ENDOGENOUS DEPRESSION TREATED WITH IPRONIAZID—A FOLLOW-UP STUDY

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A DOUBLE-BLIND controlled trial of iproniazid in endogenous depression and a comparison of its effects with those of E.C.T. was reported in this journal by Kiloh *et al.* (1960). To summarize the results—of 26 patients treated with iproniazid a good immediate response was found in 14 cases (54 per cent.) whereas only 3 of 28 patients (11 per cent.) given placebo tablets showed a significant improvement at the end of three weeks. Of 27 patients treated with E.C.T. 24 (89 per cent.) showed a good immediate response.

To date (April, 1960) only four trials have been traced in which an attempt has been made to control the study. Freymuth *et al.* (1959) carried out a double-blind trial with 64 chronic regressed schizophrenics. Of 32 cases receiving 150 mg. iproniazid daily for eight weeks, 20 per cent. improved in regard to apathy and depression and 50 per cent. showed an increase in alertness and spontaneity but became more tense and aggressive. Only 2 of the 32 controls showed "some behavioural improvement".

Hoshino and Cease (1958) carried out a similar trial on 64 chronic hospitalized schizophrenics who were described as "stabilized"; in other words they had had no active treatment during the previous six months. The dose of iproniazid given was 150 mg. daily. No difference was found between the active and control groups.

Cole *et al.* (1959) treated 89 patients belonging to several diagnostic categories all having depression as an important symptom. The cases were allocated to three groups, the choice of treatment being iproniazid, placebo and psychotherapy, the latter varying according to the therapist involved. The trial was remarkable for the large number of cases that defaulted during treatment, 39 in all, more or less equally distributed between the three groups. The authors found no difference in the efficacy of the three forms of treatment.

Pare and Sandler (1959) carried out a trial of iproniazid on 50 patients suffering from "depression, who had been considered suitable for E.C.T.". The dosage given ranged from 150 to 450 mg. daily and the duration of treatment varied from two to forty weeks. It was a trial of the cross-over variety and

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apparently was not blind. It is not clear from the paper how many patients were given placebo and the statement is made that "placebo was substituted in certain cases". The periods for which active and placebo treatment were given are not indicated. Twenty-six of the 50 patients improved on iproniazid but because 14 of these did not relapse when placebo was substituted, they were regarded as showing "coincidental improvement". This would seem to be a very high proportion of spontaneous recoveries amongst a group of depressive patients whose condition was thought to warrant E.C.T. In addition it assumes that the initial period of iproniazid treatment—the length of which is not stated—cannot lead to permanent amelioration of the depressive illness or to improvement sustained for the duration of placebo administration.

The surprising fact is therefore that in spite of the extensive literature on the use of iproniazid in psychiatry, amounting now to over 1,000 papers, no further double-blind studies of the effects of iproniazid on depression have been published. This seems regrettable.

All cases included in our trial have been followed up for at least six months from the termination of their initial three-week period of treatment. The clinical state of each patient was re-assessed at three and again at six months.

Cases Treated with Iproniazid

Of the 14 cases treated successfully with iproniazid, 10 remained well after three months and 9 after six months. Of the 5 cases that relapsed, 2 were still taking iproniazid at the time their symptoms returned, one after six weeks and the other after ten weeks. The other three cases relapsed after they ceased to take the tablets. One patient took iproniazid for four weeks and relapsed after a further two months; the second stopped after six weeks and relapsed three months later; and the third ceased to take tablets after four months and relapsed in two weeks.

A further 4 cases, three of whom were placebo failures and one an E.C.T. failure, were treated with iproniazid. One of these showed no response, the other 3 responded well and their improvement was maintained at six months. One of the latter cases had treatment for only one month, the others were still taking iproniazid at six months.

Duration of administration of iproniazid. Including those patients who were given iproniazid as a second line of treatment, 12 out of 30 cases remained well at six months. Of these, 8 were still taking iproniazid. The duration of administration of the drug in the other four cases ranged from one month to four months. It is still not clear how long it is necessary to continue the administration of iproniazid in order to avoid the danger of relapse. There is little help on this point to be obtained from the literature. Scanlon (1959) gave the drug for periods varying from two weeks to fifteen months. Joel (1959) found that in 48 of 57 cases of manic depressive psychosis, a favourable result was obtained with iproniazid; 38 cases were still taking iproniazid after periods varying from two to twenty months (in 16 cases for fifteen to twenty months) while ten cases had ceased to take the drug after periods of administration varying from two to ten months. In a further group of 49 cases of manic depressive illness, 45 showed a favourable response to iproniazid. In 28 of these the average duration of treatment was four months and they were well after follow-up periods ranging from 1–16 months (in 14 cases from 10–16 months). The remaining 17 cases were still taking iproniazid at the end of the study.

Alexander and Berkley (1959) state that of 24 successfully treated patients,

13 received iproniazid for an average of 22 weeks while the other 11 continued to take the drug after 45 weeks. Hawkins *et al.* (1959) suggested that the drug should be stopped 3–4 months after improvement had occurred.

It seems likely that the optimum period of administration of iproniazid is an individual matter and may vary from a few weeks to a year or more. One case —not included in this trial—a severe endogenous depression, made an excellent response to iproniazid and indeed became slightly hypomanic. Two attempts to stop the tablets at six and nine months were made and were promptly followed by a return of the depression. The symptoms disappeared when the iproniazid was re-instituted. Finally, after fourteen months on the drug, the patient's symptoms returned in full force although he was still taking 150 mg. of iproniazid daily. On this occasion he responded well to imipramine. The duration of treatment must be influenced by the natural periodicity of depressive illness. The suggestion has indeed been made that the only effect of anti-depressive drugs is to control symptoms until spontaneous recovery occurs. This view is difficult to refute without controlling the trial for a period of six months or longer—a procedure which would be difficult to justify on ethical grounds. Experience with the drug suggests that it achieves something more than mere symptomatic relief whilst the natural history of the illness evolves.

It seems that if iproniazid is given for a depressive illness, one should anticipate a period of administration of at least four to six months. After this time an attempt can be made to discontinue the drug but in many cases this will prove premature.

Cases Treated with E.C.T.

The relapse rate amongst cases treated initially with E.C.T. was high. Within three months, 9 of the 24 improved cases had relapsed and by six months a further two cases showed a return of symptoms. At six months, therefore, the success rate of E.C.T. had fallen from 89 per cent. to 48 per cent. In addition, E.C.T. was given as a second line of treatment to 25 cases who had failed to respond either to iproniazid or to placebo tablets. The relapse rate among these was of a similar order. In all, 49 of 52 cases (94 per cent.) given E.C.T. showed a good immediate response. Of these, 27 (52 per cent.) had relapsed within six months.

Comparison of the Effects of Iproniazid and E.C.T.

Taking all the cases treated with iproniazid, a good immediate response was obtained in 17 out of 30 patients (57 per cent.). After six months, 12 of these cases (40 per cent. of the total; 71 per cent. of those initially improved) remained well.

With ECT, 49 out of 52 cases (94 per cent.) showed a good immediate response. After 6 months, 25 of these cases (48 per cent. of the total; 51 per cent. of these initially improved) remained well.

About one half of the cases treated with E.C.T. therefore had relapsed within a period of six months. The relapse rate following successful treatment with iproniazid was considerably less than this and after the six-month period the proportions of the two groups of cases remaining well became comparable.

Eight cases which failed to respond to iproniazid showed a good response to E.C.T. but only three of these remained well after six months. One case that relapsed after treatment with E.C.T. did well on iproniazid.

These figures are very small but they do tend to confirm the fact that

E.C.T. has an immediate superiority over iproniazid, though with the passage of time it becomes less marked. They suggest, too, that there are likely to be patients who respond to the one form of treatment but not to the other.

Other monoamine oxidase inhibitors are likely to have at least the same order of efficiency as iproniazid and experience has shown that imipramine is rather more effective (Ball and Kiloh, 1959). In view of the high relapse rate following E.C.T. and the relatively low relapse rate of patients on these drugs which make the final results of the two forms of treatment equable, it seems justifiable in the majority of cases of depression to give a course of one or other of these substances before proceeding to E.C.T.

Summary

1. Although many more cases of endogenous depression show a good immediate response to E.C.T. than to iproniazid (94 per cent. as compared with 57 per cent.), the relapse rate in the six months following E.C.T. is such that after this time the response rate is comparable (48 per cent. as compared with 40 per cent.).

2. The optimal duration of treatment with iproniazid has not been satisfactorily established. In the majority of cases a period of administration of 4–6 months is likely to be necessary and in some the drug may have to be given for a year or longer.

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