

6 β -HYDROXY-3:5-CYCLOPREGNAN-20-ONE IN MENTAL STATES

By

S. W. HARDWICK, M.D., M.R.C.P., D.P.M.

Medical Superintendent

J. J. PEARSE, M.D.

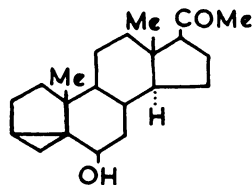
Stone House, near Dartford, Kent

and

V. PETROW, Ph.D., D.Sc., F.R.I.C.

Chief Research Chemist, The British Drug Houses Ltd.

SOME years ago we began to evaluate steroidal compounds in the treatment of mental states and now report some results obtained with 6 β -hydroxy-3:5-cyclopregnan-20-one (I), the most promising of the compounds studied.



It seems likely that normal steroidal production by the body is associated with mental health and conversely that inadequate production may predispose to altered mental states (cf. Ciba Foundation Colloquia, 1952). An extreme example of this effect is evident in Addison's disease in which destruction of the adrenal cortex with consequent disappearance of adrenal steroids leads to apathy, mental depression and frank psychosis (see for example, Cleghorn, 1951; Engel and Margolin, 1941) which are alleviated by the administration of adrenal cortical extract (Hartman, 1935). The effect of slightly lowered steroid levels upon mental states is naturally more difficult to establish. Pincus, Hoagland and their collaborators (Pincus *et al.*, 1949; Hoagland, 1953) however, have presented impressive evidence to show that dysfunction of the adrenal cortex, as measured by urinary steroids, is often present in psychotic patients. Schizophrenics appear to show subnormal adrenal responsivity to stress and to injected A.C.T.H., but do not exhibit typical Addisonian symptoms, a result which points to "a species of hypo-adrenalism occurring characteristically in the psychotics". The possibility of treating mental states by some form of replacement therapy is thus apparent. Criteria for recognizing such states, however, are not available at present. This fact enforces an empirical approach to the selection of patients for treatment and to the choice of steroid employed.

METHOD

Preliminary Investigation

Ten patients (2 males and 8 females with ages ranging from 30 to 76) were selected, mostly from the chronic population of a mental hospital. Four patients

came into the category of catatonic forms of schizophrenia, 2 paranoid forms of schizophrenia, 2 schizophrenics who had previously had prefrontal leucomotomies and 2 patients suffering from senile dementia. The patients were divided, as far as possible, into two similar groups with regard to diagnosis, sex and age. The steroid (I) and the placebo material were made up in the form of identical 100 mg. tablets known to us only by the code numbers TS.658 and TS.659.* Each patient received 1 tablet three times a day, corresponding to a daily dose of 300 mg. After 15 days, treatment was reversed, the group on TS.658 receiving TS.659 and *vice versa*. Each patient received, on the average, 15 days' treatment.

The 2 male cases showed no essential changes during and after treatment.

Four female patients out of the 8 showed marked improvement in their subjective mental condition when put on TS.658, with relapse when the treatment was changed to TS.659. The relapse occurred 7 to 15 days after reversal of the treatment. Improvement was noticed in 1 catatonic patient aged 36, 1 chronic schizophrenia paranoid type aged 67, 1 senile dementia case aged 76 and 1 post-prefrontal leucomotomy patient aged 47.

We concluded from these results that TS.658 contained the active substance and TS.659 the placebo. This was checked and found to be the case. We therefore went ahead with more extensive trials on the steroid (I).

Main Series

The patients were selected at random from a Psychiatric Out-patient Department. The steroid (I) was administered, as before, in 100 mg. tablets three times a day. No attempt was made to follow the patients' progress by objective testing. Frequent interviews and subjective accounts by the patients were the only guides used for the assessment of patients' mental changes. The exact expressions used by the patients are reported when possible.

Case No. 1. E.W., female, age 35, married.

Diagnosis. Depressive state with obsessive features.

Recent sudden onset of illness, as far as could be assessed, of not more than 4 weeks duration.

The first symptom of which she became aware was excessive worry. The progress of her domestic work was extremely hampered by checking and re-checking of each step, it finally becoming altogether impossible for her to complete her tasks. At the same time she became preoccupied by suicidal fantasies, but denied having ever experienced the impulse actually to commit suicide. Her sleeping rhythm deteriorated. She found it extremely difficult to fall asleep in the early part of the night and, when asleep, would wake suddenly in a panic. The patient's family history revealed that its various members suffered from a variety of minor neurotic symptoms.

Treatment was commenced on 22 August, 1955. After 21 days patient reported: "I am feeling much better, less depressed, but still lacking somewhat in confidence." This initial improvement did not last, however, the patient relapsing for a short period. She improved again and, after 2 months of treatment, was well enough to be discharged as fully recovered.

Case No. 2. E.E.S., female, age 34, married.

Diagnosis. Depressive state with obsessive suicidal and homicidal fantasies.

The patient had a good insight into her condition and could give an excellent account of her symptoms. It was difficult to assess the exact date of the onset of her illness, which was apparently of rather long duration.

The patient commenced treatment on 12 August, 1955. After only 6 days of treatment she reported that she was much better, more settled and less depressed. She remarked that her obsessive ideas were still present but were in the background and did not interfere with her normal life. The patient voluntarily added that she had felt better in the last week than for the last 10 years.

The patient made an uneventful recovery and was discharged on 4 November, 1955, free of complaints and able to resume her normal occupations.

* TS.658 \equiv 6β -hydroxy-3:5-cyclopregnan-20-one ("neurosterone").

Case No. 3. W.N., female, age 37, single.

Diagnosis. Anxiety state.

The illness was of very long duration. The patient was always a rather shy, solitary person, a poor mixer, rather sensitive and suspicious. As a child, she was nervous and given to day-dreaming, which persisted through adolescence into maturity. In childhood she showed frequent somatic manifestations such as stomach-ache before visits, etc. The family history was not very satisfactory; her mother was a cyclothymic.

Treatment was commenced on the 12 August, 1955. Six days later the patient reported that she was able to relax and to settle down to reading, and become aware that her thinking was much clearer. On the 9 September the patient reported: "I think that the brown tablets (i.e. the steroid) have done me good, I feel a great deal better." On 21 October she repeated more or less her previous observation, but added on this occasion that she could not do without the tablets. It might be of some interest to report another observation by the same patient that she noticed the improvement three-quarters to one hour after taking the tablets. At present the patient attends the clinic only occasionally.

Case No. 4. G.P., female, age 34, married.

Diagnosis. Anxiety hysteric.

The onset was gradual and the illness, as far as we could assess, was of very long standing. The patient's condition became aggravated about August, 1954, following the death of her friend from a brain tumour. The patient started to complain of general lassitude, difficulty in breathing, headaches and sudden attacks of claustrophobia.

Treatment was commenced on 21 September, 1955, and continued for about 1 month. There was no response.

Case No. 5. V.M., female, age 28, single.

Diagnosis. Anxiety hysteria.

The illness was of very long duration. The patient had various complaints such as headache, backache, stuffiness in the nose, salivation, frequent feeling of sickness and occasional vomiting. An immature personality, she was unable to maintain a job for any length of time.

Treatment was commenced on 20 July, 1955. On 10 August, the patient reported that she was feeling much better and was able to go out alone, which she had not been able to do for a long time. No great importance could be attached to this fact, however, as the patient was not a reliable witness and there were no doubt occasions in her history when she was free from symptoms. She reported a complete relapse at subsequent interviews. Treatment was discontinued on 21 September; the patient had not improved.

Case No. 6. D.H., female, age 53, married.

Diagnosis. Anxiety hysteria.

A rather immature personality. Her illness came on suddenly in January, 1954. The main symptoms of which she complained at the time were pains in the chest and right arm and breathing difficulties. The patient's own interpretation of these symptoms was that she was suffering from TB of the chest and spine. Although all physical examinations were negative, she remained unconvinced that she had not got TB and stayed in bed for more than 6 weeks.

Treatment was commenced on 18 August, 1955 and was abandoned 21 days later as there was no response.

Case No. 7. V.D.C., female, age 39, married.

Diagnosis. Anxiety state.

The illness was long standing with depressive features. The depressions were never severe enough to warrant hospital or other treatment such as E.C.T.

Treatment was commenced on 28 August, 1955. The patient's condition rapidly deteriorated and she became acutely depressed and agitated. On 1 October, 1955 immediate admission to a mental hospital became necessary as there was a possibility of the patient becoming suicidal. Steroid therapy was withdrawn and the patient treated with E.C.T. following which she made a good recovery.

It is thought unlikely that the steroid played a part in the patient's mental deterioration.

Case No. 8. R.D., male, age 35, married.

Diagnosis. Anxiety state.

The illness was of long standing. Its onset was difficult to assess, but the patient's condition had gradually been deteriorating for the past 4 years. The patient's main complaints were tenseness, inability to concentrate and muddle-headedness. He also complained of severe insomnia, mostly in the early part of the night. His personality, according to the patient's own description, was of the "worrying type" and his general outlook was pessimistic, always seeing danger where none existed.

Treatment was commenced on 9 September, 1955. On 21 October the patient reported in a

somewhat elated mood: "Since the tablets I am champion." He reported that he was more settled, less worried, less fatigued during the day and sleeping better during the night.

A fortunate mistake occurred at this stage when the patient was given different tablets in lieu of the steroid by the local dispenser. He relapsed shortly afterwards showing his former symptom. Although unaware of the mistake, he noticed a sudden change for the worse. He improved again when the mistake was discovered and corrected.

The patient is occasionally being followed up in the out-patient clinic.

Case No. 9. D.H., male, age 31, married.

Diagnosis. Anxiety state.

The illness had an acute onset in 1952. The immediate apparent cause was an unfortunate family experience when his wife, to whom he was devoted, developed an acute schizophrenic illness and had to be admitted to a mental hospital. He became extremely depressed, irritable and worried about himself. He was unable to dismiss from his mind the image of his wife when acutely ill prior to her admittance to a mental hospital. He had a good previous personality.

Treatment was commenced on 7 September, 1955. Fourteen days later the patient reported that he was feeling much happier, less irritable, less aggressive and able to concentrate better. He maintained his improvement and was discharged on 14 December, 1955.

Case No. 10. H.D., male, age 34, married.

Diagnosis. Compulsive, obsessive neurosis and depressive features.

The illness was long-standing. The patient was an intelligent man with a university education. The content of his obsessions was the fear that he might tread and injure insects or small animals. He felt compelled, when walking in the street, to look constantly on the ground in order to avoid small creatures. Many times he had to go back a considerable distance to check whether he had not done so.

Treatment was commenced on 29 July, 1955. On 10 September the patient reported improvement. He was able to walk more freely. Although he had not lost his obsessive ideas they appeared to be easier to manage. He was less depressed. On 14 December the patient had still maintained his improvement. He is being followed up at present.

DISCUSSION

Statistically significant results can necessarily not be drawn from such a limited number of cases. It seems likely, however, that 6β -hydroxy-3:5-cyclopregnan-20-one (I) may be of value in the treatment of a variety of mental states with the exception of those grouped under anxiety hysteria in the present series. We have the impression that administration of the material is not entirely a form of substitution therapy, as the improvements produced appear to be maintained after withdrawal of the steroid. It is tempting to ascribe this to the establishment of more normal steroidogenesis as a result of treatment (cf. Kappas *et al.*, 1956). An encouraging feature of the present trials was the apparent absence of side-effects in the patients receiving the steroid. A wider evaluation is being planned.

SUMMARY AND CONCLUSIONS

The results show that 6β -hydroxy-3:5-cyclopregnan-20-one (I) is of some value in the treatment of mental states.

The observations made appear to indicate that the steroid influences a variety of mental states extending beyond and not keeping strictly to the conventional psychiatric classifications, ranging from the organic on the one side, to the purely psychogenic mental conditions on the other.

The steroid seems to increase the general ability of the patients to cope more satisfactorily with their symptoms. To this extent the effect produced falls probably into the same category as that termed "anti-fatigue" by Hoagland and Pincus.

Patients grouped in the present series under anxiety hysteria failed to respond to treatment.

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