4	*(57)* [c]
1-9	16	2	*(12)*
10-19	13	5	*(38)*
20-49	11	2	*(18)*
50 or more	4	1	*(25)*

[a] Excluding two patients who died of non-tuberculous conditions and one patient who had his chemotherapy changed on account of toxicity.

[b] Defined as tuberculous death; bacteriologically active disease at 12 months, including change of chemotherapy owing to deterioration; or bacteriologically relapsed disease at 12 months.

[c] The parentheses indicate that the percentages are based on fewer than 25 observations.

proportion of negative results was, on the average, 16.0%, being 17.3% for males and 14.6% for females.

Response to treatment

Table 9 relates the percentage of negative urine tests on clinic specimens to the frequency of unfavourable response to treatment. The number of patients showing an unfavourable response was four (57%) of seven with no negative test results, as compared with 10 (23%) of 44 with one or more negative results. The numbers showing unfavourable response with different degrees of irregularity in taking isoniazid were seven (24%) of 29 with 1-19% negative urine test results, and three (20%) of 15 with 20% or more negative results. An analysis, not shown here, has revealed that this lack of association cannot be accounted for by the fact that patients with serious disease, and therefore a poor prognosis, took their drugs more regularly than those with less extensive disease.

There was thus no evidence that the degree of irregularity in taking isoniazid encountered in this study, as measured by urine tests, affected the response to treatment.

XI. DISCUSSION

Since isoniazid is both the cheapest and the most efficient drug available for the treatment of pulmonary tuberculosis, it would be especially suitable for use in developing countries if the results of treatment with it alone were satisfactory. In a previous study by the Centre (Tuberculosis Chemotherapy Centre, 1960), three regimens of isoniazid alone were compared—namely, a moderate dosage (7.8-9.6 mg/kg body-weight) given once daily, the same daily dosage given in two doses, and a small daily dosage (3.9-5.5 mg/kg body-weight) given in two doses daily; it was found that the moderate dosage given once daily was superior to the other two regimens, but was inferior to the much more expensive combination of isoniazid and PAS. This made it desirable to test the effect of an even larger amount of isoniazid given alone in a single daily dose.

A preliminary investigation (unpublished) suggested that the highest single daily dose of isoniazid that could be given without producing signs of acute intolerance, such as vomiting and tachycardia, was approximately 15 mg/kg body-weight. Thus a dosage of 12.5-15.2 mg/kg body-weight daily (650 mg for a patient weighing 100 lb.) was chosen for the present study.

Unfortunately, even a moderate dosage of isoniazid may lead to peripheral neuropathy, and although pyridoxine is reported to be effective in the prophylaxis of this condition it has certain drawbacks, for the generally accepted dosage of 100 mg or more daily greatly increases the cost of treatment. Moreover, it has been suggested that pyridoxine may interfere with the antituberculous properties of isoniazid (Biehl & Vilter, 1954; East African/British Medical Research Council Isoniazid Investigation, 1960), and there is experimental evidence (McCune, Deuschle & McDermott, 1957) to support this suggestion. Because of these disadvantages other substances, reported to be of use in the management of isoniazid toxicity, were tested.

A vitamin-B-complex preparation, similar to Tab. Aneurin. Co., containing no pyridoxine had been reported in 1958 by Turner (personal communication, subsequently published in 1961) to be of use in the treatment of peripheral neuropathy in East Africa even when high-dosage isoniazid (1000 mg) was continued. Another, more comprehensive B-complex preparation, containing only a small amount of pyridoxine, had been used with success in the treatment of isoniazid neuropathy at the Centre (Devadatta et al., 1960). Glutamic acid had been used with good effect prophylactically by Almeida et al. (1960)—a finding which has important implications in relation to the mechanism of production of peripheral neuropathy. The present investigation was intended as a pilot study to assess the value of Tab. Aneurin. Co. and glutamic acid in the *prevention* of isoniazid neuropathy, and a larger dosage of Tab. Aneurin. Co. and the more comprehensive B-complex preparation in the *treatment* of the condition, and also to obtain a provisional assessment of the therapeutic efficacy of a single high daily dose of isoniazid—namely, 12.5-15.2 mg/kg body-weight.

EFFECT OF SUPPLEMENTS

There was no evidence that Tab. Aneurin. Co. had an effect in preventing the development of peripheral neuropathy since there were five cases among 18 patients on it, as compared with six cases among 18 patients on the placebo. In twice the dosage in which it was used prophylactically, it failed in the treatment of the neuropathy in five of the seven patients who continued to receive the high dosage of isoniazid. This finding differs from the observations of Turner (1961), which were made on Africans in Kenya, where the staple diet is different.

The more comprehensive vitamin B complex (which contained the same three constituents as Tab. Aneurin. Co., in larger dosage, and also small amounts of pyridoxine, panthenol and cyanocobalamin) had a good therapeutic effect on the peripheral neuropathy in eight of nine patients who continued on the isoniazid regimen; this confirms the findings with the same preparation in an earlier study (Devadatta et al., 1960). It may be inferred that this vitamin preparation (or one of its constituents), having proved itself therapeutically, is likely to be effective in the prevention of isoniazid neuropathy.

Glutamic acid may have had some effect in preventing peripheral neuropathy, as the frequency of the condition among those taking it was two out of 19, as compared with six out of 18 among the placebo series. Even so, this supplement was not highly effective as there was a frequency of over 10%, and as it is also bulky and expensive, it is of little practical importance in the prevention of isoniazid neuropathy. These findings support those of Tchertkoff et al. (1956), who found that 10-12 g of glutamic acid daily (a dosage of the order of 150 mg/kg body-weight) delayed but did not prevent the neuropathy due to isoniazid given in a daily dosage of 25 mg/kg body-weight; they differ, however, from those of Almeida et al. (1960), who found that glutamic acid in a daily dosage of 200 mg/kg body-weight prevented isoniazid neuropathy in patients receiving isoniazid in a daily dosage of 20 mg/kg body-weight.

FREQUENCY OF ISONIAZID TOXICITY

Peripheral neuropathy was by far the most frequent toxic effect attributed to isoniazid; it occurred in 13 of the 55 patients. The frequency among slow inactivators (52% of 21) was significantly greater than that among rapid inactivators (6% of 34), thus confirming the observations of Devadatta et al. (1960). It is of interest to consider the frequency of peripheral neuropathy in slow inactivators unmodified by prophylactic supplement in the present and in an earlier study. In the present study there were eight slow inactivators receiving placebo and 12.5-15.2 mg/kg isoniazid daily in one dose, and five (62%) developed isoniazid neuropathy. In a previous study peripheral neuropathy occurred in 11 (28%) of 39 slow inactivators receiving 7.8-9.6 mg/kg body-weight daily in one dose and in six (14%) of 44 slow inactivators receiving the same dosage given in two doses, while no peripheral neuropathy occurred

among 51 slow inactivators receiving 3.9-5.5 mg/kg of isoniazid daily in two doses (Devadatta et al., 1960). Thus, these findings suggest an association between the dosage of isoniazid and the frequency of neuropathy.

The onset of the neuropathy, as measured by the first complaint of symptoms, occurred earlier with the high dosage of isoniazid used in this study than with the moderate dosage used in the earlier study. In the present study, eight of 13 patients first spontaneously complained of their symptoms within three months of receiving a single daily dose of 12.5-15.2 mg/kg body-weight isoniazid, as compared with four of 13 (11 slow and two rapid inactivators) in the previous study on a single daily dose of 7.8-9.6 mg/kg body-weight; by the end of five months all 13 patients in the present study, as compared with nine of 13 in the earlier study, had complained of symptoms. This earlier onset of symptoms with higher doses of isoniazid has previously been reported by Biehl & Nimitz (1954). However, even on the higher dosage of isoniazid used in the present study the physical signs take several weeks to develop; and if the patients with suggestive symptoms are seen each week they can readily be treated, and will come to no serious harm.

Three (5%) of the 55 patients suffered from generalized epileptiform convulsions and one from a toxic psychosis. Manifestations of central nervous system intoxication have been reported by others (Tchertkoff et al., 1956; Organick, 1958; Turner, 1961). Since two of the patients with convulsions were rapid inactivators of isoniazid, this complication does not appear to be closely related to the rate of inactivation and may therefore be produced by a different mechanism from that which produces peripheral neuropathy. The toxic psychosis that occurred in another patient, a slow inactivator, was probably due to isoniazid, although methyl alcohol may have played some part.

RESPONSE OF PULMONARY TUBERCULOSIS TO TREATMENT WITH ISONIAZID IN HIGH DOSAGE

Since the primary object of the study was to compare the effectiveness of various substances in the prevention and treatment of isoniazid toxicity, no concurrent comparison of the therapeutic effect of the high-dosage isoniazid regimen with that of other regimens was included. It is, however, possible to make a comparison between the results obtained with this high dosage (12.5-15.2 mg/kg body-weight) and those obtained with a moderate dosage (7.8-9.6 mg/kg body-weight) given in a single daily dose for one year (Tuberculosis Chemotherapy Centre, 1960). Although this was not a concurrent comparison with random allocation, the patients in the two studies were drawn from the same community and were subject to the same criteria for admission. Moreover, the same radiographic and bacteriological methods and standards were used throughout the year in each study. Standardization for the small pretreatment differences showed that, at one year, 73% of the patients on the high dosage of isoniazid, as compared with 72% on the moderate dosage, had attained bacteriological quiescence, and this is suggestive that raising the dosage of isoniazid from 7.8-9.6 mg/kg body-weight given in one dose to 12.5-15.2 mg/kg given in one dose does not increase the therapeutic efficiency.

Because of the possible value of giving isoniazid alone in moderate dosage after an initial period of combined treatment, the search for a cheap and effective prophylactic against peripheral neuropathy is being continued at the Centre. The findings reported here do not make it clear whether the effect of the vitamin B preparation was due solely to the small amount of pyridoxine or whether other constituents were wholly or in part responsible. This problem is being investigated in another study, which will also give further information on the therapeutic effect of isoniazid in high dosage.

XII. SUMMARY

1. A total of 56 South Indian patients with pulmonary tuberculosis was admitted to a study designed to investigate the prevention and treatment of isoniazid toxicity and to obtain preliminary information on the efficacy of treatment with isoniazid in high dosage. The mean daily dosage of isoniazid at the start of treatment was 13.8 mg/kg body-weight (range, 12.5-15.2 mg/kg).

2. Each patient received one of three randomly allocated supplementary regimens, namely:

(*a*) Tab. Aneurin. Co. (*British National Formulary*; each tablet contained 1 mg of aneurine hydrochloride, 1 mg of riboflavine and 15 mg of nicotinamide) given as three tablets twice daily (18 patients);

(*b*) *l*-glutamic acid, 0.5 g in each tablet, given as five tablets twice daily (19 patients);

(*c*) Calcium gluconate, 0.5 g in each tablet, given as five tablets twice daily (19 patients);

The trial was conducted on a "double-blind" basis; the doctors did not know the dosage of isoniazid, the nature of the supplements given, or of any subsequent change in them.

3. The analysis in the toxicity section of this report concerns 55 patients—namely, 18 who received Tab. Aneurin. Co., 19 who received glutamic acid and 18 who received the placebo calcium gluconate.

4. Isoniazid toxicity affected a total of 14 patients. Of these, 13 had peripheral neuropathy (two also had convulsions and a third a toxic psychosis). The fourteenth patient had convulsions without evidence of neuropathy.

5. The time of onset of peripheral neuropathy ranged from the second to the fifth month of treatment. It occurred in 52% of 21 slow inactivators of isoniazid and in 6% of 34 rapid inactivators ($P<0.001$).

6. Tab. Aneurin. Co. (*British National Formulary*) was ineffective in preventing peripheral neuropathy, which occurred in five (28%) of 18 patients receiving this supplement, as compared with six (33%) of 18 patients receiving calcium gluconate. Used in twice the prophylactic dose it did not prevent the progression of the neuropathy in five out of seven patients.

7. The glutamic acid appeared to have some prophylactic effect, since peripheral neuropathy occurred in two (11%) of 19 patients receiving this supplement, as compared with six (33%) of 18 patients receiving calcium gluconate; but this difference does not attain statistical significance.

8. Nine patients were treated with vitamin B complex given as three tablets twice daily. The daily dosage of the constituents was: 60 mg of aneurine hydrochloride, 30 mg of riboflavine, 300 mg of nicotinamide, 6 mg of pyridoxine, 18 mg of panthenol and 6 μg of cyanocobalamin. Improvement occurred in eight patients. It is uncertain whether the small dose of pyridoxine was solely responsible for the effectiveness of this vitamin-B-complex preparation and this point will be the subject of further investigation.

9. The analysis of the response of pulmonary tuberculosis to treatment concerns 51 patients all of whom had organisms sensitive to isoniazid on admission.

10. At the end of one year, cavitation had disappeared in 30 (67%) of 45 patients with initial cavitation, and 37 (73%) of the 51 patients showed moderate or greater radiographic improvement; 35 (69%) had bacteriologically quiescent disease and two (4%) had disease of bacteriologically doubtful status. Such bacteriological responses occurred in 16 (80%) of 20 slow inactivators and 21 (68%) of 31 rapid inactivators.

11. The response of the pulmonary tuberculosis of 51 patients in the present study who received isoniazid in high dosage has been compared with that of 64 patients in a previous study who received a single daily dose of isoniazid of 7.8-9.6 mg/kg body-weight.

12. Over the 12-month period the response to treatment in the two series was similar. Thus, radiographic improvement occurred in 88% and 86%, respectively. Clinical or radiographic detioration or death from tuberculosis occurred in 8% in both series. Cavitation had disappeared by 12 months in 67% of 45 patients in the present series and in 62% of 63 patients in the previous series. At 12 months the standardized proportion of patients whose disease was bacteriologically quiescent was 73% and 72%, respectively. Thus it appears that raising the dosage of isoniazid from 7.8-9.6 mg/kg to 12.5-15.2 mg/kg body-weight did not materially affect the therapeutic response.

13. In conclusion, this study has shown: (*a*) that a vitamin B preparation which did not contain pyridoxine was ineffective in preventing peripheral neuropathy due to a high dosage of isoniazid, while glutamic acid may have had some effect; (*b*) that a B-complex preparation containing a daily dosage of only 6 mg of pyridoxine was effective in the treatment of the condition while the high dosage of isoniazid was continued: (*c*) that it was unlikely that increasing the single daily dosage of isoniazid from 7.8-9.6 mg/kg to 12.5-15.2 mg/kg body-weight altered the therapeutic response.

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RÉSUMÉ

Cinquante-six tuberculeux pulmonaires originaires de l'Inde méridionale ont participé à une étude destinée, d'une part à codifier la prophylaxie et le traitement des accidents toxiques dus à l'isoniazide, d'autre part à obtenir les premières indications sur l'intérêt des hautes doses d'isoniazide.

Les malades ont reçu au départ une dose moyenne de 13,8 mg/kg de poids corporel (entre 12,5 et 15,2 mg/kg).

En plus de ce traitement administré à tous les patients: dix-huit malades ont reçu des pilules d'Aneurin. Co. (*British National Formulary*) à raison de 3 pilules deux fois par jour.

Chaque pilule contient:

Chlorhydrate de thiamine	1 mg
Riboflavine	1 mg
Nicotinamide	15 mg

Dix-neuf malades ont reçu chaque jour en deux prises, un total de 10 pilules d'acide *l*-glutamique (0,5 g d'acide glutamique par pilule).

Dix-neuf malades ont reçu chaque jour en deux prises, 10 pilules de gluconate de calcium (0,5 g de gluconate de calcium par pilule).

L'essai a été conduit selon la méthode dite «doublement aveugle», les médecins traitants ignorant la dose d'isoniazide et la nature de la thérapeutique complémentaire.

L'étude de la toxicité de l'isoniazide a été poursuivie chez 55 malades (dix-huit ayant reçu en plus de l'Aneurin. Co., dix-neuf de l'acide glutamique, dix-huit du gluconate de calcium, considéré comme placebo). Des effets toxiques ont été observés chez 14 d'entre eux. Treize présentaient des symptômes de névrites des membres inférieurs (deux d'entre eux ont été pris de convulsions, une troisième atteinte de psychose toxique). Un quatorzième sujet a présenté des convulsions sans atteinte névritique.

Les troubles névritiques ont apparu au bout de 2 à 5 mois de traitement. Ils se sont produits chez 52% des sujets à inactivation lente de l'isoniazide et chez 6% seulement des inactiveurs rapides. La différence est statistiquement significative ($P<0,0001$).

Les pilules d'Aneurin. Co ont été impuissantes à prévenir l'apparition des névrites qui ont été notées chez 5 (28%) des 18 malades recevant ces pilules; sur 18 témoins recevant du gluconate de calcium, 6 (33%) ont présenté les mêmes troubles. L'on a doublé la dose chez 7 malades atteints de troubles névritiques; chez 5 d'entre eux, ces troubles ont poursuivi leur évolution.

L'acide glutamique n'a pas donné de meilleurs résultats puisque des névrites ont apparu chez 2 (11%) des 9 malades recevant cette médication; la différence avec le groupe témoin (33%) n'a pas de valeur statistique.

Neuf malades ont reçu, à raison de 3 pilules deux fois par jour, une préparation contenant, par pilule, des éléments du complexe vitaminique B:

Chlorhydrate de thiamine	10 mg
Riboflavine	5 mg
Nicotinamide	50 mg
Pyridoxine	1 mg
Acide pantothénique	3 mg
Cyanocobalamine (vitamine B_{12})	1 μg

Sur ces neuf malades ainsi traités, huit furent grandement améliorés. L'on ne sait pas bien si cet effet favorable est uniquement dû à la présence d'une petite quantité de pyridoxine dans la préparation; ce point fera l'objet de recherches ultérieures.

L'analyse de l'effet du traitement sur la tuberculose pulmonaire porte sur 51 malades porteurs, à l'entrée, de germes sensibles à l'isoniazide. Au bout d'un an, les cavernes ont disparu chez 20 (44%) des 45 malades présentant une ou plusieurs cavités; en tout, 37 (73%) des 51 malades ont présenté une amélioration radiologique modérée ou marquée. Trente-cinq (69%) ont vu leur expectoration négativée, cependant que chez 2 (4%) d'entre eux, cette négativation reste douteuse. Les bons résultats enregistrés sur le plan bactériologique ont été observés chez 16 (80%) des 20 inactivateurs lents et chez 21 (67%) des 31 inactivateurs rapides de l'isoniazide.

L'effet sur la tuberculose pulmonaire de l'isoniazide administré, dans la présente série de 51 malades, à hautes doses, a été comparé à celui obtenu en 1960 chez 64 malades recevant une dose journalière unique de 7,8 à 9,6 mg/kg de poids corporel. Cette comparaison montre qu'au bout de 12 mois, la réponse au traitement a été identique dans ces deux séries. C'est ainsi que l'amélioration radiologique a été observée respectivement chez 73% et 78%; l'aggravation, pouvant aller jusqu'à la mort, a été

de 8% dans les deux séries. Les excavations ont, au bout de 12 mois, disparu chez 44% des 45 malades de la série actuelle et chez 77% des 63 malades de la série recevant une dose moins forte (série HI-1). Au bout de 12 mois également, la négativation bactériologique a été de 73% dans les deux séries. Il semble donc que le fait de faire passer les doses quotidiennes de 7,8-9,6 mg/kg à 12,5-15,2 mg/kg ne change pratiquement rien au résultat thérapeutique.

L'on peut donc tirer de cette étude les conclusions suivantes:

1. Une préparation vitaminique B ne contenant pas de pyridoxine n'a aucune valeur pour la prévention des névrites toxiques dues à l'administration de fortes doses d'isoniazide; il est par contre possible que l'acide glutamique ait une action protectrice.

2. L'administration journalière, en association avec d'autres vitamines B, de 6 mg seulement de pyridoxine a donné des résultats favorables dans le traitement de ces névrites, alors que les fortes doses d'isoniazide étaient toujours administrées.

3. Il ne semble pas que le fait d'élever de 7,8-9,6 mg/kg à 12,5-15,2 mg/kg la dose journalière d'isoniazide ait la moindre incidence sur le plan thérapeutique.

REFERENCES

Almeida, F. N., De Campos, L. E. B., Rodrigues, F. C., De Oliveira, G. A., Abranches, A. J. P., Martins, M. A. G. & Vasconcelos, M. (1960) *Acta. tuberc. scand.*, **38**, 168

Biehl, J. P. & Nimitz, H. J. (1954) *Amer. Rev. Tuberc.*, **70**, 430

Biehl, J. P. & Vilter, R. W. (1954) *Proc. Soc. exp. Biol. (N. Y.)*, **85**, 389

Devadatta, S., Gangadharam, P. R. J., Andrews, R. H., Fox, W., Ramakrishnan, C. V., Selkon, J. B. & Velu, S. (1960) *Bull. Wld Hlth Org.*, **23**, 587

East African/British Medical Research Council Isoniazid Investigation (1960) *Tubercle (Lond.)*, **41**, 83

Gangadharam, P. R. J., Bhatia, A. L., Radhakrishna, S. & Selkon, J. B. (1961) *Bull. Wld Hlth Org.*, **25**, 765

Gangadharam, P. R. J., Mitchison, D. A., Subbaiah, T. V. & Short, E. I. (1958) *Tubercle (Lond.)*, **39**, 191

Jensen, K. A. (1955) *Bull. int. Un. Tuberc.*, **25**, 89

McCune, R., Deuschle, K. & McDermott, W. (1957) *Amer. Rev. Tuberc.*, **76**, 1100

Organick, A. B. (1959) *Amer. Rev. Tuberc.*, **79**, 799

Schettino, B. (1953) *Boll. Soc. ital. Biol. sper.*, **29**, 41

Selkon, J. B., Fox, W., Gangadharam, P. R. J., Ramachandran, K., Ramakrishnan, C. V. & Velu, S. (1961) *Bull. Wld Hlth Org.*, **25**, 779

Tchertkoff, I., Akad, S., Adamson, C. & Yilmaz, H. (1956) *Sea View Hosp. Bull.*, **16**, 62

Tuberculosis Chemotherapy Centre (1959) *Bull. Wld Hlth Org.*, **21**, 51

Tuberculosis Chemotherapy Centre (1960) *Bull. Wld Hlth Org.*, **23**, 535

Turner, P. P. (1961) *Lancet*, **1**, 1175

Velu, S., Andrews, R. H., Angel, J. H., Devadatta, S., Fox, W., Gangadharam, P. R. J., Narayana, A. S. L., Ramakrishnan, C. V., Selkon, J. B. & Somasundaram, P. R. (1961) *Bull. Wld Hlth Org.*, **25**, 409

Velu, S., Andrews, R. H., Devadatta, S., Fox, W., Radhakrishna, S., Ramakrishnan, C. V., Selkon, J. B., Somasundaram, P. R. & Subbaiah, T. V. (1960) *Bull. Wld Hlth Org.*, **23**, 511