DISSEMINATED SCLEROSIS TREATED WITH ISONIAZID WITH A METHOD OF EVALUATING CHRONIC NEUROLOGICAL DISORDERS

BY

BARBARA M. ANSELL and EDWIN CLARKE

From the Postgraduate Medical School of London and Hammersmith Hospital

Recently a new therapeutic agent has been added to the list of substances that have been suggested for the treatment of disseminated sclerosis. Kurtzke and Berlin (1954) have reported encouraging results from the use of isoniazid and, in view of this, the evaluation of its effect on a small number of patients was thought desirable.

Material

Eleven patients suffering from undoubted disseminated sclerosis were studied. They had all been seen on account of a recent relapse, or, in one case, because of steady deterioration; patients manifesting the initial features of the disease were not included. Five were men and six were women with ages ranging from 27 to 48 years (mean 38 years). The disease had been present for periods of two to 21 years with a mean duration of 10. However, in only one case had it been progressive from the onset, the remainder having experienced several relapses before permanent disability appeared; the mean duration of the latter was five years. In all but one an aggravation of the existing deficits or the appearance of new features had occurred within the last two years—the average for this being nine and a third months.

Methods

In any long-standing disease, regular attendance at hospital, new treatments, and the enthusiasm of the medical attendant tend to encourage the patient and thus false assumptions may be made. From the patient's point of view, his ability to perform everyday tasks such as walking, dressing, eating, and writing are of paramount importance. Therefore, in order to reduce subjective error both on the part of the patient and the examiner the functional state of each patient was recorded on a special form (Fig. 1) at regular intervals. The assessment was made on the basis of self-care, ambulation, and function tests, in the first two the

ability to perform tasks being indicated by "yes" or "no". Improvement was judged by an absolute increase in the number of positive responses and deterioration by an increase in the negative ones. These changes were amplified whenever possible by tests aimed at assessing normal function. They consisted of the strength of the grip, the time taken to walk a given distance, and the time taken to climb a set number of stairs. The distance and other circumstances, such as support, were suited to the individual patient. Standards were established from the average of repeated performances by healthy individuals. Note was also taken of change in the patient's mental state, speech, sphincter control, and physical signs. It was then possible to assemble patients into groups according to their functional abilities:

Group I.—Able to lead a normal life.

Group II.—Minimal incapacity; able to lead a normal life but aware of disabilities.

Group III.—Can walk, with or without support, but has considerable limitation of activities; can do light work or household duties.

Group IV.—Confined to a wheel chair for all practical purposes.

Group V.—Completely helpless.

Of our 11 patients, initially five were in Group III, five in Group IV, and one in Group II. The majority were investigated in hospital to establish the diagnosis beyond doubt, and an initial assessment for the purposes of this trial was made before discharge. Otherwise it was carried out at the first out-patient attendance. They were all placed on regular out-patient physiotherapy which was maintained throughout the trial, and monthly assessments were made as described above. One month after starting physiotherapy isoniazid was introduced at a standard dosage of 100 g. t.d.s. and this has been continued for periods of two and a half weeks to

SELF-CARE		Date
1. Change position in bed		
2. Move from lying to sitting	Aided	
	Alone	
3. Move from sitting to standing	Aided	
	Alone	
4. Move from bed to chair	Aided	
	Alone	
5. Dress	Partly	
	Completely	
6. Feed self	Partly	
	Completely	
7. Write name and address		
8. Use toilet without assistance		
9. Bath without assistance		
AMBULATION		
1. Able to walk with 2 sticks or instructors		
2. Able to walk with 1 stick or instructor		
3. Able to walk alone		
4. Able to walk 500 yd.		
5. Able to climb stairs holding on to railing		
6. Able to climb stairs alone		
MENTAL STATE	Abnormal	
	Normal	
SPHINCTER CONTROL	Abnormal	
	Normal	
OTHER		
FUNCTION TESTS		
Walking time (distance—manner)		
Climbing time (number of steps—manner)		
Grips	Right	
	Left	
Functional status (1-5)		
Change in physical signs (+, -, u)		
Overall change (+, -, u)		

FIG. 1.—Chart used for serial evaluation of functions : + = improvement, — = deterioration, u = unchanged.

eight months. Three subjects discontinued the drug at their own request two and a half, nine, and 16 weeks from beginning therapy. Six patients have received therapy for six months or more and the other two for five and one month respectively. The

first assessment was designated - 1, that immediately before therapy 0, and subsequently the number indicated the month from the start of isoniazid therapy (Fig. 2). During the initial period of physiotherapy the function tests were performed at each attendance in order that the patient could get used to them and avoid apparent improvement due to familiarization with the tests. No other therapy was given at any time in this investigation and placebos were not employed.

Results

These are summarized in the Table, where cases are grouped according to the period over which the drug was administered; individual exacerbations are not shown.

TABLE
RESULTS IN 11 CASES OF DISSEMINATED SCLEROSIS
TREATED WITH ISONIAZID

Month of Trial	Results			Total No. of cases.
	Better	No change	Worse	
1	0	7	4	11
2	0	8*	2	10
4	2†	5	1	8
6	1	6†	1	8
8	1	—	1	2

Patient terminated therapy at own request, * at 2½ weeks, † at 9 weeks, and ‡ at 16 weeks (see Case 1).

After treatment had begun, a total of seven patients showed an exacerbation of their pre-existing state and in two it occurred twice with intervals of seven and five weeks respectively. In three it occurred in the first month, in two in the second, and in two in the third month of treatment. In five an aggravation of a previous defect such as ataxia, paraesthesiae, or blurring of vision took place, but in the other two new symptoms and signs appeared while the drug was being given. Of the five that deteriorated, the following case is typical.

4 Case 1.—In a woman aged 40, disseminated sclerosis had begun 21 years previously with transient blurring of vision, followed by temporary diplopia and retention of urine seven and 11 years later respectively. The first permanent disability had developed six years previously and consisted of leg weakness and ataxia, which fluctuated in severity. Ten weeks before isoniazid therapy was begun there was a sudden aggravation of these disabilities. Shortly after beginning therapy the symptoms increased further but then improved, only to recur with increased severity in the third month of treatment. This deterioration was adequately reflected in the function tests. Treatment was continued for a further month but as there was no improvement and a state of depression had supervened, the patient refused to cooperate further. In the next three months, with the aid of continued physiotherapy, she gradually returned to her pre-treatment level (Fig. 2).

The improvement in two patients was an increase of limb power and a decrease of ataxia. That this change might have been due to the natural course of the disease is shown by the following case :—

Case 2.—In a man aged 35 years the onset of disseminated sclerosis had been 10 years previously and was characterized by transient numbness of the legs. There were two further relapses but for five years before treatment he had noted residual disabilities in the legs and arms. Six weeks before treatment began, weakness and ataxia of the left limbs increased markedly. The physical signs were appropriate. After 11 weeks of therapy he started to improve and in six weeks returned to the state preceding the exacerbation. This state was maintained for a further three months while he was still receiving isoniazid. Limb power has increased and ataxia is less, these changes being reflected in the function tests.

In the other case improvement on the pre-treatment state was noted seven weeks after therapy had been discontinued at her own request, because of a marked exacerbation. Its relationship to the administration of the drug is thus in doubt.

Toxic Effects

Two patients suffered distressing gastro-intestinal symptoms due to their relatively small body mass (Pleasure, 1954). A third had a major epileptic seizure on the ninth day of treatment but although isoniazid was continued for a further five months he has had no more fits.

Discussion

Our findings differ considerably from those of Kurtzke and Berlin (1954) who, on the basis of an accidental observation, advocated the use of isoniazid in disseminated sclerosis. Whereas we found it of little or no value, they report excellent results, inasmuch as 90% of their patients were improved by the drug. However, the series were not strictly comparable for our patients were older, the disease was more chronic, and women were

FIG. 2.—Deterioration of function while receiving isoniazid, as shown by change in time to climb up and down 10 steps and to walk 50 yards (Case 1).

included. Otherwise, like theirs, all our patients had shown evidence of activity within the two years preceding treatment. Only two of our patients showed any improvement and in each it was not dramatic and may have represented a spontaneous fluctuation in the course of the disease. The others were either unchanged or worse. There was no indication that deterioration was but a prelude to more favourable results as Brickner (1932) observed when using quinine. One patient developed symptoms and signs of a fresh lesion while having the drug and others have also observed this (Campbell, 1955). If isoniazid is of any value in disseminated sclerosis it would have been expected to prevent relapses and produce at least some unequivocal evidence of improvement. As neither of these events has been forthcoming in a small but carefully studied series of cases there seems to be no justification for raising unnecessarily the hopes of patients with disseminated sclerosis of the type that we have investigated. The uniform failure of this medication did not induce us either to extend our series, introduce placebos, or construct a control group from previous records. We have no information, however, concerning the treatment of patients with the initial features of the disease, and relapse

rates have not been obtainable. Evaluation of these would be more difficult and demand a survey such as that proposed by Compston (1953), as well as an observation period of at least five years (MacLean and Berkson, 1951). Studies of this nature are being carried out elsewhere (McAlpine, 1955).

The criteria suggested by McAlpine, Compston, and Lumsden (1955) to evaluate the results of treatment in disseminated sclerosis are (1) the effect on acute symptoms, (2) the prevention of relapses, and (3) the effect on disability. Two of our patients had a relapse involving acute and new features but in neither were they affected by isoniazid; in five, exacerbations were not prevented and the degree of disability, admittedly severe in all, was increased more often than decreased. By this assessment, therefore, our results were extremely disappointing.

There is no experimental evidence to suggest that isoniazid should be of any value in favourably affecting the pathological process in disseminated sclerosis. In our cases there was no reason to suppose that the drug was having any influence for it was unable to prevent exacerbations and relapses. As at times it seemed to aggravate the patient's condition, its effect was perhaps deleterious. Isoniazid may at times have toxic influences upon the nervous system (Pleasure, 1954), and, although the peripheral neuropathy that is a well recognized complication (Gammon, Burge, and King, 1953) was not observed in the present cases, one patient had a major convulsion (Reilly, Killam, Jenney, Marshall, Tausig, Apter, and Pfeiffer, 1953). The features of optic neuritis in one patient were probably due to the disease process itself rather than a toxic effect of the drug that is known to occur (Keeping and Searle, 1955).

The quantitative evaluation of the patients was an important aspect of the study. Kurtzke and Berlin (1954) and Kurtzke (1955) when assessing their cases used a scheme which was a mixture of functional state, symptoms, and signs. They thus devised 10 groups some of which would appear to be superfluous. The rehabilitation programme of Zarling (1954), which included activity rating scores, and the method used by Alexander (1951) are available for the minute consideration of patients but are too detailed for everyday use. Our method is simpler and based only upon the functional state of the patient. It has proved to be entirely adequate in the cases comprising this report, and can be readily applied to other forms of chronic neurological disease.

When the response of a neurological condition to a new therapeutic agent is being considered, objec-

tive evaluation must be used and, if possible, a quantitative method of assessing progress employed.

Summary

Eleven patients suffering from chronic disseminated sclerosis were given isoniazid for periods ranging from two and a half weeks to eight months, while assessment of their functional state was made at regular intervals.

In no case did unequivocal improvement occur; seven patients showed an exacerbation of their previous symptomatology and two experienced a relapse with new features while receiving the drug.

It is concluded that in the moderately advanced cases considered here, isoniazid is of no therapeutic value.

A simple quantitative method of assessing changes in chronic neurological disorders is suggested.

Addendum

Since the completion of this paper further reports on the ineffectiveness of isoniazid in the treatment of disseminated sclerosis have appeared (Dekaban, 1955; Korengold, Haase, Berg, and Magee, 1955; Lønnum, 1955; Hinterbuchner, Goldner, Rogoff, and Rabiner, 1956). On the other hand, Tschabitscher, Wanko, Schinko, and Fust (1955) thought it was beneficial in their patients (see also Georgi and Jordan, 1956) and Schinko, Tschabitscher, and Wanko, (1955), together with Ahrringsmann (1955), have resurrected the theories concerning the tuberculous origin of disseminated sclerosis and have actually identified mycobacteria in the cerebrospinal fluid of patients with this disease.

REFERENCES

- Ahrringsmann, H. (1955). *Schweiz. med. Wschr.*, **85**, 884.
- Alexander, L. (1951). *A.M.A. Arch. Neurol. Psychiat.*, **66**, 253.
- Brickner, R. M. (1932). *Ibid.*, **28**, 125.
- Campbell, A. M. G. (1955). Personal communication.
- Compston, N. D. (1953). *Lancet*, **2**, 271.
- Dekaban, A. (1955). *Canad. med. Ass. J.*, **73**, 478.
- Gammon, G. D., Burge, F. W., and King, G. (1953). *A.M.A. Arch. Neurol. Psychiat.*, **70**, 64.
- Georgi, F., and Jordan, D. (1956). *Schweiz. med. Wschr.*, **86**, 321.
- Hinterbuchner, L. P., Goldner, M. G., Rogoff, J. B., and Rabiner, A. M. (1956). *A.M.A. Arch. Neurol. Psychiat.*, **75**, 115.
- Keeping, J. A., and Searle, C. W. A. (1955). *Lancet*, **2**, 278.
- Korengold, M. C., Haase, G. R., Berg, L. R., and Magee, K. R. (1955). *Neurology*, **5**, 801.
- Kurtzke, J. F. (1955). *Ibid.*, **5**, 580.
- , and Berlin, L. (1954). *Amer. Rev. Tuberc.*, **70**, 577.
- Lønnum, A. (1955). *Nord. Med.*, **54**, 1319.
- McAlpine, D. (1955). *Lett. Brit. med. J.*, **1**, 1392.
- , Compston, N. D., and Lumsden, C. E. (1955). *Multiple Sclerosis*. Livingstone, Edinburgh.
- MacLean, A. R., and Berkson, J. (1951). *J. Amer. med. Ass.*, **146**, 1367.
- Pleasure, H. (1954). *A.M.A. Arch. Neurol. Psychiat.*, **72**, 313.
- Reilly, R. H., Killam, K. F., Jenney, E. H., Marshall, W. H., Tausig, T., Apter, N. S., and Pfeiffer, C. C. (1953). *J. Amer. med. Ass.*, **152**, 1317.
- Schinko, H., Tschabitscher, H., and Wanko, T. (1955). *Wien. med. Wschr.*, **105**, 717.
- Tschabitscher, H., Wanko, T., Schinko, H., and Fust, B. (1955). *Schweiz. med. Wschr.*, **85**, 556.
- Zarling, V. R. (1954). *Neurology*, **4**, 147.