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THE EFFECTS OF ISONIAZID ON PATIENTS WITH MULTIPLE SCLEROSIS

Preliminary Report

JOHN F. KURTZKE AND LOUIS BERLIN

(Received for publication August 16, 1954)

INTRODUCTION

Multiple sclerosis is a common disease of unknown etiology, variable course, and undefinable prognosis for the individual (1). The evaluation of therapy in this disease is fraught with many difficulties because attacks or exacerbations may last for varying periods, and the completeness of remission is unpredictable. With due recognition of these many difficulties, it is believed appropriate at this time to report certain observations on the course of multiple sclerosis during the administration of isoniazid. The observations were made on a group of patients, hospitalized for multiple sclerosis in the past eighteen months, who were given isoniazid. This group of patients was compared with a similar group of persons hospitalized for multiple sclerosis in the last ten years. Individuals of both groups were classified on admission and discharge in accordance with a rating scale devised by the writers. The results of this comparison are presented to show the apparent influence of isoniazid on manifestations of multiple sclerosis.

As an agent for study in multiple sclerosis, isoniazid was suggested accidentally when a chronically ill patient, who had received isoniazid for another purpose, was noted to speak more distinctly. The drug was then tried sporadically in various dosages on a few other patients and, when there seemed to be some effect, a formal program was instituted.

PLAN OF INVESTIGATION

In the present study, the patients given isoniazid\(^2\) were compared with a group of 175 patients with multiple sclerosis who had been admitted to this hospital from 1944 to 1953, inclusive. Patients admitted between 1944 and 1950 were classified on the basis of the hospital records, and all patients admitted after 1950 were evaluated by one or both of the writers on admission and discharge, in addition to the evaluations by the patients' own staff physicians. The percentage of patients in the comparison group who improved during these years of personal observation by the writers (31 per cent) was the same as the percentage of previous patients (34 per cent) whose improvement had been recorded in the hospital records.

An additional 45 patients with multiple sclerosis were not included in the comparison group because the status of their multiple sclerosis had not changed within the two-year period preceding admission to the hospital. Of this group,

\(^1\) From the Neurology Section, Veterans Administration Hospital, Bronx, New York.

\(^2\) Supplied as Rimifon by Hoffman La Roche, Inc., Nutley, New Jersey.
none improved and 5 became worse. (In the writers’ experience, two years represents the maximal period a particular clinical manifestation of multiple sclerosis may persist and there yet be some possibility of significant spontaneous improvement).

Isoniazid, 300 mg. daily in divided doses, was given to patients with multiple sclerosis throughout their hospitalization. “Maintenance” therapy of 200 mg. per day has been given to a number of these patients after discharge from the hospital. Most of the patients were unaware of their diagnosis until discharge from the hospital. None were told prior to discharge that they were receiving any special medication. Suggestion was minimal. Therapy otherwise was in accordance with previous standards at this hospital, including physical medicine and rehabilitation procedures; the only exception was that no other medication was given. Even supplementary vitamins were not given to the patients who received isoniazid.

The duration of hospitalization was determined by the progress of the patient’s illness. A period of two to four weeks of stabilization of the illness was required before a patient was discharged as having attained maximal hospital benefit. As this is not a chronic-disease hospital, no exceedingly prolonged periods of hospitalization were encountered in any of the groups.

Classification of Status

In order to evaluate the course in this protracted disease, the classification or status of an individual patient was made in accordance with a scale devised by the writers in such a way that, first, it would be applicable to all patients and, second, that it would represent the sum of neurologic dysfunction.

The usual course of multiple sclerosis results in greater incapacity of the legs than of the arms. The usual involvement of head segment functions, in the absence of pyramidal disorder, is a minor disability. The scale used, with categories from 0 to 10, is one of a progression (not necessarily arithmetical) with different levels of functional ability in each category:

0 - normal neurologic examination
1 - minimal signs, no symptoms or incapacity (extensor plantar response, minimal finger-to-nose ataxia, diminished vibration sense)
2 - minimal symptoms (slight weakness or stiffness, mild disturbance of gait, awkwardness, mild visuomotor disturbance)
3 - moderate symptoms (monoparesis, mild hemiparesis, moderate ataxia, disturbing sensory loss, prominent urinary or eye symptoms, or combinations of lesser dysfunctions)
4 - relatively severe symptoms not preventing ability to work or carry on normal activities of living, excluding sexual functions
5 - symptoms severe enough to preclude working, with maximal motor function permitting walking unaided up to several blocks
6 - assistance required for walking (canes, crutches, braces)
7 - restricted to wheelchair (able to maneuver chair and enter and leave chair without aid)
8 - restricted to bed but with effective use of arms
9 - totally helpless bed-patient
10 - death due to multiple sclerosis
Upon the basis of the records of 300 cases of multiple sclerosis and the reports in the literature, the occurrence of significant dysfunction which is not suitably assignable in this classification is extremely rare. It may be seen that "in incapacitation" (inability to walk unaided) includes categories from 6 on. While this grouping is not perfect, it provides a means of evaluating all of the 250 cases.

Improvement, as defined in the present report, means a gain of at least one category between admission to and discharge from the hospital.

Composition of the Two Groups

The isoniazid group consisted of 30 white male veterans. The comparison group contained but one female (0.6 per cent) and 6 Negroes (3.5 per cent); the remainder were white male veterans.

The two groups included only those patients whose illness was characterized by an exacerbation within two years of admission except for one patient (No. 29) in the isoniazid group, whose present episode was of three years' duration.

The two groups were essentially identical in age at the time of admission, age at onset of disease, and duration of the present exacerbation before admission to the hospital. There was no significant difference between the groups with respect to length of time in the hospital and total duration of illness from onset of first symptoms. The mean age on admission to the hospital was 32.1 years for the comparison group and 33.2 years for the isoniazid group. The mean age at the time of onset of the multiple sclerosis was 27.6 years (comparison) and 27.2 years (isoniazid). The mean duration of the present exacerbation or episode to admission was 182 days (comparison) and 174 days (isoniazid), respectively. The mean total duration of illness in the comparison group was fifty-one months, with a mean of seventy-one months for the isoniazid patients. The mean length of hospital stay was one hundred and four days (comparison) and seventy-nine days (isoniazid).

Observations

Course of illness in comparison group: In the comparison group of 175 patients, improvement (or remission) occurred in 58 patients (33 per cent), with an average gain of two categories between admission and discharge. The comparison group also contained 88 patients (50 per cent) whose status remained the same and 29 (17 per cent) whose illness became worse (with an average loss of two categories) during hospitalization.

On admission to the hospital there were 21 members (12 per cent) of the comparison group with minimal or no symptoms (category 2, or less), and on discharge 48 patients (27 per cent) were of such status. Fifty-eight patients, or one-third of the comparison group, were in category 6 or higher, both on admission and on discharge. In categories 3 through 5 (moderate impairment), there were 96 patients (55 per cent) on admission and 69 patients (39 per cent) on discharge.

Of the 21 patients admitted in category 2 or less, 6 improved and one worsened while in the hospital. Of the 96 patients admitted in categories 3 through 5, 34
(35 per cent) improved and 14 (15 per cent) worsened; of the 58 patients in category 6 or higher on admission, 18 (31 per cent) improved and 14 (24 per cent) became worse during hospitalization. The remainder in each subgroup experienced no change in status between admission and discharge.

Course of illness in isoniazid group: In the group of 30 patients who received isoniazid, 27 (90 per cent) showed improvement in the status of their multiple sclerosis by an average of three categories. In 2 patients (7 per cent), the disease remained unchanged and, in one, it became worse. The one patient whose disease worsened was a man (patient No. 29) admitted with disease of category 9 who, without change in neurologic status, died of bronchopneumonia and hemorrhagic cystitis. The outcome of this patient is classified as a failure even though his present episode was a progressive one of three years' duration. Of the other 2 patients who did not improve (patients Nos. 17 and 30), one had had unchanged manifestations of multiple sclerosis for almost two years before admission; the other had first experienced his present episode only six months previous to admission.

Only one member of the isoniazid group had minimal symptoms at the time of admission to the hospital, whereas 15 of the 30 isoniazid patients had minimal or no symptoms when discharged from the hospital.

Inability to walk unaided (category 6 and higher) was present in 19 of the 30 isoniazid patients on admission and was still present in 10 at the time of discharge.

Moderate involvement (categories 3 through 5) was present on admission in 10 patients and was still present in 5 patients on discharge.

![Diagram](image-url)

Fig. 1. Comparison group "A". Course in hospital of patients with multiple sclerosis whose present episode is two years or less.
Fig. 2. Isoniazid group. Course in hospital of patients with multiple sclerosis.

Figs. 1 and 2. These figures graphically present the admission and discharge status of each patient with multiple sclerosis. The abscissa represents the discharge status in accordance with the categories of involvement devised by the writers and presented in the body of the paper. The ordinate similarly represents admission status. The larger the status number, the more severe the impairment. The boxes bisected by the diagonal line represent no change in status between admission and discharge. In figure 1, each patient is represented by a dot; in figure 2, each patient is depicted as a small square. The localization of each dot or square depends on admission and discharge status. For example, in figure 2, there are 3 squares in the box which is along "6" on the ordinate (admission) and "3" on the abscissa (discharge); this represents three patients admitted as category 6 and discharged as category 3, i.e., these patients gained 3 categories in the hospital.

More patients who received isoniazid improved in each sub-class than did those in the equivalent sub-class of the comparison group. The percentage of

Statistical methods were used to compare the percentage of patients who improved in the hospital in the comparison group (33 per cent) with the percentage who improved in the isoniazid group (90 per cent). The results showed that there was a highly significant difference well beyond the 0.1 per cent level.

Chi-square test using Yate's correction for fourfold contingency tables (with one degree of freedom):

\[ \chi^2 = \frac{(ad - bc)^2 - N}{2N} \]

\[ a = 58 = \text{number of "successes" in comparison group} \]
\[ b = 27 = \text{number of "successes" in isoniazid group} \]
\[ c = 117 = \text{number of "failures" in comparison group} \]
\[ d = 3 = \text{number of "failures" in isoniazid group} \]
\[ N = 205 = a + b + c + d \]
TABLE 1
ISONIAZID IN MULTIPLE SCLEROSIS: SUMMARY OF 30 CASES

<table>
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<th>Days Present Episode</th>
<th>Months Total Duration</th>
<th>Age at Onset</th>
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Improvement or worsening was not markedly different in all three sub-classes (minimal, moderate, and severe) from the percentages for the total group of 175 patients, and the same was true for the isoniazid series of 30 when compared with its own sub-classes.

As noted above by the system of rating used, the isoniazid group was, in general, a more severely ill group than the comparison series at the time of admission to the hospital. Despite this, in the isoniazid group the average gain was three categories in comparison with an average gain of two categories among those who improved in the comparison series. A comparison was made of the discharge distribution among the various categories of the isoniazid group with the discharge distribution of the comparison group. It should be noted that the
latter group was weighted against the isoniazid group in this respect because of the larger admission percentage of less severely involved patients. Nevertheless, the distribution of the isoniazid group at discharge showed a higher proportion of patients with less severe disability, and this difference between the two groups was significant at the 5 per cent level.4

All of the above data are presented graphically in figures 1 and 2 and, in addition, a summary of the pertinent information concerning the 30 patients in the isoniazid group is presented in table 1.

Relation of Isoniazid Administration to Remission or Relapse

The course of the manifestations of illness in 4 of the patients who received isoniazid is of particular interest with respect to the question of an influence of isoniazid on the course of multiple sclerosis. Isoniazid was administered to each of these patients (Nos. 1, 4, 7, and 12) and they promptly showed improvement of their illness. The drug was then stopped and an exacerbation of the illness occurred. Isoniazid was reinstituted and, concomitant with this, improvement again occurred in each of these patients, and in each case resulted in a status superior to that present on admission. Brief case reports of these patients follow:

Case 1. The patient, J. B., 33 years of age, was admitted to the hospital on April 8, 1953, with left sided weakness and numbness for three weeks. Four months and also two years before admission, he had had episodes of paresthesias of the right leg and weakness of both arms and right leg, each lasting several weeks. Examination showed marked scanning of speech, nystagmus, poor convergence, diplopia on left lateral gaze, and skew deviation on inferior gaze. There was marked left hemiparesis, hemihypalgesia, and hemihypesthesia. The cerebrospinal fluid protein was 55 mg. per 100 ml.

Isoniazid (200 mg. daily) was started on April 18; marked improvement in power, sensation, and eye movements followed. The drug was stopped on April 21, with a subsequent exacerbation, so that by April 28 the patient was unable to stand. He had a marked quadriparethesia, ataxia of the arms, decreased position and vibration sense in the legs, and bilateral extensor plantar responses.

Isoniazid (200 mg. daily) was again given from May 8 to 22, with immediate reversal of the course of illness. From May 27 to discharge on August 10, 1953, the patient received isoniazid, 150 mg. daily. By June 19, head functions were normal except for minimal blurring of vision, coordination was normal, gait but slightly ataxic, power was good, sensation

4 Chi square test for twofold distribution (Fisher):

\[ \chi^2 = \sum (A_p - \bar{A})^2 \]

for \( n = 10, \ p = 0.05 \) at \( \chi^2 = 18.31 \)

\( n = \) degrees of freedom = (rows -1) (columns -1) = 10

\( A_p = \) number of isoniazid patients in any row, e.g., 4 in category 0

\( A' = \) number of comparison patients in same row, e.g. 11 in category 0

\( \frac{p'}{A'} = \bar{A}' \)

\( \frac{A'}{N} = 30/205 = 0.146 \)

\( \frac{N} = 30/205 = 0.854 \)

\( N = \) total number of cases

(See figures 1 and 2 for the numbers in each A subgroup.)
normal, reflexes physiologic, and once again he was potent sexually. He remained in this status until the present time, sixteen months after the onset.

Case 4. F. G., a 36-year old man, was admitted to the hospital on October 19, 1953, with progressive dysarthria, ataxia, and stiff legs for two years. Examination revealed unilateral nystagmus and left external rectus palsy. His speech was dysarthric and slightly scanning. There was marked limb ataxia and moderate gait ataxia with pyramidal tract signs in all of the four extremities and weakness of the left foot, with decreased position and vibration in the legs and dysaesthesia of the left hand. The cerebrospinal fluid had a D curve with 39 mg of protein per 100 ml and a gamma globulin of 9.2 mg per 100 ml.

There was no change in the patient's status until October 28, when isoniazid (300 mg. daily) was started. In three days his gait improved. By November 17, the plantar response was normal; and power, gait, sensation, and coordination were normal. The left sixth-nerve palsy persisted. Isoniazid was stopped on November 20 and within three days progressive dysfunction reappeared with mild dysarthria, ataxia of gait and limbs, and fatigue. From December 1, 1953, to discharge on January 6, 1954, isoniazid (300 mg. daily) was again given, with the return of improvement. On discharge there was persistence of the left sixth weakness without diplopia and minimal difficulty in heel-to-toe walking with eyes closed. At present the patient is asymptomatic.

Case 7. F. K., a 31-year old man, was readmitted to the hospital on July 8, 1953, because of multiple sclerosis which had first been noted in 1950. For his third episode he had been admitted for one month in 1952 without change, at which time he had marked ataxia, nystagmus, decreased sensation in the arms, and pyramidal tract signs. Since that time the course of the illness had been generally progressive and for one month before the present admission he had been bedridden. Examination on admission to the hospital showed triplegia with ataxia of the remaining limb, scanning speech, nystagmus, diplopia, and diminished sensation below the head. From July 9 to 22, he received isoniazid (200 mg. daily) with "50 per cent improvement." By August 5, two weeks after cessation of isoniazid, he could walk (spastic-ataxic) with canes, and arm strength was fairly good. On August 7, however, he developed urinary incontinence, blurred vision, and diplopia. Cystometry showed spastic neurogenic bladder. Within a week these new symptoms partially abated, and the course was then stable. Isoniazid, 300 mg. daily, was begun again on October 29 and the gait improved. By January 10, 1954, speech had returned to normal, there was no diplopia or nystagmus, and arm strength was good. The gait was still spastic-ataxic but cane walking was well performed and unimpaired ambulation was managed for short distances. Improvement has been maintained until the present date.

Case 12. L. P., a 33-year old man, was admitted to the hospital on August 4, 1953. Nine years before he had had an episode of ataxia, with another bout two years later. For the two years before admission to the hospital he had difficulty maintaining balance, clumsiness of the hands, intermittent diplopia, urinary urgency, and inability to maintain erections. Three weeks before admission, progressive weakness of the right leg began. Dissociation of eye movements, unicocular and bilateral nystagmus, and temporal pallor were observed. Extremely severe limb and truncal ataxia plus severe spastic right leg weakness and decreased position and vibration sense in the legs were noted. Isoniazid (100 mg. daily) was given from August 7 to September 4, with increased power of the right leg. Upon cessation of the drug, his status immediately began to worsen so that by September 14 he was severely quadriplegic and bedridden, with diplopia, more nystagmus, and even greater ataxia. Isoniazid (100 mg. daily) was resumed on September 14. By September 21 the patient could walk without loss of balance. On discharge on October 16, 1953, there was still some urinary urgency, mild ataxia and nystagmus, decreased vibration of the feet, and mild weakness of the right leg; but all other functions were normal.
ISONIAZID IN MULTIPLE SCLEROSIS

These 4 patients with typical multiple sclerosis had an apparent response to isoniazid on two separate occasions during the same period of hospitalization, with a recrudescence of symptoms when administration of the drug was halted. With only 3 other patients was the drug stopped before discharge, and these men maintained their improved status.

DISCUSSION

Thirty patients with multiple sclerosis were given isoniazid while in the hospital and all but 3 showed significant improvement in the status of their disease, i.e., a gain of one or more of the ten rating categories of involvement described above. Four of these patients had exacerbation of illness with cessation of the drug and improvement on again receiving isoniazid. The course of illness of these 30 patients was compared with that of 175 patients with multiple sclerosis who were equivalent in age, sex, duration of present exacerbation, duration of total illness, and length of hospitalization. Of this comparison group, 33 per cent had showed improvement of their disease and in 17 per cent it had become worse.

It is realized that evaluation of “therapy” in multiple sclerosis is extremely difficult. Previously it was considered impossible to evaluate a drug in less than one year’s time, with five years being preferred. MacLean and Berkson (2) state that an effective therapy should result in “stabilization (or improvement) of symptoms in at least 96 of 100 patients followed for one year.” Compston (3) states “the essential criterion of efficacy of any form of therapy must be its ability to prevent relapses,” and believes that five years is necessary for evaluation.

The present writers believe that by the use of large series and well-defined criteria the course of multiple sclerosis observed under standardized hospital conditions should permit evaluations of therapy. The comparison group used in the present study is considered to be representative of multiple sclerosis as a whole. The finding that one-third of the comparison group were “incapacitated” (unable to walk unaided) fifty-one months after onset is in accord with the findings of MacLean and Berkson (2). They evaluated more than 400 cases and reported that one-third were incapacitated seven years after onset and two-thirds were incapacitated (unable to walk or work) five years later. Muller (4) found that 40 per cent of 810 patients were incapacitated within five years after onset.

The fact that one-third of the comparison group of the present study experienced improvement while in the hospital is in agreement with the results reported for patients under various forms of management (5, 6). Of Merritt’s (5) group of 33 patients with multiple sclerosis who were treated with corticotropin, one-third showed improvement during hospitalization, and the illness of the remainder stayed essentially unchanged. Improvement of multiple sclerosis in one-third to one-half of the patients during various other forms of therapeutic management has been reported by a number of investigators (6) and may be
taken as a fair index of the expected course in the hospital of groups of patients with multiple sclerosis.

It is realized that 30 cases is indeed a small number from which to draw inferences in a disease so difficult to evaluate as multiple sclerosis. Nevertheless, the fact that measurable improvement occurred in such a high proportion of consecutively treated patients seems impressive.

The use of the chi-square test mitigates this objection to the size of the treated series to some extent, as it, of necessity, incorporates the numbers used. Although this statistical test cannot be used as a basis for evaluating the efficacy of a drug, the results of this test indicate that the outcome in the two groups was significantly different. The only differences of which the present writers are aware are the administration of isoniazid and the fact that the comparison group and the isoniazid group were not studied concurrently. With respect to the latter difference, it should be noted that all members of the comparison group who were admitted to the service during the three years immediately preceding the isoniazid study were examined by one or both of the present writers. All factors which could be equated were so handled, and the two groups were comparable in sex, age, and duration of illness.

Because there may be hidden differences, in the present study it cannot be stated with certainty that isoniazid is an effective treatment in multiple sclerosis. The only way in which the question can definitely be settled is by study of concurrently observed patients with comparable illnesses whose therapy with either isoniazid or a placebo is determined solely by a chance selection method. At present the inferences from the present study are in the post hoc ergo propter hoc class. In the 4 cases presented in detail, the fact that a temporal relationship of isoniazid to improvement appeared to exist on two separate occasions during the same hospital stay certainly seemed highly suggestive of a drug effect.

The objection may also be raised that the observations in the present study were made with an unrecognized categorization of the manifestations of multiple sclerosis. The classification used, however, is based on the evaluation of the disabilities of 300 patients, and the same criteria were used for both the comparison and the isoniazid patients.

Since discharge, the isoniazid group has been followed for twelve to seventeen months (8 patients), six through eleven and five-tenths months (9 patients), four through five and five-tenths months (9 patients), and less than four months (4 patients). There has been no new attack, no regression of status, no new abnormality. Some of the more severely handicapped patients are still improving while continuing to receive isoniazid.

Isoniazid (isonicotinic acid hydrazide) (7) is an agent which is markedly inhibitory for tubercle bacilli. The drug is almost completely absorbed from the digestive tract, and one-half to three-fourths of a single dose is excreted in the urine within twenty-four hours. The peak serum concentration is attained one to three hours after an oral dose. It is generally nontoxic for humans in daily doses up to 5 mg. per kg., and the suggested range of therapy in tuberculosis is
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3 to 5 mg. per kg. daily. In man (8a), the cerebrospinal fluid concentrations of isoniazid have been found to be high; the drug easily passes the "blood brain barrier." In cerebrospinal fluids with no evidence of infection, concentrations of 0.5 μg per ml. have been observed three to five hours after the administration of 1.5 to 2 mg. per kg. by mouth (8 b); this is slightly higher than simultaneously determined plasma concentrations.

The pharmacologic actions of isoniazid in man are few (9). There is no vasodilator action, despite its apparent chemical relationship to nicotinamide. There is no histamine or antihistamine activity and no effective autonomic action.

It is possibly relevant to the present study that isoniazid can affect neural tissue to induce seizures and peripheral neuropathy. Indeed, the effects on the nervous system are the chief side reactions of isoniazid although a miscellany of untoward reactions has been recorded (10). Some of the latter instances are perhaps attributable to the earlier confusion of isoniazid with the more toxic isopropyl derivative of the hydrazide (iproniazid). Pyridoxine seems to counteract the deleterious nervous system effects of isoniazid (11); isoniazid increases the urinary excretion of pyridoxine. The incidence of damage to the peripheral nerves appears to vary inversely with the degree of in vivo acetylation of the drug, a process which has a marked but individual variation (12).

In recent investigations (13, 14), it has been reported that there is no effect of isoniazid on mood or mentation. Hence, it seems improbable that improvement in the manifestations of illness of the patients of the present study can be attributable to euphoria.

Thus, although there is no rationale immediately at hand for the use of isoniazid in multiple sclerosis, it can be said that the drug is known to have a definite influence on the nervous system when administered in a sufficient dosage. Moreover, the safety of isoniazid for humans in the doses used in the present study has been well established from the studies in the chemotherapy of tuberculosis. Hence, the continued investigation of isoniazid in multiple sclerosis need not await long-term studies of its toxicity in man.

It is suggested that isoniazid and other related hydrazides be tried in the experimental allergic demyelinating encephalomyelitides. Therapeutic efficacy could easily be demonstrated; and, in such conditions, without entering into the relationship of these conditions to multiple sclerosis, a better drug than isoniazid might more readily be found—if isoniazid should prove to be an active therapeutic agent in multiple sclerosis.

Further work with isoniazid in multiple sclerosis is indicated. The proof of efficacy lies in blind placebo-and-isoniazid regimens prescribed on a random basis in different centers. By this means it will be possible to compare the degree of improvement as well as the per cent improved. It remains to be ascertained whether the drug should be taken continuously, like insulin, or merely for each episode as with penicillin. One must investigate whether there is “escape” from the efficacy of isoniazid, as occurs in certain circumstances with tubercle bacilli, or whether it is an active prophylactic agent and will prevent exacerbations.
The dosage must also be established. Here the individual variation of the degree of acetylation must be correlated with the apparent effect or its failure to appear. Long-term toxicity, although unlikely, must be considered, and there is one point in this connection which is worthy of emphasis. There is reason to believe, from experience in tuberculosis chemotherapy, that seizures as a toxic reaction to isoniazid are more apt to be precipitated in epileptics or in persons with localized lesions in the brain than in other persons. As a consequence, if isoniazid is to be used in patients with neurologic disease, this possibility should be kept in mind and appropriate precautionary measures taken.

These various problems await solution; the goal of an effective treatment for multiple sclerosis may then be closer to attainment.

SUMMARY

Thirty patients with multiple sclerosis were given isoniazid during hospitalization. With one exception, all of the patients had experienced an episode of activity of this disease within a two-year period prior to the use of isoniazid. These 30 patients were compared with 175 patients with multiple sclerosis admitted between 1944 and 1953 and similarly treated except for the administration of the isoniazid.

Of the isoniazid group, 90 per cent of the patients improved, 7 per cent were unchanged, and 3 per cent were worse. Of the comparison group, 33 per cent of the patients improved, 50 per cent were unchanged, and 17 per cent were worse on discharge. The difference between the two groups is significantly well beyond the 0.1 per cent level ($P < 0.001$).

On admission, 33 per cent of the comparison group and 53 per cent of the isoniazid-treated group were unable to walk unaided; on discharge this disability rate was unchanged in the comparison group but, in the group treated with isoniazid, the patients who required assistance in walking had dropped to 33 per cent of the total.

Of the comparison group admitted with mild to moderate disabilities (categories 1 through 5), a total of 116 patients (50 per cent) were unchanged at the time of discharge, 20 per cent were improved by one or more categories, and 24 per cent were worse. In the group treated with isoniazid, 11 were in the mild to moderate categories on admission (categories 1 through 5), but on discharge 100 per cent of these had improved.

In the categories of moderate to severe impairment (categories 6 through 10), there were 58 patients in the comparison group. Of this group, 53 per cent were unchanged, 24 per cent were worse, and 23 per cent had improved during hospitalization. In the group treated with isoniazid, there were 19 patients in categories 6 through 10. Of these, 85 per cent improved, 10 per cent were unchanged, and 5 per cent (one patient) died while in the hospital.

Those with minimal or no symptoms on discharge constituted 27
per cent of the comparison group and 50 per cent of the isoniazid-treated group, although the isoniazid-treated group was more severely disabled than the comparison group at the time of admission.

Four patients showed improvement on isoniazid, worsening with cessation of administration, and then improvement concomitant with reinstitution of the drug. Three other patients had no exacerbation after removal of this agent prior to discharge.

The two groups were comparable at the time of admission in age, age of onset, and duration of illness.

Improvement has been maintained for one to one and one-half years in 8 patients and from one-half to one year in 9 patients of the isoniazid group. The remainder have not been followed as long after discharge from the hospital.

It is concluded that, in the present series of patients, the administration of isoniazid seemed to exert a favorable influence on those manifestations of multiple sclerosis which had been present for less than two years when the isoniazid administration was initiated.

SUMARIO

Los Efectos de la Isoniacida en los Enfermos de Esclerosis en Placas

Treinta enfermos que tenían esclerosis en placas recibieron isonicacida durante su hospitalización. Con una excepción, todos habían experimentado un episodio de actividad de la dolencia durante el periodo de dos años anterior al uso de la droga. Esos 30 enfermos fueron comparados con 175 enfermos de esclerosis en placas recibidos entre 1944 y 1953 y tratados en forma semejante, excepto por la administración de isonicacida.

Del grupo de la isonicacida, 90 por ciento mejoraron, 7 por ciento no variaron y 3 por ciento empeoraron. Del grupo de comparación, 33 por ciento mejoraron, 50 por ciento no variaron y 17 por ciento empeoraron o fueron dados de alta. La diferencia entre los dos grupos queda significativamente bien más allá del tenor de 0.1 por ciento (P < 0.001).

Al ingreso, 33 por ciento del grupo de comparación y 50 por ciento del tratado con isonicacida no podían caminar sin ayuda; los enfermos de alta, ese coeficiente de incapacidad no había variado en el grupo de comparación, pero en el grupo tratado con isonicacida, los sujetos que necesitaban ayuda para caminar habían descendido a 33 por ciento del total.

En el grupo de comparación, considerando los recibidos con incapacidad leve a moderada ( categorías 1 a 5 inclusive), un total de 116 enfermos (40 por ciento) no habían variado al darlos de alta, 26 por ciento habían mejorado hasta una u otra categoría y 24 por ciento habían empeorado. En el grupo de la isonicacida, 11 correspondían a su ingreso a la clínica. clases leve a moderada (categorías 1 a 5 inclusive), pero al darlos de alta, 100 por ciento de ellos habían mejorado.

En las categorías de incapacidad moderada a grave (categorías 6 a 10 inclusive), hubo 58 enfermos del grupo de comparación. De ellos, 53 por ciento no variaron, 24 por ciento empeoraron y 23 por ciento mejoraron durante la hospitalización. Del grupo tratado con isonicacida, 19 enfermos quedaban en las categorías 6 a 10 inclusive. De ellos, 45 por ciento mejoraron, 10 por ciento no variaron y 5 por ciento (un enfermo) fallecieron en el hospital. Los que tenían síntomas mínimos o no tenían síntomas al darlos de alta constituían 27 por ciento del grupo de comparación y 50 por ciento del tratamiento con isonicacida, aunque al ingreso, los últimos estaban más incapacitados que los del otro grupo.
Cuatro enfermos revelaron mejoría con la isoniazida, emperoamiento al cesar la administración y mejoría de nuevo al reanudarse la droga. Otros tres enfermos no manifestaron exacerbación al suspenderse dicho agente antes del alta.

Los dos grupos eran comparables en la fecha del ingreso en cuanto a edad, edad a la iniciación y duración de la enfermedad.

Se ha mantenido la mejoría de un año a año y medio en 8 enfermos y de medio a un año en 9 enfermos del grupo de la isoniazida. Los demás no han sido mantenidos en observación tanto tiempo después del alta del hospital.

Dedúcese que, en la serie actual de enfermos, la administración de isoniazida pareció ejercer un influjo favorable sobre las manifestaciones de la esclerosis en placas que habían existido menos de dos años al iniciarse la administración de isoniazida.

**RESUME**

*Les effets de l'isoniazide sur les malades atteints de sclérose en plaques*

Trente patients atteints de sclérose en plaques ont été traités par l'isoniazide au cours de leur séjour à l'hôpital. A l'exception d'un seul cas, tous les malades avaient présenté une période d'activité de l'aflection au cours des deux années précédant l'emploi de l'isoniazide. Une étude comparative a été effectuée entre ces 30 cas et 175 autres cas de sclérose en plaques hospitalisés entre 1944 et 1953 et qui avaient été traités de façon similaire, sauf l'administration de l'isoniazide.

Parmi le groupe traité par l'isoniazide, 90% des cas ont été améliorés, 7% n'ont présenté aucun changement, 3% étaient aggravés au sortir de l'hôpital. Parmi le groupe témoin, 33% des cas étaient améliorés, 50% sans changement, 17% étaient aggravés au sortir de l'hôpital. L'écart entre les deux groupes dépasse largement la proportion significative de 0,1 pour 100 ($P < 0,001$).

À l'admission, 33% du groupe de comparaison et 53% du groupe traité par l'isoniazide ne pouvaient marcher sans aide. Au sortir de l'hôpital, cette proportion persistait pour le groupe de comparaison et elle s'abaissait pour le groupe traité par l'isoniazide, 33% des malades seulement avaient encore besoin d'assistance pour marcher.

Parmi le groupe de comparaison présentant à l'admission une invalidité légère ou modérée (catégories 1 à 5 inclusivement), 116 cas en tout, soit 50%, ne présentaient aucun changement à la sortie de l'hôpital, 26% étaient améliorés d'un ou plusieurs degrés et 24% étaient aggravés. Dans le groupe traité par l'isoniazide, 11 figuraient dans les catégories d'invalidité légère ou modérée (catégories 1 à 5 inclusivement) à l'admission, mais à la sortie de l'hôpital 100% de ces cas étaient améliorés.

Dans les catégories d'invalidité modérée ou sévère (catégories 6 à 10 inclusivement) il y avait 58 patients dans le groupe de comparaison. Parmi ce groupe, 53% des cas étaient sans changement, 24% étaient aggravés, et 23% s'étaient améliorés au cours de l'hospitalisation. Dans le groupe traité par l'isoniazide, il y avait 19 patients appartenant aux catégories 6 à 10 inclusivement. Parmi ceux-ci, 85% des cas étaient améliorés, 10% étaient sans changement, et 5% (1 malade) représentent les décès au cours de l'hospitalisation.

Les cas dont les symptômes étaient minimes ou nuls à la sortie de l'hôpital représentaient 27% du groupe de comparaison et 50% du groupe traité par l'isoniazide, bien qu'à l'admission l'invalidité n'ait été beaucoup plus accusée parmi le groupe traité par l'isoniazide que dans le groupe témoin.

Quatre patients ont présenté une amélioration avec l'isoniazide, une aggravation lorsque l'administration du composé a été interrompue, puis une amélioration associée à la reprise de ce médication. Trois autres patients n'ont présenté aucune exacerbation de l'aflection lorsque la médication a été interrompue avant la sortie de l'hôpital.

Les deux groupes étaient comparables au moment de l'admission en ce concerne l'âge du malade, l'âge auquel la maladie avait débuté et la durée de l'affection.
L'amélioration a été maintenue pendant un an à un an et demi, chez 8 patients, et pendant six mois à un an, chez 9 patients du groupe traité par l'isoniazide. Les autres n'ont pas été suivis pendant une période aussi longue après la sortie de l'hôpital.

En conclusion, dans la série actuelle de malades, l'administration de l'isoniazide a paru exercer une influence favorable sur les symptômes de la sclérose en plaques qui existaient depuis moins de deux années au moment de l'instauration du traitement par l'isoniazide.

REFERENCES


