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Peripheral Neuritis due to Isoniazid *

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It is well known that in the treatment of tuberculosis with isoniazid the complication of peripheral neuritis may arise. This complication is normally rare when small dosages of the drug are used, but a high incidence of the neuropathy has recently been observed in East Africa in a group of malnourished tuberculous patients receiving isoniazid in comparatively low dosage (4-6 mg/kg body-weight daily). The present paper reports on 20 cases of peripheral neuritis encountered in Madras, India, among 338 poorly nourished tuberculous patients during a trial of four isoniazid regimens, two of low and two of high dosage (3.9-5.5 and 7.8-9.6 mg/kg body-weight daily, respectively). Nineteen of the 20 cases occurred in the two groups of patients receiving the high dosage and these 19 patients were found to have a higher mean serum level of free isoniazid than the patients in the same groups who did not develop the complication. The authors consider that dosages of 7.8-9.6 mg/kg body-weight daily should not be used for the mass therapy of poorly nourished patients unless steps are taken to prevent the development of peripheral neuritis. Pyridoxine has been reported to be an effective preventive, but is too expensive for use on a large scale. This study indicates, however, that administration of the cheaper vitamin B complex might give satisfactory results and warrants further investigation.

INTRODUCTION

Peripheral neuritis is a well-known complication of isoniazid therapy. It rarely occurs when small dosages of the drug are used (Great Britain, Medical Research Council, 1952, 1953a, 1953b, 1955; Mount, Jenkins & Ferebee, 1953; Tuberculosis Chemotherapy Centre, 1959), although Money (1959) encountered a high incidence of the neuropathy in malnourished tuberculous patients in East Africa on a comparatively low dosage of isoniazid (4 mg/kg to 6 mg/kg body-weight daily). The complication is more frequent with higher dosages of isoniazid (Gammon, Burge & King, 1953; United States Public Health Service, 1954; Biehl & Nimitz, 1954; Wood, 1955; Tchertkoff et al., 1956). This paper reports 20 cases of peripheral neuritis encountered in a controlled chemotherapeutic trial of four regimens in patients with active pulmonary tuberculosis undertaken at the Tuberculosis Chemotherapy Centre, Madras. The patients allocated to two of the regimens received a low dosage of isoniazid (in practically all patients 3.9 mg/kg to 5.5 mg/kg body-weight daily) and those allocated to the remaining two regimens received a moderately high dosage of the drug (7.8 mg/kg to 9.6 mg/kg body-weight daily). The patients were drawn from the lower income groups in Madras City and were on a poor diet (Tuberculosis Chemotherapy Centre, 1960 [1]). Alcohol has been prohibited in Madras State for the past 12 years and none of the patients, as far as is known, was an alcoholic.

PLAN AND CONDUCT OF THE CHEMOTHERAPY STUDY

In all, 341 patients with active pulmonary tuberculosis were allocated at random to four regimens of antituberculosis chemotherapy for a year. Three of these patients have been excluded from this report because they had previously received chemotherapy which included isoniazid. The four regimens were:

PH (96 patients)

These patients received cachets each containing isoniazid 25 mg and PAS 1.25 g. The number of cachets prescribed depended on the patient's weight

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

[1] See article on page 535 of this issue.

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

Treatment series	Body-weight		No. of tablets or cachets prescribed daily		Total daily dosage of isoniazid (mg)	Daily dosage of isoniazid in relation to body-weight (mg/kg)
	(lb.)	(kg)	morning	evening		
PH and H	45-59	20.4-27.1	3	3	150	7.3-5.6
	60-79	27.2-36.2	3	3	150	5.5-4.2
	80-99	36.3-45.3	3	4	175	4.8-3.9
	100-119	45.4-54.3	4	4	200	4.4-3.7
HI-1	45-59	20.4-27.1	4	0	200	9.8-7.5
	60-69	27.2-31.7	5	0	250	9.2-8.0
	70-79	31.8-36.2	6	0	300	9.4-8.4
	80-99	36.3-45.3	7	0	350	9.6-7.8
	100-109	45.4-49.8	8	0	400	8.8-8.1
	110-119	49.9-54.3	9	0	450	9.0-8.3
HI-2	45-59	20.4-27.1	2	2	200	9.8-7.5
	60-69	27.2-31.7	2	3	250	9.2-8.0
	70-79	31.8-36.2	3	3	300	9.4-8.4
	80-99	36.3-45.3	3	4	350	9.6-7.8
	100-109	45.4-49.8	4	4	400	8.8-8.1
	110-119	49.9-54.3	4	5	450	9.0-8.3

(Table 1). The dosage of isoniazid ranged from 3.9 mg/kg to 5.5 mg/kg body-weight, approximately, and the dosage of PAS from 0.2 g/kg to 0.3 g/kg body-weight, daily. The cachets were to be taken in two doses each day.

H (94 patients)

These patients received tablets each containing 25 mg of isoniazid. The dosage range of isoniazid was the same as that for the PH patients and the tablets were to be taken in two doses each day (Table 1).

HI-1 (74 patients); HI-2 (74 patients)

The patients in both the HI-1 and the HI-2 series received tablets containing 50 mg of isoniazid, the total daily dosage ranging from 7.8 mg/kg to 9.6 mg/kg body-weight, approximately (Table 1). The HI-1 patients were to take the drug in one dose in the morning, and the HI-2 patients in two doses, one in the morning and the other in the evening.

The great majority of the patients were ambulant and attended the Centre weekly to collect their supply of medicine. They were examined monthly as a routine. If, at a monthly examination, a patient was found to have gained weight and to have moved into a higher weight category, the number of cachets or tablets was increased appropriately; if a patient had lost weight and had fallen into a lower weight category, the number was *not* decreased. All patients continued on the allocated regimen for 12 months, unless a radiographic deterioration or a severe toxic reaction to either of the drugs, necessitating a change of chemotherapy, had occurred. At the end of 12 months, patients with bacteriologically quiescent disease were allocated at random, either to isoniazid alone prescribed as a single tablet daily, the dosage being the same as in the H regimen, or to no further specific chemotherapy. Patients who still had active disease at the end of 12 months continued on the originally prescribed chemotherapy.

DIAGNOSIS OF PERIPHERAL NEURITIS

A record was kept of any *spontaneous* complaint which could be attributed to peripheral neuritis. The patients were not questioned to elicit symptoms,

TABLE 2
INCIDENCE AND TIME OF ONSET OF PERIPHERAL NEURITIS IN THE TWO HIGH-DOSAGE ISONIAZID SERIES

Months after start of treatment	HI-1			HI-2		
	cases of peripheral neuritis			cases of peripheral neuritis		
	new cases	cumulative total		new cases	cumulative total	
		No.	%		No.	%
1	0	0	*0*	0	0	*0*
2	2	2	*3*	0	0	*0*
3	2	4	*5*	2	2	*3*
4	3	7	*10*	0	2	*3*
5	2	9	*12*	0	2	*3*
6	0	9	*12*	0	2	*3*
7	1	10	*14*	2	4	*5*
8	1	11	*15*	1	5	*7*
9	1	12	*16*	0	5	*7*
10	1	13	*18*	1	6	*8*
11	0	13	*18*	0	6	*8*
12	0	13	*18*	0	6	*8*

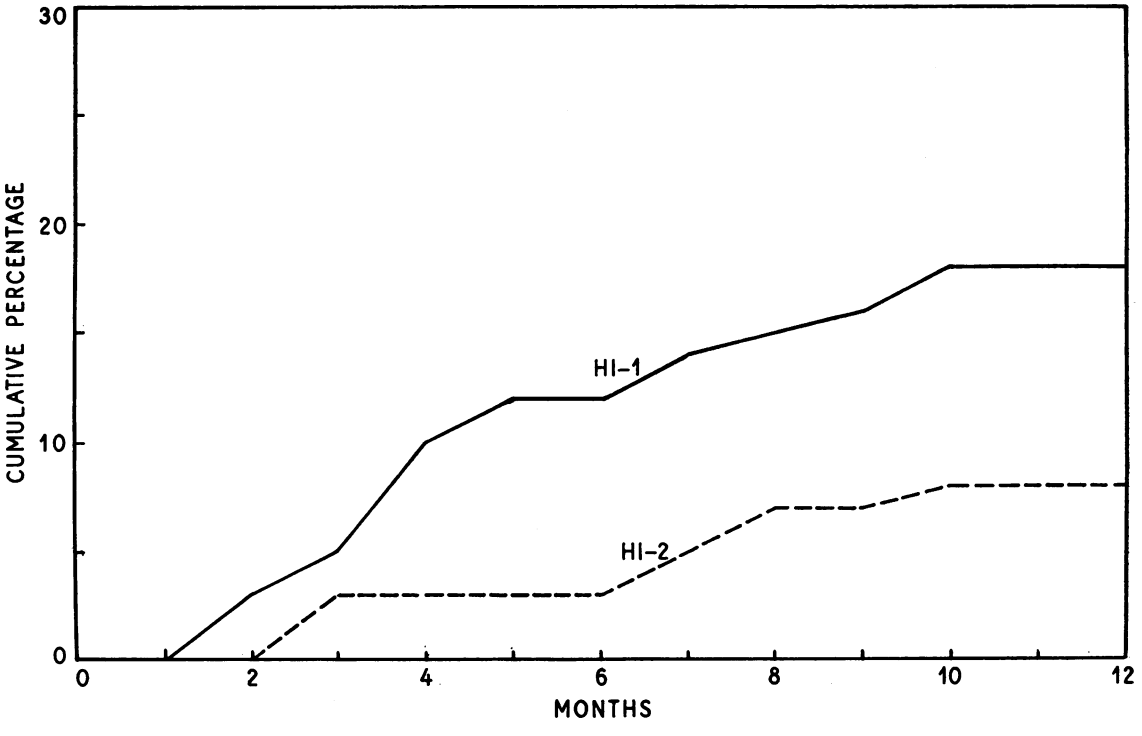
nor was the Centre's nursing staff informed of the possible occurrence of the neuropathy. A physical examination was not performed when a patient first made a spontaneous complaint, unless the symptoms were prominent. If the symptoms persisted, neurological examinations were performed, the frequency depending on the severity of the symptoms. If any physical sign of peripheral neuritis was obtained, the patient was referred to an independent assessor, who was unaware of the patient's chemotherapeutic regimen. Of the 20 cases who form the subject of this report, the diagnosis was confirmed by an independent assessor in 18. The other two patients developed peripheral neuritis early in the study before the procedure of examination by an independent assessor had been established. With increasing experience of the symptoms and signs presented by isoniazid peripheral neuritis, there was a tendency for cases to be referred earlier for an independent assessment. Dr K. S. Sanjivi and Dr C. E. Klontz acted as the independent assessors.

INCIDENCE AND ONSET

One (1%) of 96 PH, none of 94 H, 13 (18%) of 74 HI-1 and six (8%) of 74 HI-2 patients developed peripheral neuritis in 12 months. (An account of the PH patient is given separately on page 592.) The cumulative incidence month by month for the HI-1 and HI-2 series is shown in Table 2 and in the figure overleaf. The month in which a patient first made a spontaneous complaint has been regarded as the month of onset even if the physical signs did not develop until later. The difference in the cumulative incidence of peripheral neuritis between the two series did not attain statistical significance in any month of treatment. The time of onset lay between the second and the tenth month. Nine of 13 patients in the HI-1 series compared with two of six in the HI-2 series first presented symptoms in the first six months of treatment.

Seven HI-1 and 14 HI-2 patients failed to complete 12 months on the allocated regimens either because they had shown radiographic deterioration and their treatment had been changed, or because they had discharged themselves against medical advice, or because they had died. The incidence of the neuropathy in 12 months among the remaining patients was 13 (19%) of 67 HI-1 patients and six (10%) of 60 HI-2 patients. It will be appreciated that the figures based on all the patients allocated to a regimen

CUMULATIVE PERCENTAGES OF PATIENTS IN THE HI-1 AND HI-2 SERIES WHO DEVELOPED PERIPHERAL NEURITIS DURING THE 12 MONTHS



represent an underestimate and the figures based on only those who completed 12 months of isoniazid therapy an overestimate of the true incidence of peripheral neuritis.

CLINICAL FEATURES

The clinical features of the peripheral neuritis in the HI-1 and HI-2 series were similar. The first symptoms were always paraesthesiae, confined to the feet in some patients but also involving the hands in others. The symptoms consisted of one or more of the following: burning sensation, pricking pain, feeling of numbness or tingling. Three patients also complained of weakness of the hands; two were unable to button their shirts and the third, an artist, had difficulty in holding his brush.

Physical signs

Some of the more important physical signs elicited in the 19 patients were:

Motor signs. Muscular weakness of the limbs (five patients). This involved the feet in all five patients and the hands in three of them.

Reflexes :

(*a*) Loss of ankle jerks (14 patients).

(*b*) Loss of knee jerks (three patients).

Sensory signs :

(*a*) Loss of light touch (eight patients). This was confined to the feet in three patients; it also involved the lower third of the legs in one patient, the lower half in three patients and the lower two-thirds in one patient. The last-mentioned patient also had anaesthesia over the right side of the face and over the right shoulder and scapular region.

(*b*) Loss of pain sensation (four patients). The area of analgesia involved both feet in two of the patients, extended to the middle of the legs in one and rather higher in the fourth.

(*c*) Loss of position sense in the toes (seven patients).

(*d*) Loss of vibration sense (16 patients). The loss of this modality occurred in the toes in all 16 patients and extended to the ankles in nine of them.

(*e*) Tenderness of the calf muscles (five patients).

Course

The usual course was a slow progression of the symptoms and a gradual spread of physical signs proximally. Two cases, however, presented an acute onset and a rapid progression. Usually, the first signs elicited were loss of vibration sense in the toes and loss of ankle jerks, followed by anaesthesia and loss of position sense. The more severe cases developed loss of knee jerks and muscular weakness, but none showed any severe motor disability such as foot drop.

Other features

One patient (HI-1), in whom the symptoms were rapidly progressive, complained of a severe burning sensation in the feet, which exhibited excessive sweating and extreme flushing. These manifestations were worse at night and prevented sleep. The symptomatology in this case was very similar to that encountered by Money (1959) in three of 16 patients with isoniazid peripheral neuritis, and which he terms "vasculo-neuropathy". Another patient (HI-1) exhibited signs of mental disturbance coincident with the onset of symptoms of peripheral neuritis. He was extremely apprehensive and had premonitions of death. One patient (HI-1) also had other signs of vitamin B deficiency—namely, glossitis and angular stomatitis.

TREATMENT AND RESPONSE

Treatment

1. Nine cases, encountered early in the study, were treated with pyridoxine. In eight of these the isoniazid was stopped and pyridoxine was given orally in a dose of 200 mg daily. It was also given intramuscularly for the first three months, as 300 mg in one injection daily for the first two weeks, then 300 mg twice a week for six weeks, and in the third month 300 mg once a week. The remaining case continued to receive the high dosage of isoniazid and was given pyridoxine orally, in a dose of 120 mg daily, for two months only.

2. Seven cases, encountered later in the study, were treated with a vitamin B complex preparation, two tablets, three times a day. (The stated formula per tablet was: thiamine, 10 mg; riboflavine, 5 mg; pyridoxine, 1 mg; niacinamide, 50 mg; panthenol, 3 mg; cyanocobalamine, 1 μg. In order to ensure that each tablet contained these minimum quantities until their date of expiry, extra active principle was added as a routine by the manufacturers—namely, 33% more of thiamine, 10% of riboflavine, 10% of pyridoxine, 10% of panthenol and 50% of cyanocobalamine.) Four [1] of the seven patients continued on the high dosage of isoniazid and in one isoniazid was stopped. The remaining two patients were on a low dosage of isoniazid when treatment with vitamin B complex was commenced in the second year (see page 588), although their initial symptoms of peripheral neuritis occurred in the first year of chemotherapy.

3. Three patients with very mild peripheral neuritis did not receive any specific treatment for it.

Response

The response of the patients to the above regimens has been as follows:

1. The eight patients treated with pyridoxine, with the discontinuation of isoniazid, have received it for almost a year at the time of writing. They have shown very slow but definite amelioration of the symptoms and signs. All three patients in this group who had developed muscular weakness in the limbs have gradually regained power. The paraesthesiae have disappeared completely in one and improved in seven. The ankle jerks are still absent in all of them, but one of three patients has regained the knee jerks. Of the five patients with anaesthesia, three have regained sensation and in two the area affected has diminished. All the three patients who had lost sensation to pain in the lower limbs have regained this modality and three of four patients have regained position sense. All eight patients had lost vibration sense at the ankles and toes; six have regained this modality at the ankles but none so far has regained it in the toes. The patient who was mentally disturbed became normal within three months. Although these eight patients are left with some neurological signs, all except one are leading a normal life and are in full-time employment—four as housewives, one as a mill worker, one as a salesman and one as a car

[1] Two of these four patients received yeast tablets initially for some weeks instead of vitamin B complex.

driver. The exception is a patient who is in sanatorium because his pulmonary tuberculosis needs further treatment. The patient who continued on the high dosage of isoniazid and received pyridoxine lost his symptoms.

2. Of the patients who were treated with vitamin B complex, the four who continued on the high dosage of isoniazid have received the vitamin preparation for a period of nine months, seven months, four months and three months, respectively, at the time of writing. They had developed only limited physical signs when treatment for the neuropathy was commenced. There was no progression of the symptoms and signs even though they continued to receive the high dosage of isoniazid. Two of them are now completely asymptomatic and the other two have improved. The patient who received vitamin B complex with the discontinuation of isoniazid therapy became completely asymptomatic in two months.

The two patients who first received vitamin B complex in the second year were then on isoniazid in a reduced dosage—namely, 4.2 mg/kg and 4.4 mg/kg daily, respectively. They have received vitamin B complex for seven months and five months, respectively, at the time of writing. Both have improved and are leading a normal life, one of them being completely asymptomatic.

3. The symptoms in the three patients with very mild neuritis, who continued on high isoniazid dosage but received no treatment for this complication, disappeared spontaneously, although the minimal physical signs still remain.

NOTES ON A TYPICAL CASE OF PERIPHERAL NEURITIS

A male aged 47 years commenced the HI-1 regimen on 16.11.58. He had received on the average 8.4 mg/kg body-weight of the drug daily when he first complained of a feeling of numbness in the hands and feet on 19.3.59. These symptoms persisted and a neurological examination on 26.3.59 revealed loss of both ankle jerks and of vibration sense in the toes. There was a gradual spread of the paraesthesiae proximally (without the development of fresh physical signs) and treatment with yeast was begun on 23.4.59 while he continued to receive isoniazid. From 7.5.59 onwards he received vitamin B complex (two tablets three times a day) instead of yeast. After seven months of treatment the symptoms have improved but the signs still persist. He has returned to full-time employment as a workshop instructor. This patient received isoniazid for the full 12 months, even though the peripheral neuritis presented in the fifth month of treatment.

THE PH PATIENT WHO DEVELOPED PERIPHERAL NEURITIS

One of the 96 patients in the PH series developed peripheral neuritis. This was a woman aged 45 years who had received isoniazid in an average dose of 4.9 mg/kg body-weight daily when she first complained of paraesthesiae in the seventh month of treatment. By the thirteenth month she had developed muscular weakness of the limbs, tenderness of the calf muscles, loss of ankle jerks and loss of vibration and position sense in the toes, even though treatment had been stopped at one year as the disease was quiescent. At the time of writing she has received vitamin B complex for two months and her symptoms have improved. She is leading a normal life as a housewife.

AGE, SEX AND ECONOMIC STATUS

Combining the HI-1 and HI-2 series there was a greater incidence of peripheral neuritis in the older age-groups—namely, eight (17%) of the 47 patients aged 35 years or more compared with 11 (11%) of 101 patients under 35 years of age; the difference does not attain statistical significance. Of the 96 males, 12 (13%) developed peripheral neuritis compared with seven (13%) of 52 females.

The patients in this study came from a poor section of the community in Madras city (Tuberculosis Chemotherapy Centre, 1960 [1]) but there was no association between the family incomes of the patients and the development of peripheral neuritis.

TOTAL DAILY DOSAGE

The average daily dosage of isoniazid prescribed for each patient up to the time of the first spontaneous complaint attributable to peripheral neuritis was calculated. This was found to be 8.6 mg/kg body-weight daily for the 13 HI-1 patients and 8.7 mg/kg body-weight daily for the six HI-2 patients. Similar calculations were made for the whole 12 months or until isoniazid therapy was changed, if this was earlier than 12 months, for the 61 HI-1 patients and the 68 HI-2 patients who did not develop peripheral neuritis. The mean value for

[1] See article on page 535 of this issue.

the control HI-1 group was 8.7 mg/kg and for the HI-2 group was 8.6 mg/kg body-weight daily. In both series the isoniazid dosage for the patients who developed peripheral neuritis and for those who did not was, therefore, closely similar.

SERUM ISONIAZID ASSAYS

Serum isoniazid estimations were performed on 143 of the 148 patients on the HI-1 and HI-2 regimens. All chemotherapy was stopped for 48 hours before the day of the test. Each patient received an intramuscular dose of isoniazid of 3 mg/kg body-weight and the concentration of free isoniazid in the serum four-and-a-half hours later was estimated by microbiological assay. The full details of this method will be reported elsewhere (Gangadharam et al., to be published).

Table 3 gives the distributions of the serum isoniazid levels of the patients who developed peripheral neuritis and of those who did not in the HI-1 and HI-2 series. The mean serum isoniazid level was 0.53 μg/ml for the HI-1 patients who did not develop peripheral neuritis as compared with 0.99 μg/ml for those who developed the neuropathy. The corresponding figures in the HI-2 series were 0.62 μg/ml and 0.96 μg/ml, respectively. (The serum isoniazid level of the patient who developed peripheral neuritis in the PH series was 0.82 μg/ml).

TABLE 3
DISTRIBUTION OF SERUM ISONIAZID LEVELS

Serum isoniazid levels (μg/ml)	HI-1		HI-2	
	patients without peripheral neuritis	patients with peripheral neuritis	patients without peripheral neuritis	patients with peripheral neuritis
Rapid inactivation of isoniazid				
<0.18	4	0	1	0
0.18-	5	0	5	0
0.25-	12	0	13	0
0.35-	6	1	4	0
0.49-	3	1	5	0
Slow inactivation of isoniazid				
0.60-	2	1	2	1
0.70-	4	2	6	0
0.99-	14	6	23	5
1.39-	3	2	5	0
1.97-	5	0	2	0
⩾2.78	0	0	0	0
Total patients	58	13	66	6
Mean (μg/ml)	0.53	0.99	0.62	0.96

The patients with serum isoniazid levels of 0.60 μg/ml or higher have been regarded as slow inactivators of isoniazid and those with levels below 0.60 μg/ml as rapid inactivators (Gangadharam et al., to be published). Eleven (28%) of 39 slow inactivators compared with two (6%) of 32 rapid inactivators developed peripheral neuritis in the HI-1 series. This difference attains statistical significance ($P<0.05$). In the HI-2 series, six (14%) of 44 slow inactivators and none of 28 rapid inactivators developed the neuropathy, a non-significant difference ($P>0.10$). Combining the HI-1 and HI-2 series, the difference between the incidence of peripheral neuritis in the slow and in the rapid inactivators of isoniazid attains statistical significance ($P<0.01$).

There was no association between the serum isoniazid level and the month of treatment in which peripheral neuritis developed.

Although the test dose of isoniazid was proportional to the body-weight, the lighter patients were found to have lower serum levels than the heavier ones in this investigation (Gangadharam et al., to be published) in agreement with the findings of Evans (1959). However, an analysis (not tabulated here) did not reveal any association between the weights before or during treatment and the development of peripheral neuritis.

REGULARITY IN SELF-ADMINISTRATION OF ISONIAZID

In this study one of the methods used to determine whether patients were taking the isoniazid tablets regularly was to test the urine for the presence of the drug (Gangadharam et al., 1958; Tuberculosis Chemotherapy Centre, 1960 [1]) at the routine weekly visits of the patients to the Centre. Since the results of this test might differ among slow and rapid inactivators and since 17 of the 19 patients who developed peripheral neuritis were slow inactivators of isoniazid, an analysis was undertaken to see whether there was any association between the regularity of the self-administration of isoniazid and the development of the neuropathy among the slow inactivators. Table 4 relates the percentage of urine

[1] See article on page 535 of this issue.

TABLE 4

INCIDENCE OF PERIPHERAL NEURITIS RELATED TO THE PROPORTION OF NEGATIVE TEST RESULTS ON URINE SPECIMENS COLLECTED AT ROUTINE VISITS TO THE CENTRE AMONG THE PATIENTS CLASSIFIED AS SLOW INACTIVATORS OF ISONIAZID

Percentage of urine tests with negative results	HI-1		HI-2	
	patients without peripheral neuritis	patients with peripheral neuritis	patients without peripheral neuritis	patients with peripheral neuritis
0	7	8	18	5
1-4	12	1	13	1
5-9	6	2	2	0
10-14	2	0	0	0
15-19	0	0	2	0
20 or more	1	0	3	0
Total	28	11	38	6

tests with negative results to the frequency of the development of peripheral neuritis among the *slow inactivators* in the HI-1 and HI-2 series. Combining the two series, 13 (34%) of 38 patients, *all* of whose urine tests were positive, developed the neuropathy compared with four (9%) of 45 patients whose urine specimens were negative on one or more occasions. This difference is statistically significant (P=0.01). Considering the two series separately, the corresponding difference attains statistical significance in the HI-1 series (P=0.01) but does not do so in the HI-2 series.

The 11 slow inactivators in the HI-1 series who developed peripheral neuritis had a total of 235 urine tests at their routine visits to the Centre during the year (the tests performed after the onset of symptoms not being considered) of which three (1.3%) were negative. In contrast, the 28 slow inactivators in the HI-1 series who did not develop this complication had 1361 such tests during the year of which 54 (4.0%) were negative. This difference just attains statistical significance (P=0.05). Correspondingly, one (0.7%) of 151 tests was negative in the six HI-2 patients who developed the neuropathy compared with 83 (4.8%) of 1715 tests in the 38 slow inactivators in the HI-2 series who did not develop this complication. This difference is also statistically significant (P=0.01). There was, therefore, evidence in this study that the patients who developed peripheral neuritis had taken their isoniazid tablets more regularly than those who did not develop the complication.

SEVERITY OF THE TUBERCULOSIS

Since peripheral neuritis may develop in patients with tuberculosis in the absence of specific treatment (Dixon, Roberts & Tyrrell, 1956), an analysis was undertaken to see whether peripheral neuritis in this study was associated with initially extensive pulmonary disease. Of the 55 patients in the HI-1 and HI-2 series who had no cavitation or slight cavitation, six (11%) developed peripheral neuritis compared with 13 (14%) of the 93 patients with moderate or extensive cavitation. The disease involved one to three lung zones in 58 patients and of these seven (12%) developed the neuropathy compared with 12 (13%) of 90 patients with four or more zones involved. There was, therefore, hardly any suggestion of an association of peripheral neuritis with the initial extent of disease.

DISCUSSION

Isoniazid has been very widely used for the past eight years in the treatment of pulmonary tuberculosis. In low dosage, presumed side-effects such as drowsiness, hyper-reflexia, tremors, constipation, flushing and skin disorders are usually mild and transient (Great Britain, Medical Research Council, 1952). With larger dosages the more serious com-

plication of peripheral neuritis is encountered. Biehl & Nimitz (1954) reported a definite relation between the dosage of isoniazid and the incidence of peripheral neuritis, which rose from less than 10% for a dosage of 6 mg/kg to 10 mg/kg body-weight daily to 44% when the dosage was increased to 16 mg/kg to 24 mg/kg body-weight daily.

In the present study 19 cases of peripheral neuritis with definite physical signs occurred in a series of 148 tuberculous patients on a poor diet who received isoniazid in a range of 7.8 mg/kg to 9.6 mg/kg body-weight daily, in either one or two doses. For the patients receiving one dose a day the incidence during the 12 months was 18% and for those receiving two doses a day it was 8%. However, the clinical response of the tuberculosis to treatment was superior among the former group of patients (Tuberculosis Chemotherapy Centre, 1960 [1]). The difference in the incidence of the peripheral neuritis between the two dosage schedules does not attain statistical significance and may therefore be a chance finding; on the other hand it may be related to the higher peak level of isoniazid in the serum which is associated with the single dose (Gangadharam et al., to be published); there is no evidence that the patients receiving one dose of isoniazid a day took their drug more regularly than those on two doses a day (Tuberculosis Chemotherapy Centre, 1960 [1]). In the United States Public Health Service (1954) series, where a dosage of 10 mg/kg of the drug was used, the occurrence of peripheral neuritis in a 12- to 20-week period was 3.4%. In the series reported here, the incidence in five months was 12% for patients receiving the high dosage of isoniazid in one dose daily and 3% for those receiving it in two doses daily, the latter rate being similar to that observed in the American series. We encountered only one case of peripheral neuritis during a year of chemotherapy among 190 patients on isoniazid 3.9 mg/kg to 5.5 mg/kg body-weight daily either alone or in combination with PAS. Money (1959), however, reported 16 cases (20%) of the neuropathy among 84 malnourished patients in East Africa on isoniazid 4 mg/kg to 6 mg/kg body-weight daily in combination with PAS during a period of six to 12 months.

Not only was peripheral neuritis more frequent in the patients receiving the isoniazid in one dose a day but the onset was rather earlier than for those on two doses a day; thus, nine out of 13 of the former patients presented within the first six months compared with two out of six of the latter. Biehl & Nimitz (1954) reported that there was a tendency for the neuritis to occur earlier with increasing dosages of isoniazid. The United States Public Health Service (1954) reported symptoms between the 42nd and 95th day of treatment at a dosage of 10 mg/kg daily, with an average of 65 days, during an observation period of 12 to 20 weeks. The symptoms and signs of the peripheral neuritis in the present series were mainly sensory in nature and were usually characterized by slow progression, in keeping with the reports of Gammon, Burge & King (1953) and Biehl & Nimitz (1954). Gammon, Burge & King (1953) state that the symptomatology in their cases closely resembled arsenical neuropathy. Only one patient in our series had evidence of a mental disturbance, a complication reported by several authors (Wiedorn & Ervin, 1954; Wood, 1955; Money, 1959).

There is evidence that isoniazid peripheral neuritis is associated with a pyridoxine deficiency state. Thus, pyridoxine has been used successfully both in the prophylaxis (Biehl & Vilter, 1954; Tchertkoff et al., 1956) and in the treatment of the complication (Oestreicher, Dressler & Middlebrook, 1954; Tchertkoff et al., 1956). Also, Biehl & Vilter (1954) found an increase in the excretion of vitamin B_6 in the urine with isoniazid treatment and Vilter et al. (1953) reported the occurrence of sensory neuritis among patients treated with desoxypyridoxine, an antagonist of pyridoxine. In eight of the cases reported here the isoniazid was stopped and large doses of pyridoxine were administered. All the patients improved, but since the discontinuation of isoniazid in itself results in improvement (Gammon, Burge & King, 1953; Katz et al., 1954) it is not possible to evaluate the part played by the pyridoxine in the amelioration of the peripheral neuritis.

Wood (1955), Turner (personal communication, 1958) and Money (1959) have reported the efficacy of vitamin B complex in the treatment of isoniazid peripheral neuritis. Money (1959) treated 16 cases with yeast tablets, while the isoniazid was continued. Thirteen patients responded to this treatment and the remaining three required parenteral vitamin B complex. Turner (personal communication, 1958) treated five cases who developed severe peripheral neuritis, when receiving 1000 mg of isoniazid daily, with a vitamin B complex preparation which did not contain pyridoxine. Although the large dosage of isoniazid was continued, the physical signs disappeared within a few weeks. In the present series,

[1] See article on page 535 of this issue.

seven cases of peripheral neuritis were treated orally with a vitamin B complex preparation, four of them continuing on the high dosage of isoniazid and two on a reduced dosage, while the drug was discontinued in the seventh case. All seven improved even though the daily dosage of pyridoxine was only 6 mg. There was therefore evidence that the vitamin B complex used in this study exerted a beneficial effect even when isoniazid was continued, although the response in our patients was less dramatic than that in Turner's cases. It is difficult to say which of the components of vitamin B complex was responsible for the improvement of the neuritis. In the preparation used, the pyridoxine content was low. Other factors possibly responsible for the improvement are thiamine and nicotinic acid. Lack of thiamine is a well-known cause of peripheral neuritis and it has been suggested that deficiency of nicotinic acid may be responsible for the isoniazid neuropathy (Jones & Jones, 1953).

It has been shown in this study that the mean serum level of free isoniazid was higher in the patients who developed peripheral neuritis than in those who did not develop this complication on the same high dosage of isoniazid and that the difference between the incidence of peripheral neuritis in the slow and in the rapid inactivators of isoniazid was statistically significant. Our results therefore confirm the findings of Biehl & Skavlem (1953) and are in keeping with the urinary findings of Hughes et al. (1954), who reported a higher incidence of peripheral neuritis in those who inactivated isoniazid (by acetylation) to a lesser degree. The dosage of isoniazid is a factor of importance in the development of peripheral neuritis, for only one case was encountered among 190 patients on isoniazid 3.9 mg/kg to 5.5 mg/kg body-weight daily, either alone or in combination with PAS, compared with 19 cases among 148 patients treated with isoniazid 7.8 mg/kg to 9.6 mg/kg body-weight daily. However, within the higher dosage range, there was no evidence that the patients who developed peripheral neuritis had a higher mean daily dosage than those who did not, the factor of importance being the rate of isoniazid inactivation.

It may be concluded that since isoniazid given in a dosage of 7.8 mg/kg to 9.6 mg/kg body-weight daily produced a noteworthy incidence of peripheral neuritis, especially when the drug was given in one dose daily, dosage schedules of this order are unsuitable for wide application in patients with a poor diet (as in the community under study), unless measures are taken to prevent the development of the neuropathy. Although pyridoxine is effective in the prophylaxis of this complication (Biehl & Vilter, 1954), its use is limited in under-developed countries because of its high cost. In this study there was an indication that the cheaper vitamin B complex may have a beneficial effect on peripheral neuritis even when patients continue to receive a high dosage of isoniazid. The efficacy of vitamin B complex in the *prevention* of the neuropathy is being investigated and will be the subject of a further report.

SUMMARY

1. Twenty cases of peripheral neuritis due to isoniazid were encountered in a chemotherapy study in which 338 patients with previously untreated pulmonary tuberculosis were allocated at random to four treatment regimens for a year. These regimens were:

Isoniazid in low dosage (3.9 mg/kg to 5.5 mg/kg body-weight daily), either

(*a*) in combination with PAS, in two doses daily (PH regimen), or

(*b*) alone, in two doses daily (H regimen).

Isoniazid in high dosage (7.8 mg/kg to 9.6 mg/kg body-weight daily), given alone either

(*a*) in one dose daily (HI-1 regimen), or

(*b*) in two doses daily (HI-2 regimen).

2. One (1%) case of peripheral neuritis occurred among the 96 PH patients, none among the 94 H patients, 13 (18%) among the 74 HI-1 patients and six (8%) among the 74 HI-2 patients.

3. The time of onset of symptoms of peripheral neuritis ranged from the second month to the tenth month of treatment, and was earlier in the HI-1 patients than in the HI-2 patients.

4. The symptoms and signs were mainly sensory in nature (with loss of reflexes) and there was slow progression. Five patients also developed muscular weakness. One case (HI-1) with peripheral neuritis also exhibited signs of mental disturbance.

5. Nine cases were treated with pyridoxine; in eight of them the isoniazid was discontinued. Gradual improvement was noted.

6. Seven cases were treated with vitamin B complex, six continuing on isoniazid, the dosage being lowered in two. All seven cases improved.

7. Three cases with very mild peripheral neuritis improved spontaneously without any specific treatment and without discontinuing the isoniazid.

8. The only patient who developed peripheral neuritis in the PH series improved with discontinuation of the chemotherapy and treatment with vitamin B complex.

9. Serum isoniazid assays were performed in 143 of the 148 patients allocated to the HI-1 and HI-2 regimens. Considering both series together, the 19 patients with peripheral neuritis had a higher mean serum level of isoniazid when compared with that of the 124 patients who did not develop this complication. The difference between the incidence of peripheral neuritis in the slow and in the rapid inactivators of isoniazid attained statistical significance.

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RÉSUMÉ

On sait que la névrite périphérique peut être une complication du traitement de la tuberculose par l'isoniazide (INH). Elle est rare si le médicament est administré à petites doses. Mais récemment des cas proportionnellement nombreux sont survenus en Afrique orientale, parmi des tuberculeux souffrant de malnutrition, soumis à une cure d'INH d'une année et recevant des doses relativement faibles de ce médicament (4-6 mg/kg de poids corporel).

Cette étude est consacrée à l'examen de 20 cas de névrite périphérique observés à Madras, Inde, parmi 338 malades souffrant de malnutrition, au cours d'une cure d'INH, comportant pour les uns 3,9-5,5 mg/kg et pour les autres des doses plus fortes, de 7,8-9,6 mg/kg. 19 cas sur ces 20 se produisirent dans le groupe recevant la dose la plus élevée. On trouva chez eux un taux sanguin d'INH libre supérieur à celui des sujets ne présentant pas de complication. La névrite est apparue du 2e au 10e mois de traitement. Les symptômes étaient essentiellement sensoriels, avec perte des réflexes, et progression lente. Cinq malades présentèrent de la faiblesse musculaire, et un des troubles mentaux. Les cas les plus bénins guérirent spontanément, sans même que l'on interrompe le traitement. La pyridoxine ou le complexe vitaminique B furent efficaces dans les autres cas. Les auteurs estiment qu'une posologie quotidienne de 7,8-9,6 mg/kg est excessive pour la thérapie de masse, chez des populations mal nourries, à moins que l'on ne prévienne les complications par l'administration du complexe vitaminique B, moins coûteux que la pyridoxine.

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