

# THE OPTIMUM DOSAGE, RHYTHM AND DURATION OF ISONIAZID THERAPY IN PULMONARY TUBERCULOSIS

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## Introduction :

Isoniazid is the most effective, cheapest and most widely used drug in the chemotherapy of pulmonary tuberculosis. The optimum dosage, rhythm and duration of therapy with this drug are those which are maximally effective with minimal risk of toxicity. This paper is based mainly on studies carried out at the Tuberculosis Chemotherapy Centre, Madras, India and also, to a lesser extent, on those in Great Britain and East Africa. It discusses the implication of these studies on isoniazid therapy for the developing as well as for the economically favoured countries and indicates possible lines for future investigations.

## Condition of patients on Admission to Treatment in Five Madras Studies :

It is necessary to consider the extent of the disease in patients before dealing with the therapeutic efficacy of the various regimens. Table 1 shows the results of pretreatment radiographic and bacteriological assessments undertaken on 775 patients in the main analyses of the 5 studies carried out at Madras, (Tuberculosis Chemotherapy Centre, Madras 1959, 1960, 1963a, 1963b, 1964). It will be seen that most of the patients had advanced disease on admission to study. Thus, 89.8% of the patients had cavitated disease including 63.1% with moderate or extensive cavities. In all, 64.6% of the patients had 4 or more lung zones involved. Isoniazid-sensitive tubercle bacilli were obtained from all the patients and 87.5% had a positive smear from a single overnight collection sputum specimen.

## Dosage and Rhythm of Isoniazid alone Regimens in Relation to Response to Treatment

Table 2 relates dosage and rhythm of isoniazid administration to bacteriological quiescence<sup>1</sup> at the end of a year of treatment in patients admitted to 3 Madras Studies (Tuberculosis Chemotherapy Centre, 1960, 1963a, 1963b). In all 44% of patients on 2.2 mg/kg body weight twice daily, 58% on 4.4 mg/kg body weight twice daily, 73%, on 8.7 mg/kg body weight once daily and 68% on 13.9 mg/kg body weight once daily, attained bacteriologically quiescent disease.

<sup>a</sup> These include patients classified as having disease of bacteriologically "doubtful" status for reasons given by Vein et al (1960, 1961).

The patients had multiple specimens of sputum (usually 2 overnight collection and 2 'spot') examined by smear and culture before commencement of treatment. In the 3 most effective isoniazid alone regimens there were altogether 26 patients in whom the direct smear examination of the first collection specimen was negative although the culture was positive for tubercle bacilli. All these patients attained bacteriologically quiescent disease (not tabulated).

Table 3 relates the rate of inactivation and peak serum isoniazid concentrations to the proportion of patients who responded favourably. The method of determination of inactivation rates and serum levels have been described

TABLE 1

*Condition of patients on admission to treatment to 5 Madras studies*

Assessment on admission to treatment	All patients	
	No.	%
<i>Extent of cavitation</i>		
Nil	79	10.2
Slight	206	26.8
Moderate	348	44.8
Extensive	142	18.3
<i>Number of lung zones involved</i>		
1, 2 or 3	274	35.4
4, 5 or 6	501	64.6
<i>Bacterial content of sputum</i>		
Direct smear negative	97	12.5
Direct smear positive		
1-plus (scanty)	139	17.9
2-plus (moderate)	310	40.0
3-plus (heavy)	229	29.5
Total patients	775	1000

elsewhere (Gangadharam et al 1961a, 1961b). There is a consistent but slight (and statistically no-significant) association between the rate of inactivation and response to treatment in *each* of the 4 regimens (Table 3, second and fifth columns see also Selkon et al 1961). There was a definite association between the peak serum isoniazid concentrations, up to that

attained by patients receiving isoniazid 8.7 mg/kg body weight once daily, and response to treatment (Table 3, third and fifth columns).

#### Incidence of Isoniazid Toxicity

Nearly all patients who developed isoniazid toxicity in these studies manifested symptoms and signs of a peripheral neuropathy but a few

TABLE 2

*Dosage and rhythm of isoniazid alone regimens in relation to response to treatment for 1 year*

Regimen	No of patients	Single dose of isoniazid (mg/kg)	No of doses a day	Percentage of Patients with bacteriologically quiescent disease (%) at 1 year
H <sub>650</sub> *X <sub>1</sub>	143	13.9	1	68
H <sub>400</sub> *X <sub>1</sub>	64	8.7	1	73
H <sub>200</sub> *X <sub>2</sub>	66	4.4	2	58
H <sub>100</sub> *X <sub>2</sub>	86	2.2	2	44

\* These figures represent the single dose of isoniazid in mg for a 45.4 kg (100 lb) patient.

TABLE 3

*Dosage rate of isoniazid inactivation and peak Serum concentration in relation to response to treatment*

Regimen	Rate of isoniazid inactivation	Peak serum concentration (ug/ml)	Number of patients	Percentage with quiescent disease at 1 year %
H <sub>650</sub>	Slow	(10.9)*	81	69
	Rapid	(7.0)*	62	66
H <sub>400</sub>	Slow	6.6	36	69
	Rapid	4.2	32	66
H <sub>200</sub> X <sub>2</sub>	Slow	2.6	39	59
	Rapid	1.9	27	56
H <sub>100</sub> X <sub>2</sub>	Slow	1.2	46	48
	Rapid	0.7	36	44

\* The peak serum level in these patients are not available, but have been extrapolated on the basis of the values obtained in patients on the other 3 regimens. It was assumed that the peak concentration increased proportionally with the individual dose of isoniazid.

psychosis and/or convulsions (see Devadatta et al 1960, Tuberculosis Chemotherapy Centre 1963a, 1963b). Table 4 relates isoniazid dosage, rate of inactivation, and peak serum concentrations to the proportion of patients with toxicity. Development of toxicity was associated with isoniazid dosage and rate of inactivation Table 4, first and fifth columns). The proportion ranged from 0% in patients receiving 2.2 mg/kg body weight twice daily to 27% in those receiving 13.9 mg/kg body weight once daily. The proportion among the slow and rapid inactivators in the 3 regimens where toxicity occurred was 46% and 10%, 28% and 6%, 14% and 0% respectively. All these differences attain statistical significance. There is, however, a poor association between peak serum isoniazid concentrations (Table 4, column 3) and the proportion of patients who developed toxicity (column 5).

Mitchison (1962) has related an empirical function  $P/Kt$ , with the proportion of patients with isoniazid toxicity, where P was the peak serum concentration (ug/ml), K was the descending slope of the line joining the 2 hour and 6 hour serum isoniazid concentrations on a logarithmic scale ( $K_{slow} = 0.100$  or  $0.10$  and  $K_{rapid} = 0.198$  or  $0.20$  to two significant figures) and t was the period in hours between the doses of isoniazid (24 for the once and 12 for the twice a day regimen). Table 5 relates the proportion of patients developing isoniazid toxicity with  $P/Kt$ . There is a good correlation ( $r=+0.986$ ), and the regression equation was  $N = \frac{118P}{kt} - 7.4$ . Where N is the percentage of patients expected to develop toxicity and K has been multiplied by 10 for simplification and is, therefore, 1.0 for slow and 2.0 for rapid inactivators.

There was also a good correlation between the peak serum concentrations of isoniazid in the three regimens where these were directly determined and the individual dose of isoniazid ( $r$  for the slow inactivators was  $+0.996$  and for rapid inactivators was  $+1.000$ ).

The regression equations are

$$P_s = 0.84D - 0.81$$

$$P_r = 0.54D - 0.48$$

where  $P_s$  and  $P_r$  are the peak serum isoniazid concentration (ug/ml) in the slow and rapid inactivators respectively and D the individual dose of isoniazid (mg/kg body weight). From these three equations it is possible to derive, by elimination of P, ones correlating the incidence of isoniazid toxicity with the dose and rhythm of administration of isoniazid.

Ind. J. Tub., Vol. XIII, No. 4

These are

$$N_s = \frac{99D - 96}{t} - 7.4 \text{ and } N_r = \frac{64D - 57}{2t} - 7.4$$

where  $N_s$  and  $N_r$  are the percentage of patients expected to develop toxicity among the slow and rapid inactivators respectively.

The rate of isoniazid inactivation was determined in 480 patients in 3 Madras Studies and of these 282 (58.8%) were slow and the remainder rapid inactivators (Gangadharam et al 1961a, Tuberculosis Chemotherapy Centre, 1963a, 1963b). It is therefore possible to derive an equation for a South Indian population namely

$$N = \frac{143D - 136}{2t} - 7.4$$

#### Clinical Features of Isoniazid Toxicity

Of the 40 patients with toxicity (Table 4), encountered in three isoniazid studies all but one developed peripheral neuropathy (Devadatta et al 1960, Tuberculosis Chemotherapy Centre, 1963a, 1963b). The remaining patient had convulsions. Of the patients with peripheral neuropathy 3 also developed convulsions, 2 psychosis and 1 convulsions and psychosis. All 5 with convulsions and 2 of the 3 with psychosis were encountered in patients receiving the high dosage of isoniazid (13.9 mg/kg body weight once daily).

The neuropathy was mainly sensory in nature. The usual course was a slow progression of the symptoms and gradual spread of the physical signs proximally. Usually, the first signs elicited were loss of vibration sense in the toes and ankles and loss of ankle jerks, followed by anaesthesia, loss of position sense in the toes and loss of knee jerks.

#### The Time of Onset of Isoniazid Toxicity

There was a tendency for an earlier development of toxicity with increasing individual daily dose of isoniazid. Thus of the 21 patients who developed toxicity on 13.9 mg/kg body weight once daily (Table 4), 12 first complained of toxic symptoms in the first 3 months, 9 in the next 3 months and none in the remaining part of the therapeutic year. The corresponding figures for 13 such patients receiving 8.7 mg/kg body weight once daily was 4, 5 and 4 respectively and for the 6 patients receiving 4.4 mg/kg body weight twice daily they were 2, 0, and 4 respectively.

#### Prevention and Treatment of Isoniazid Toxicity

Pyridoxine in a dosage of only 6 mg. once

TABLE 4  
*Dosage, rate of inactivation and peak serum concentration in relation to isoniazid toxicity*

Regimen	Rate of inactivation	Peak serum concentration (ug/ml.)	Number of patients	Patients with toxicity*	
				No.	%
H <sub>650</sub>	Slow	10.9	37	17	46 27
	Rapid	7.0	42	4	10
H <sub>400</sub>	Slow	6.6	39	11	28 18
	Rapid	4.2	32	2	6
H <sub>200x2</sub>	Slow	2.6	44	6	14 8
	Rapid	1.9	28	0	0
H <sub>100x2</sub>	Slow	1.2	51	0	0
	Rapid	0.7	36	0	0
				40*	0

\* All but one developed peripheral neuropathy. Five of them developed convulsions also and 3 psychosis.

TABLE 5  
*An empirical serum concentration-time function related to isoniazid toxicity*

Regimen	Rate of inactivation	Proportion of patients with toxicity (%)	P/kt*
H <sub>650</sub>	Slow	46	4.54
H <sub>400</sub>	Slow	28	2.75
H <sub>200x2</sub>	Slow	14	2.17
H <sub>650</sub>	Rapid	10	1.46
H <sub>400</sub>	Rapid	6	0.88
H <sub>200x2</sub>	Rapid	0	0.79
H <sub>100x2</sub>	Slow	0	1.00
H <sub>100x2</sub>	Rapid	0	0.29

\* P=Peak serum isoniazid concentration (ug/ml.)  
 K=A constant 0.10 for slow inactivators and 0.2 for rapid inactivators (see text, page 2).  
 t=Time interval in hours between each dose of isoniazid.

a day was effective both in the prevention and treatment of toxicity in patients receiving a high dosage of isoniazid, namely 13.9 mg/kg body weight once a day (Tuberculosis Chemotherapy Centre, 1963a, 1963b). On an isoniazid dosage of 13.9 mg/kg body weight once daily, of 24 patients who received a Vit B complex preparation without pyridoxine 7 (29%) developed peripheral neuropathy compared with none among 26 who received pyridoxine 6 mgm with each dose of isoniazid (Tuberculosis Chemotherapy Centre, 1963b). In 3 toxicity studies 17 patients who developed the neuropathy were treated with 6 mgm of pyridoxine either alone or in combination with other constituents of Vit. B complex while isoniazid was continued (Devadatta et al, 1960, Tuberculosis Chemotherapy Centre, 1963a, 1963b). In 15 patients, there was improvement, in 2 no change and in 1 deterioration of the manifestations of the neuropathy. It was possible to continue isoniazid for a full year in all but the last patient. One patient who developed a psychosis and another convulsions were treated successfully with pyridoxine 6 mg daily in combination with other constituents of Vit. B complex, while isoniazid in a dosage of 13.9 mg/kg body weight once a day was continued. Since Vit. B complex without pyridoxine was unsuccessful both in the prevention and treatment of isoniazid toxicity it is obvious that the 6 mgm of pyridoxine was the effective agent in patients developing both the peripheral nerve and cerebral toxicity. In another study one patient developed peripheral neuropathy and another convulsions on a twice weekly high dosage (13.9 mg/kg body weight) of isoniazid in combination with streptomycin. Both patients were successfully treated with pyridoxine 6 mgm given with each dose of isoni-

azid without modification of the chemotherapy (Tuberculosis Chemotherapy Centre, 1964).

#### Dosages of Isoniazid when used with other anti-tuberculosis drugs

Table 6 shows the therapeutic efficacy of various dosages of isoniazid used in combination with other drugs in Madras, East Africa and Great Britain on patients excreting drug sensitive tubercle bacilli. Isoniazid in a dosage of 100 mgm. (2.2 mg/kg body weight) twice daily in combination with paraminosalicylic acid (PAS) twice a day for a year produced bacteriological quiescence of the disease in 87% of patients in Madras (Tuberculosis Chemotherapy Centre 1959, 1960, 1964), 84% in East Africa (East African/British Medical Research Council, 1960a, 1960b, 1963) and 82% in Great Britain (British Medical Research Council, 1962). At Madras the proportion for the 27 patients without cavitation was 96% (not tabulated). Isoniazid in a dosage of 300 mgm. in combination with thiacetazone 150 mgm. once a day for a year produced bacteriological quiescence of the disease in 88% of patient in East Africa. However, on the regimen of isoniazid 200 mgm. with thiacetazone 150 mgm. once a day only 64% of patients attained bacteriological quiescence of the disease (East African/British Medical Research Council 1963). In a Madras Study isoniazid in high dosage (650 mgm. for a 100 lb. patient or 13.9 mg/kg body weight) in combination with streptomycin both given twice weekly for a year produced bacteriological quiescence of the disease in 94% of patients (Tuberculosis Chemotherapy Centre 1964). In Great Britain bacteriologically quiescent disease is achieved in 100% of patients receiving isoniazid 100 mgm. twice or

TABLE 6

*Isoniazid in combination with other drugs*

Place of study	Number of patients	Dose of soniazid (mg)	Companion drug and I dose	Rhythm	Percentage of patients with quiescent	Percentage of patients with isoniazid
					disease %	toxicity %
Madras	315	100	PASSg	Twice a day	87	0.3
East Africa	238	100	PAS5g	Twice a day	84	0.0
Great Britain	74	100	PAS 5 g	Twice a day	82	0.0
East Africa	60	300	Thiacetazone 150 mg	Once a day	88	1.6
East Africa	70	200	Thiacetazone 150 mg	Once a day	64	1.4
Madras	72	650	Streptomycin 1 g	Twice a week	94	2.8

thrice a day in combination with streptomycin once a day (not tabulated, see Crofton 1959).

#### Duration of Chemotherapy

Table 7 shows the effect of isoniazid alone in a dosage of 200 mgm. (4.4 mg/kg body weight) once daily in the second year in patients with bacteriologically quiescent disease after a year of chemotherapy in a Madras Study (see Velu et al 1961). In patients without residual cavitation at 1 year bacteriological relapse occurred in the second year in none of the 103 patients on isoniazid and 10 (9%) of 107 on a placebo. This difference is statistically significant. On the other hand, among patients with residual cavitation there was little difference between the proportion of relapsing on isoniazid and the proposing relapsing on a placebo in the second year. The proportion of these patients (with the open negative syndrome) at the end of a year who relapsed in the second year was 8 out of 97 patients.

Table 8 shows the effect of 100 mgm. of isoniazid in combination with PAS 5 g. twice daily in the second and third years in patients, with bacteriologically quiescent disease with residual cavitation at the end of a year of chemotherapy, in a study in Great Britain (British Medical Research Council 1962). The proportion relapsing bacteriologically in the second and third years among patients who had their chemotherapy stopped at the end of 1 year was 12 (24%) of 50, among patients who continued chemotherapy in the second year (but not in the third) was 2 (6%) of 34 and among those who continued chemotherapy in the second and third years was 1 (4%) of 24 patients.

#### DISCUSSION

Isoniazid is always used in the treatment of patients with newly-diagnosed pulmonary tuberculosis. Most authorities believe that the best results are achieved when isoniazid is combined with at least one other anti-tuberculosis drug. However, as pointed out by Fox (1964), in many clinics, in developing countries, where patients present with advanced disease, it is economically possible to administer only isoniazid. It is therefore important to determine the optimum dosage, rhythm and duration of therapy with isoniazid either alone or in combination with other drugs.

The Madras Studies have shown that the therapeutic efficacy of isoniazid alone in a dosage of 8.7 mg/kg body weight (400 mg. for a 100 lb. patient) once a day was superior to the same dosage divided into 2 daily doses. However, no further increase in therapeutic

efficacy was noted when the dosage of isoniazid was increased to 13.9 mg/kg body weight (650 mgm. for a 100 lb. patient) once daily. The maximum effect of isoniazid alone in the Madras patients, the great majority of whom had advanced disease (Table 1), was the attainment of bacteriologically quiescent disease at the end of a year of chemotherapy in about 70%. However, all 26 patients receiving the three most successful isoniazid alone regimens, in whom the first or only overnight 'collection' sputum specimen was negative on direct smear examination, attained bacteriologically quiescent disease. Phillips (1959) found that isoniazid alone was as effective as isoniazid plus PAS in

TABLE 7

*The effect of isoniazid alone in the second year on patients with bacteriologically quiescent disease at the end of 1 year of chemotherapy (Madras)*

Treatment during second year	All patients	Bacteriological relapse in second year
<i>Non-cavitated</i>		
Placebo	107	10 (9%)
Isoniazid*	103	0 (0%)
<i>Cavitated</i>		
Placebo	42	4 (10%)
Isoniazid*	55	4 (7%)

\* 4.4 mg/kg body weight once daily (200 mg for a 100lb patient).

TABLE 8

*The effect of isoniazid plus pas in the second and third year on patients with the "open-negative" syndrome at the end of a year of chemotherapy\**

Duration of chemotherapy*	All patients	Bacteriological relapses in the 2nd and 3rd years
One-year	50	12 (24%)
Two-years	34	2 (6%)
Three-years	24	1 (4%)

\* From British Medical Research Council (1962).  
\*\* Isoniazid 100 mg in combination with PAS 5 g twice a day.

minimal or moderately advanced non-cavitated disease in American patients. Furthermore, isoniazid alone may be more acceptable to patients than a combined regimen, and thus may yield better therapeutic dividends in smear-negative non-cavitated patients, even in the economically favoured countries.

Since the maximum effect of the isoniazid alone regimens in *all* the Madras patients was sputum conversion in about 70% of patients, it is interesting to speculate whether any better results could be obtained with more intensive regimens of isoniazid alone in developing countries. The minimum single daily dosage required to obtain the maximum therapeutic effect in the Madras patients is not known. This dosage is greater than 4.4 mg/kg body weight and may possibly be 6.6 mg/kg or 8.7 mg/kg body weight (300 or 400 mg. for a 100 lb. patient). It is therefore possible that regimens of 6.6 mg/kg or 8.7 mg/kg *twice* daily might produce bacteriologically quiescent disease in more than 70% of the patients. However, in East Africa isoniazid alone in a dosage of 10 mg/kg body weight twice daily produced bacteriological quiescence in only 40% of patients: (East African/British Medical Research Council 1960a). This proportion was 51% in another study where isoniazid 300 mgm. was given in combination with thiacetazone 100 mg. once a day (East African/British Medical Research Council 1963).

Several possible explanations could be suggested for the poorer response to isoniazid of the East African patients than could be expected from the Madras studies. First, large doses of pyridoxine were given with isoniazid 10 mg/kg body weight twice daily and there is experimental evidence (Mc Cune et al 1957) that pyridoxine may interfere with the anti-tuberculosis activity of isoniazid. It is uncertain precisely what effective dosage of isoniazid these patients received. The patients in the second East African study mentioned, however, did not receive any pyridoxine. Secondly, it is possible that the East African patients had, on average, more extensive disease on admission to treatment than the Madras patients. Thirdly, it is possible that pretreatment cultures of tubercle bacilli from East African patients, on average, were more virulent than those from Indian patients (see Mitchison 1964).

Since the reason for the difference in response to isoniazid between the East African and Madras patients is not known with certainty there is a case to assess the therapeutic efficacy of a moderate dose of isoniazid (300 mg. or 400 mg.) twice a day, in some other developing area. It is possible that the efficacy of this regimen might approach, equal or even

exceed that of the usual low dose of isoniazid (100 mg.) in combination with PAS twice daily.

The most frequent manifestation of isoniazid toxicity encountered in the Madras Studies was peripheral neuropathy. Convulsion and psychosis occurred much less frequently. It was found that the proportion of patients who developed toxicity was associated with the individual dose of isoniazid (D) and the rate of inactivation. It was also associated with a ratio of the peak serum isoniazid concentration (P) to a constant (K which varied with rate of inactivation) and the time interval between the individual doses of the drugs (t). Since P is related to D, it was possible to derive an equation expressing the proportion of patients expected to develop isoniazid toxicity in terms of D and t for the slow and rapid inactivators. A similar equation was also derived for a population in which the proportion of slow inactivators is assumed to be 58.8% as in the Madras patients.

It is obvious that these equations are of limited value and probably only applicable to South Indian patients, since there may be factors like the pyridoxine content of the diet affecting the occurrence of isoniazid toxicity. Other possible factors are the criteria used in the diagnosis of isoniazid neuropathy and duration of therapy. For example, in West Africa, peripheral neuropathy was encountered in 16 of 84 patients on isoniazid 2 mg/kg. to 3 mg/kg. body weight in combination with PAS twice a day (Money, 1959) compared with only 1 of the 324 patients from 3 Madras Studies receiving similar chemotherapy. On the other hand in an East African Study only 1 of 145 patients on isoniazid 300 mgm. (6.6 mg/kg body weight) once daily in combination with thiacetazone developed the neuropathy but from the equation derived from the Madras Studies the expected proportion on this regimen of isoniazid is 9%.

A Madras Study has shown that pyridoxine in as low a dose as 6 mgm. can prevent toxicity due to isoniazid 13.9 mg/kg. body weight once a day. This finding is of obvious importance to developing countries. Other workers have used much higher doses ranging from 25 mg. (Oestreicher et al 1954) to 300 mg. (East African/British Medical Research Council 1960a). Pyridoxine 6 mgm once a day was also successful in the therapy of patients developing toxicity even when isoniazid was continued. Although such patients can be managed by substituting isoniazid by another drug, there are definite advantages in retaining the most powerful and cheapest anti-tuberculosis drug.

Thus pyridoxine 6 mgm can be given prophylactically with each dose, if the suggested isoniazid regimen of 300 mg. or 400 mg. twice daily is investigated. Alternatively, as a less expensive measure, pyridoxine can be given in the same way only to patients who develop toxicity. This is feasible as isoniazid neuropathy is of the slowly progressive sensory type. This is true even when a high dosage of 650 mg. (13.9 mg/kg body weight) once a day is used, although the symptoms occur rather earlier than when a lower dosage is used.

Low doses of isoniazid given twice a day have been used in combination with other antimicrobial drugs and thus isoniazid toxicity is not a problem in such regimens. Isoniazid in a dosage of 100 mg. (2.2 mg/kg body weight) in combination with PAS 5 g., twice a day for 1 year was found in 3 Madras Studies to produce bacteriological quiescence in 87% of the patients. This result is much better than any of the isoniazid alone regimens used there. Since in the lower ranges the response to treatment is associated with peak serum isoniazid concentrations even better therapeutic results might be obtained with 300 to 400 mg. in combination with PAS once daily.

Of the 27 patients in 3 Madras Studies, without cavitation before commencement of treatment with isoniazid 100 mg in combination with PAS 5 g. twice a day, 26 (96%) had bacteriologically quiescent disease at the end of a year of chemotherapy. This observation suggests that isoniazid when combined with PAS is probably as effective as when combined with streptomycin in patients without cavitation. In the United States of America, Livings (1959) found no bacteriological or radiographic advantage of isoniazid plus streptomycin over isoniazid plus PAS at the end of eight months.

In an East African Study a cheap combination of isoniazid 300 mgm with thiacetazone 150 mgm once a day for a year produced bacteriologically quiescent disease in 88% of patients. An increase in the isoniazid dosage to 400 mgm might further increase the efficacy of the regimen. In the study a marked fall in the therapeutic efficacy was observed when isoniazid in this combination was reduced to 200 mgm once a day.

In Great Britain isoniazid in dose of 100 mgm twice a day in combination with streptomycin or 1 g. a day has produced bacteriological quiescence of the disease in 100% of patients (Crofton 1959). However, if the patient is receiving this treatment as an outpatient, it is easier to administer 200 or 300

mgm isoniazid in 1 dose under supervision with the streptomycin injection.

A Madras Study has shown that isoniazid in a dosage of 13.9 mg/kg body weight (650 mgm for a 100 lb. patient) with streptomycin *both* given twice *weekly* produced bacteriological quiescence of the disease in 68 (94%) of 72 patients. If a patient who died on the day treatment was begun is excluded this proportion increases to 96%. It is not known whether a lower dose of isoniazid (say 6.6 mg/kg or 8.7 mg/kg body weight) or the substitution of streptomycin by PAS or an increase in the intermittency of the regimen would equally favourable results. The last principle is being investigated at Madras.

The high efficacy of this twice weekly regimen is of great importance in developing countries as it is much cheaper than the usual daily combination of isoniazid plus PAS. It is also possible that this intermittent regimen, which approaches 100% success in patients with advanced disease at Madras may be completely successful in certain economically favoured countries where the disease, on average, is less advanced. It may produce less streptomycin toxicity and may be more acceptable to patients and therefore prove more successful than the usual daily regimens of isoniazid plus streptomycin.

“We know when to begin chemotherapy for tuberculosis, but we do not know when to stop” (Annotation, Lancet, 1962). Studies at Madras and Great Britain have shed light on this problem. In the Madras Studies isoniazid 200 mgm (4.4 mg/kg body weight) once daily for the whole of the second year prevented bacteriological relapses in the second and third years in patients with bacteriologically quiescent disease *without* residual cavitation at the end of a year of chemotherapy. This observation may be applied to the treatment of patients even in the economically favoured countries. It is not known whether a shorter period of isoniazid therapy in the second year (say 6 months) would also have prevented relapses. Isoniazid in a dosage of 200 mgm once daily for the whole of second year did not, however, prevent relapse in patients with bacteriologically quiescent disease *with* residual cavitation (open negative syndrome) at the end of a year of chemotherapy. Bacteriological relapses occurred in 8% of such patients. In Great Britain isoniazid 100 mgm in combination with PAS 5 g, twice a day in a second year considerably reduced bacteriological relapse in the second and third years in patients with the ‘open-negative syndrome’ at the end of one year. Continuation of this

combined chemotherapy for another (third) year did not confer additional benefit.

Thus these studies have shown that the optimum duration of chemotherapy in all patients, irrespective of the extent of the disease pretreatment, is 2 years. They, therefore, do not support the views that chemotherapy should be given for indefinitely prolonged periods (Worbec et al 1960) or in selected cases for life (American Thoracic Society 1961). The patients whose disease has attained bacteriological quiescence without residual cavitation at the end of one year can be given isoniazid alone for another year and those with residual cavitation isoniazid plus PAS. It is, however, unrealistic to consider combined chemotherapy for a second year in patients in developing countries but it is possible that a higher dosage of isoniazid (e.g. 300 or 400 mgm once a day) could prevent relapses in patients with residual cavitation.

#### Summary

(1) This paper is based mainly on the Madras Studies and also, to a lesser extent on those carried out in Great Britain and East Africa. From the results of these studies suggestions are made regarding the optimum dosage, rhythm and duration of isoniazid therapy in pulmonary tuberculosis.

(2) Of the isoniazid *alone* regimens studies in patients at Madras, the great majority of whom had advanced disease, 8.7 mg/kg body weight once a day (400 mgm for a 100 lb patient) has yielded the best results. This dosage produced bacteriologically quiescent disease in 73% of 64 patients.

(3) The therapeutic response was associated with the peak serum concentration of isoniazid up to that achieved by a dosage of 8.7 mg/kg body weight *once daily*. A higher single daily dosage, producing a higher peak concentration, did not produce better therapeutic results.

(4) Nearly all patients who developed isoniazid toxicity manifested symptoms and signs of peripheral neuropathy but a few of convulsions and/or psychosis. Toxicity occur red significantly more frequently in the slow than in the rapid inactivators of isoniazid.

(5) An equation was derived relating the proportion of patients expected to develop isoniazid toxicity with the individual dose of isoniazid and the interval between the doses for the slow and rapid inactivators. Since the proportion of slow and rapid inactivators among the Madras patients is known an equation was also derived for a South Indian population.

(6) Pyridoxine in a low dosage of 6 mgm was successful in the prevention of toxicity due to isoniazid administered in a dosage of 13.9 mg/kg body-weight (650 mg. for a 100 lb. patient) once daily. 6 mg. of pyridoxine was also successful in the treatment of toxicity even when the isoniazid was continued.

(7) Isoniazid in a low dosage of 2.2 mg/kg body weight (100 mg. for a 100 lb. patient) in combination with PAS 5 g. twice a day for a year produced bacteriological quiescence of the disease in 87% of patients in Madras, 84% in East Africa and 82% in Great Britain. In the 27 Madras patients with cavitation this proportion was 96%.

(8) Isoniazid 300 mg in combination with thiacetazone 150 mg once daily for a year produced bacteriologically quiescent disease in 88% of patients in East Africa,

(9) Isoniazid 100 mg twice or thrice a day in combination with streptomycin 1 gm once a day has produced bacteriologically quiescent disease in 100% of patients in Great Britain.

(10) Isoniazid in a high dosage of 13.9 mg/kg body weight in combination with streptomycin 1 gm both given twice weekly for a year has produced bacteriologically quiescent disease in 94% of patients in Madras.

(11) Studies in Madras and Great Britain have revealed that the optimum duration of chemotherapy is 2 years. Isoniazid alone 200 mgm once a day can be given in the second year to patients with bacteriologically quiescent disease without cavitation at the end of a year of chemotherapy. Patients with the "open-negative syndrome" at the end of one year should *if possible* receive combined chemotherapy in the second year.

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