# THE EFFECT OF ISONIAZID ON DEPRESSIVE STATES

By

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ISONICOTINYL Hydrazide or Isoniazid has for some years now been used in conjunction with other compounds in the treatment of pulmonary tuberculosis. During this treatment certain workers (Robitzek *et al.*, 1952) noted the development of a state of euphoria in their patients. Since Isoniazid was known to exert toxic effects on nervous tissue (Gammen *et al.*, 1953) the hypothesis was made that the substance might be capable of producing an elevation of mood by direct action on the central nervous system. Acting on this hypothesis, Salzer and Lurie (1953) treated a group of patients suffering from various depressive conditions with Isoniazid given orally in the dosage of 50 mgm. t.d.s. for one week. If no toxic effects occurred the dosage was raised to 100 mgm. t.d.s. for a further two weeks, while in a few cases only higher doses were given. These workers maintained this level of dosage in order to avoid the advent of toxic side effects. Their results, which will be discussed later in this paper, led them to the conclusion that isoniazid had a specific therapeutic effect upon certain depressive disorders.

The object of this study, arising out of the work mentioned, was to carry out an initial survey of the effects of isoniazid on the affective component of various depressive states. If any demonstrable therapeutic action had been noted a larger, controlled, and more systematic study would have been undertaken but in view of the results obtained this further project has now been abandoned.

## STUDY

Thirty-three female patients with various types of depressive states were selected for treatment. As this was essentially a pilot study, no effort was made to select the patients in regard to age or duration of illness, but care was taken to exclude the possibility of organic factors or those pertaining to other psychiatric conditions. The cases of depression selected fell under four diagnostic headings: involutional depression, manic-depressive psychosis, recurrent endogenous depression and senile depression, the second and third categories being separated by the presence or absence of manic phases.

The patients were all interviewed by myself and after a diagnosis had been made were given a routine physical examination. A blood picture was obtained before and after treatment. Isoniazid was given by mouth over a period of three weeks, the dosage being 50 mgm. t.d.s. for the first week and 100 mgm. t.d.s. for the second and third weeks. The patients were then reassessed at interview, and a further follow-up carried out two months later. In some cases a course of E.C.T. was then given, with further follow-up interviews. Patients were assessed after treatment as being unchanged, improved, or recovered.

During the isoniazid therapy no other treatment was given except for symptomatic remedies, including nocturnal sedation when needed. As in no case were any toxic effects noted, these will not be alluded to in the results.

In no case was the treatment found to be unpleasant, so that its management was simple and uneventful. No consistent trend either upwards or downwards was noted in the patients' weight after treatment.

## RESULTS

These are summarized below in Table I.

TABLE I

| Diagnosis | No. of Patients | No. of Recoveries: Immediate | No. of Recoveries: Within Two Months | No. of Improvements: Immediate | No. of Improvements: Within Two Months | Total |
|---|---|---|---|---|---|---|
| Involutional Depression .. | 17 | – | – | 1 | – | 1 |
| Manic Depressive Psychosis | 5 | – | – | – | 2 | 2 |
| Recurrent Endogenous Depression .. .. | 7 | 1 | – | – | 1 | 2 |
| Senile Depression .. .. | 4 | – | – | – | – | – |
| Total .. .. .. | 33 | 1 | – | 1 | 3 | 5 |

It can be seen that from a total group of thirty-three patients given the treatment, one patient recovered immediately, one improved immediately, while three others improved within two months of finishing the isoniazid therapy.

These results have been further tabulated above under diagnostic headings which will be discussed below. In all, five out of thirty-three patients given the treatment showed some degree of clinical improvement. This figure in itself is very small and might well be accounted for by chance spontaneous improvement, and in order to examine further the latter possibility brief summaries of these five cases are appended so that the significance of their improvements can be further assessed:

*Case 1.* Miss B.S., aged 50 was admitted to Cane Hill Hospital on 26.3.54 complaining of depressive symptoms of several weeks duration. In November, 1946 she had been treated for a few weeks in West Park Hospital for a depressive state. At that time she was mute and retarded, but she made a rapid spontaneous recovery and was discharged the following month. On admission to Cane Hill the patient was depressed and anxious, displayed psychomotor retardation and suffered from insomnia. A diagnosis of recurrent endogenous depression was made and isoniazid therapy commenced on 7.4.54, finishing on 28.4.54. The patient was still slightly tense and depressed but became symptom-free during the following week. She was discharged on 21.5.54 and had remained symptom-free up to 22.7.54 when she was seen as an out-patient for follow-up purposes.

*Case 2.* Mrs. M.L., aged 61 was admitted to Cane Hill on 27.1.54 with a history of four weeks depression, She had previously become depressed in October, 1951 and had remained so until her admission to Cane Hill in January 1953. At that time she was given six E.C.T., made a rapid recovery, and was discharged in February, 1953. She relapsed the following June, was readmitted to Cane Hill and given a course of eight E.C.T. She again recovered and was discharged in August, 1953. On the present admission she was depressed, retarded, harboured delusions of guilt and complained of insomnia. A diagnosis of Involutional Depression was made and a course of isoniazid was given between 6.2.54–27.2.54. At this time the patient was well except for a mild degree of subjective depression, but by 1.5.54 she had relapsed with severe depression, anxiety and insomnia.

*Case 3.* Mrs. I.M., aged 31 was admitted to Cane Hill on 28.11.52 with a history of elation and hyperactivity of a few weeks duration. At the age of 16 she had been admitted to the Maudsley Hospital with depressive symptoms. While there she recovered rapidly but relapsed and was transferred to St. Ebbas' Hospital where she made a rapid recovery. The patient continued to have numerous mild episodes of mania and depression until her present admission. At this time she was elated and overactive, and a diagnosis of manic depressive psychosis—manic phase—was made. Following two E.C.T. the patient improved but remained hypomanic until a sudden change to normality in March, 1953. The following month she became depressed; in July she was given three E.C.T. with no effect. During the following month a

course of "artificial hibernation" was given, also with no effect, and in October, 1953 she was noted to be depressed, suicidal, and having delusions of guilt. A course of isoniazid was given from 16.10.53–6.11.53 with no immediate effect, but by January, 1954 the patient had improved though she was still slightly depressed and tense. In February, 1954 a course of five E.C.T. was given with no effect and the patient remained unchanged up to the following May.

*Case 4.* Miss L.V.H., aged 33 was admitted to Cane Hill on 13.11.53 with a history of depression with obsessional features over a period of five months, there having been no previous episodes. On admission she was severely depressed and retarded, with considerable obsessional anxiety. A diagnosis of Endogenous Depression was made and isoniazid was given from 16.11.53 to 4.12.53 with no immediate effect, but during the following weeks the patient made a gradual improvement and was discharged on 3.1.54 with residual symptoms. On 9.3.54 she was seen at out-patients but had relapsed, though still managing to work.

*Case 5.* Mrs. E.E., aged 65 was admitted to Cane Hill on 22.4.54 suffering from depressive symptoms of a few weeks duration. In 1920 after her mother's death she was treated for depression and mania for seven months in the Bethlem Royal Hospital. She then remained well until her husband's death in 1943 when she became acutely depressed; she was admitted to Cane Hill where she was given four E.C.T. and discharged recovered after two months. In 1951 she was again admitted to Cane Hill following a sudden recurrence of depressive symptoms. She recovered after six E.C.T. but relapsed quickly. In January, 1952 after a further three E.C.T. she was discharged recovered. In May, 1952 she again relapsed and was admitted to Cane Hill. She recovered completely after five E.C.T. and remained well until her discharge the following October. She then relapsed immediately and was readmitted when she made a gradual recovery until her discharge in August, 1953. On the present admission she was depressed, agitated and hypochondriacal and a diagnosis of Manic Depressive Psychosis—depressive phase—was made. Isoniazid therapy was given from 3.5.54 to 24.5.54 with no effect, but by July she was noted to be much less depressed and anxious, more active and sleeping better.

The majority of patients, as has been stated, did not show any clinical improvement from isoniazid therapy. As it might be argued that many of these patients would not have improved with any other treatment, those previously or subsequently treated with E.C.T. are enumerated below in Table II.

TABLE II

| Diagnosis | No. of Patients | No. of Patients Previously Recovered or Improved by E.C.T. | No. of Patients Subsequently Recovered or Improved by E.C.T. |
|---|---|---|---|
| Involutional Depression .. .. | 16 | 6 | 5 |
| Manic Depressive Psychosis .. | 3 | 2 | 1 |
| Recurrent Endogenous Depression | 5 | 2 | 2 |
| Senile Depression .. .. .. | 4 | 2 | 0 |
| Total .. .. .. | 28 | 12 | 8 |

From Table II above it can be seen that among the twenty-eight patients unaffected by isoniazid, twelve had previously improved after E.C.T. while eight subsequently improved with this treatment.

## DISCUSSION OF RESULTS

From a total group of thirty-three patients suffering from depressive states, five improved to some extent after isoniazid therapy. Brief histories of these five cases have been outlined, from which it can be seen that in Cases 2, 3 and 5, isoniazid produced clinical results inferior to those previously effected spontaneously or by E.C.T. In Case 1 the effect of isoniazid was approximately equal to that previously attained without specific treatment, while in Case 4 no comparisons can be made. In none of these cases therefore can isoniazid be shown to be superior to no treatment at all while in three of the five cases it would appear to have been less effective than E.C.T. given previously.

This apparent superiority of E.C.T. over isoniazid is also reflected in those cases not improved by the latter, over half of whom had either previously or

subsequently been benefited by E.C.T. It is interesting to note that the superiority of E.C.T. over isoniazid is least manifest amongst the cases of manic-depressive psychosis in whom the tendency for spontaneous remissions is great, but in the other diagnostic groups, in whom this tendency is less marked, the superiority of E.C.T. over isoniazid is obvious, even in those patients suffering from senile depression.

In conclusion it may be stated that from this study there is no evidence that isoniazid has any therapeutic effect upon depressive states, and furthermore, that if it has any such effect this is markedly inferior to that of E.C.T.

## General Discussion

These findings do not agree with those of Salzer and Lurie, whose results are appended:

| Diagnosis | No. of Cases | No. Improved |
|---|---|---|
| Agitated Depression .. .. .. | 12 | 8 |
| Psychoneurotic Depression .. .. | 17 | 11 |
| Manic Depressive Psychosis .. .. | 11 | 8 |
| Anxiety Neurosis .. .. .. | 1 | 1 |
| Total .. .. .. .. | 41 | 28 |

Differences in selection may in some degree explain this discrepancy. Salzer and Lurie treated cases of anxiety neurosis and psychoneurotic depression which were not included in this study, and none of their other cases were severely depressed or suicidal. In spite of these differences in selection there remains a marked discrepancy between the results obtained by these authors in their groups of patients with agitated depression and manic depressive psychosis and those obtained in this study. Since none of Salzer's and Lurie's patients were severely depressed, however, it is possible that factors other than isoniazid may have accounted for the improvements noted.

The negative results from this study are in agreement with those obtained by other workers. Wilson (1953) in a series of non-tuberculous patients with depressive disorders found isoniazid to have no therapeutic effect. Hunt and Wassersug (1953) treated a group of tuberculous patients who were also schizophrenic and concluded that isoniazid only produced euphoria as a concomitant of its beneficial effect upon the tuberculous process, and this conclusion was also obtained by Bennett *et al.* (1954) in a series of chronic schizophrenic patients.

It is interesting to note that in this study isoniazid was not associated with any constant increase in weight. Since the anorexia associated with depressive symptoms was in only a few cases improved, this finding is hardly surprising. It indicates that isoniazid has no inherent tonic effect, a conclusion consistent with the finding of Silverman (1954) who in a comparison of the effects of Isoniazid and Modified Insulin Therapy in matched groups of psychoneurotics, found the former to produce no increase in weight while in the latter treatment a consistent rise was recorded in most cases.

No toxic effects were noted amongst the patients in this study, but this was anticipated by keeping the dosage under 300 mgm. per day (Gammen *et al.*, 1953).

## Summary

(1) A group of thirty-three patients suffering from depressive states were treated with isoniazid over a period of three weeks.

(2) No evidence of clinical improvement attributable to the isoniazid therapy was found.

(3) Evidence was adduced in a number of patients that E.C.T. was greatly superior to isoniazid in the treatment of depression.

(4) No increase in weight nor toxic effects were associated with the isoniazid treatment involving doses of less than 300 mgm. per day.

(5) These results were discussed in the light of recent work.

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