USE OF DEHYDROISOANDROSTERONE IN PSYCHIATRIC TREATMENT

A PRELIMINARY SURVEY

BY

E. B. STRAUSS, D.M., F.R.C.P.

D. E. SANDS, F.R.C.P.Ed., D.P.M.

A. M. ROBINSON, D.Sc.

W. J. TINDALL, M.D.

AND

W. A. H. STEVENSON, B.M., B.Ch.

Having noted the work of Hemphill, Reiss, and others on the relationship of "steroid" excretion to mental states, we decided to investigate the effect of dehydroisoandrosterone in selected cases of schizophrenia and "schizoid psychopathy." Our case-material was limited to patients who showed abnormal 17-ketosteroid excretion, to patients whose mental illness was mild or who were slowly deteriorating, and, as things turned out, to patients who gave the appearance of physical immaturity.

The group investigated in the first instance (Cases 1-5) consisted of males between the ages of 16 and 35 in whom the total 24-hour ketosteroid output, and particularly the alpha-beta ratio, was found to be abnormal. The normal 17-ketosteroid output for this age group in men is taken to be 6-21 mg. per 24 hours, of which the beta fraction constitutes 5-15%. Each case was independently investigated by at least two of the following: E. B. Strauss, W. A. H. Stevenson, and L. Rose, of St. Bartholomew's Hospital, and D. E. Sands, G. H. A. Chamberlain, and M. E. F. Woollaston, of St. Ebba's Hospital. The chemical investigations were carried out by A. M. Robinson at St. Bartholomew's Hospital and by W. W. Kay for St. Ebba's Hospital at West Park Group Laboratory. W. J. Tindall examined the first five cases and advised on the clinical and endocrinological aspects throughout. The last three cases (Nos. 6-8) are relevant and interesting in spite of the fact that it was possible to estimate the total ketosteroid output only—that is, without fractional differentiation.

Case 1

A man aged 33. Diagnosis, paranoid schizophrenia. Estimated duration of disorder, 14 years. Prior to this he had been a reasonably well-adjusted individual. The family history contained evidence of psychological instability and endocrine imbalance. Symptoms included incongruity of affect, outbursts of aggression, violent screaming attacks, and paranoid and other delusional ideas. Sexual interest had never developed. Previous treatment included hormone injections, psycho-analysis, and full insulin coma, without materially arresting the progress of the disease. Rorschach tests pointed to a diagnosis of paranoid schizophrenia. The total 17-ketosteroid excretion for 24 hours was 19.1 mg., of which the beta fraction was 7.5 mg.—an unusually high reading.

He received a total of 33 50-mg. (intramuscular) injections of dehydroisoandrosterone, at first daily and later at longer intervals, and showed unexpected improvement after a few days. His final social adjustment appeared normal; he took up an occupation satisfactorily, and his outbursts became increasingly rare. He began to show some sexual interest. The Rorschach test was repeated after the twentieth injection;

on this occasion there was no evidence of the more florid indications of schizophrenia, and the general picture showed a process of recovery. After treatment was completed his total 17-ketosteroid excretion was 18.7 mg., but it is to be noted that the beta fraction had dropped to the more normal figure of 3.5 mg. Some deterioration was noticed three weeks afterwards, but he was seen 17 months later, when his condition appeared much better than before treatment.

Case 2

A youth aged 17. Diagnosis, schizophrenia. Estimated duration of illness three years, with a marked predisposition and an unstable family history. Symptoms included mutism, repetitive actions, outbursts of violence, incontinence of urine and faeces, and bizarre postures. He was sexually inhibited. Previous treatment included electroplexy (E.C.T.) and deep insulin coma, without benefit. His total 17-ketosteroid excretion for 24 hours was 6.6 mg., the beta fraction being approximately 0.1 mg.—that is, below measurable limits.

He received a course of dehydroisoandrosterone, beginning with 5 mg. on alternate days, whereupon his picture altered rapidly. He was shortly able to hold a conversation and describe his personal and domestic difficulties. There was a spontaneous outburst of emotion on one occasion (abreaction), after which he became sexually less inhibited. His condition at one time resembled hysteria rather than schizophrenia: there was a period of anorexia, and later he expressed great fear of recovery in case he had to return to his home situation; his toilet habits became clean. His condition later deteriorated, but not to its previous low level. He was eventually transferred to St. Ebba's Hospital, where investigations were continued by Dr. Chamberlain. At first his treatment was chiefly abreactive in order to cope with the presenting hysterical symptoms. It seemed that the psychopathology of this side of the picture was centred on his inability to face the home situation, the most difficult aspect of which depended on parental quarrels. He frankly expressed his preference for an ordered, sheltered, hospital routine. He was later given a course of deep insulin treatment, 32 comas in all, from which he appeared to benefit somewhat, in the sense that he talked more freely and for a while became more cheerful.

During the 15 weeks of abreactive and insulin-coma treatment he continued to receive 5 mg. of dehydroisoandrosterone on alternate days. He was pleased when these injections were discontinued, since the good subjective results clashed with his overtly expressed desire for permanent stay in hospital. The clinical picture became progressively more schizophrenia-like and less hysterical—so much so that leucotomy was considered. The patient at first consented, but later withdrew his consent; nor were the parents agreeable. He left hospital in the care of his mother, but has since been admitted to another mental hospital.

Case 3

A man aged 24. Diagnosis, schizophrenia, with personality structure relatively intact. Estimated duration of illness 11 years, with rapidly increasing deterioration in the six months prior to his coming under medical care. Symptoms included impulses to assault people, blind rages, strong homosexual feelings, emotional impoverishment, a delusion that his life was guided by "beings" who made malign suggestions to him by signs and sounds. He had received no treatment apart from superficial psychotherapy. His total 17-ketosteroid excretion for 24 hours was 10.4 mg. with a negligible beta fraction.

He received a course of dehydroisoandrosterone (10 mg. and 20 mg. on alternate days) and his mood and thought-content altered rapidly. After his first injection he experienced his first heterosexual feelings. He had been withdrawn, suspicious, and depressed, but now became exalted, grandiose, and overactive. Further investigations were carried out at St. Ebba's Hospital, mainly by Dr. Woollaston,

and his mental state showed some variability. In one phase he developed florid delusions of an ecstatic religious nature which did not appear to interfere with his prevailing mood of contentment. At other times he became tense and irritable, with destructive impulses which he usually managed to keep under control. He continued to receive dehydroisoandrosterone injections for two periods of seven and six weeks respectively. The drug appeared to make him feel depressed and irritable and more subject to feelings of rage than at other times. His delusional ideas, which were originally mainly religious and ecstatic in quality, became frankly paranoid and unpleasant. Between these two courses of dehydroisoandrosterone he was given 31 insulin comas and five electrically induced convulsions. The insulin was associated with increased excitement but produced no real benefit. On the suggestion of one of us (E. B. S.) stilboestrol was given in order to reduce the sexual desire (conscious and unconscious) to a minimum, but he refused to co-operate after four days. At the time of writing his mental state is still very variable, but the general picture is one of paranoid schizophrenia with expansive delusions.

His total 17-ketosteroids were estimated on 10 occasions, but the ratio between the alpha and beta fraction was not worked out. There appeared to be no correlation between his total ketosteroid output and his mental state at any given moment.

Case 4

A man aged 27. The differential diagnosis was as between a slowly progressive process-schizophrenia and post-schizophrenic defect. The duration of illness was difficult to assess. From the age of 18 onwards he had spent three years in an American mental hospital. His symptoms included timidity, apprehensiveness, ineffectiveness, diminished (almost absent) sexual awareness, strange mannerisms, paranoid ideas, and aggressive outbursts. He had been previously treated with endocrine and vitamin preparations; he had also had a course of insulin coma. The Rorschach and Wechsler tests tended to confirm the diagnosis of schizophrenia. His estimated I.Q. was 78. His total 17-ketosteroid excretion for 24 hours was 8.1 mg., with a negligible beta fraction.

We first treated him by means of injections of testosterone propionate. Daily doses in excess of 10 mg. tended to be associated with a desultory type of aggressiveness and purposeless overactivity, without any effect on the underlying schizophrenic picture. Treatment was discontinued for two months, by which time he had reverted to his habitual state of lethargy. We gave him a short course of dehydroisoandrosterone (5-mg. injections). After three days he became more active and talkative. By the ninth day we had reduced the dose, as his response was tending to become excessive. As compared with the testosterone, it might be said that the beneficial mental change was more far-reaching and better integrated. This time he was able to discuss his personal problems, and developed a measure of self-criticism and ambition and more self-confidence. His ambitions were, however, beyond his capacity for achievement, and treatment was accordingly terminated. Some time later it was reported that he had remained more active and self-reliant.

Case 5

A youth aged 18. Diagnosis, schizophrenia simplex. Estimated duration of illness 10 years, with deterioration over the past two years. Symptoms included impaired concentration, indecision, thought-block, restlessness, depression, withdrawal, and a compulsion to imitate the undesirable actions of people in his environment. He had many tics and mannerisms. His pre-psychotic temperament was "hyperaesthetic schizothyme"—that is, quiveringly sensitive, lacking in drive, shy, and timid in social contacts. There was a family history of instability. He had received no previous treatment. His total 17-ketosteroid excretion for 24 hours was 9.9 mg. with again a negligible beta fraction—less than 0.1 mg.

He responded well to a course of dehydroisoandrosterone. The picture improved as a whole: he gained more insight into his mental state; his mannerisms became markedly diminished; he became more confident and active; and his depression lessened. He would have passed for "normal" with the ordinary observer; however, his ambivalence was well beyond the limits of normality. Every impulse tended to be accompanied by its counter-impulse; and whenever any constructive plan was suggested he would automatically come forward with objections to it. He has been followed up over a period of eight months: improvement has been well maintained in spite of severe outside stresses.

Case 6

A man aged 22. Diagnosis, schizophrenia in an immature person who had recently been suffering from pulmonary tuberculosis. There was a one-year history of apathy and withdrawal, with self-consciousness to the point of ideas of reference—that is, a delusional conviction that people laughed at him. He found life "too complicated," and was mildly confused. He was of superior intelligence, but had always been a "lone wolf" type. There were indications, in the Rorschach test, of both generalized immaturity and schizophrenic tendencies.

The first ketosteroid estimation (July 30, 1951) was 6.5 mg. for 24 hours. A single injection of dehydroisoandrosterone was followed by an immediate improvement. Progress was continuous throughout the course. After four weeks he became less tense, more animated and sociable, and less inclined to ruminate, with a corresponding subjective improvement. His total ketosteroid output had by then risen to 12.1 mg.

In November, 1951, it was decided to conduct a control experiment with the patient by substituting distilled water for the dehydroisoandrosterone injections and later administering inert tablets. It is noteworthy that after two weeks a change for the worse was observed: he felt tired, weak, depressed, and so indifferent that he did not even bother to proceed home on leave. He recently restarted treatment with dehydroisoandrosterone, and has once again improved.

Case 7

A man aged 29. The diagnostic label was schizoid psychopathy with obsessional features, together with general immaturity. He had always been sensitive, reserved, and shut in. For the past 14 years he had been odd, hypochondriacal, and given to obsessional preoccupations.

His total 17-ketosteroid excretion before treatment was 4.6 mg. for 24 hours. He was treated with dehydroisoandrosterone for two periods of six weeks. The dose varied from 0.5 to 2 ml. (10 to 40 mg.) daily. Treatment was accompanied by a subjective improvement: he felt "warmer in mood," steadier, and less obsessional. This gain was only temporary—he relapsed when treatment was stopped—and there was no essential objective change. He is still under observation in the out-patient department.

Case 8

A man aged 22. Diagnosis, schizophrenia occurring in a person of striking generalized immaturity and retarded development. He had been rejected by his father and over-indulged by his mother. He had always been unusually egocentric. He told fantastic stories about himself and sought to be the centre of attention. Of late months he had become quite uncontrolled and given to outbursts of rage. He talked absurdly to complete strangers, and developed grandiose delusions of a quasi-religious nature. He gave a generalized impression of childishness.

His total 17-ketosteroids were within normal limits. The only effect of dehydroisoandrosterone injections—even in a small daily dose of 0.5 ml. for five weeks—was to increase his tendency to rage and aggression. This continued for a while after the injections were stopped.

Results of Treatment

Roughly speaking, the results of treatment can be considered under two main headings, subjective and objective, although there is bound to be some overlapping.

Subjective.—Most patients stated that they felt less fearful and apprehensive and that the outside world appeared to be brighter and more real; there was an increase in self-confidence, combined with a slight euphoria; they felt more energetic and active.

Objective.—Behaviour-patterns became less withdrawn, and the patients seemed to be less apathetic and scared, and better adjusted to their environment. Their general attitude became manifestly more sthenic and virile. Those patients who had shown an undifferentiated or homosexual orientation began to develop heterosexual interests, although there were no observable changes from the anatomical point of view. Two patients became more accessible so far as analytical psychotherapy and rehabilitation were concerned.

Cases 2 and 8 became more deluded and paranoid, and so aggressive that treatment had to be discontinued.

Conclusions

It is clear that dehydroisoandrosterone can alter mental states even in the case of schizophrenic illness of long standing. The chief effect of the drug would seem to be to increase self-confidence and to induce a slight euphoria. In the case of two patients, in whom delusion-formation was a prominent symptom, increased aggressiveness and nervous tension occurred in the course of treatment.

Further work will be needed to show whether these changes are in any way related aetiologically to the re-establishment of the normal spectrum of 17-ketosteroid excretion, either by substitution therapy as in Cases 2 to 5 or by suppression of an abnormality, as might explain the result in Case 1. It is perhaps noteworthy that all the patients mentioned in this paper were constitutionally immature, and more or less conformed to Kretschmer's description of pubertal retardation. In some cases the symptomatology resembled that of prolonged unresolved pubertal crises—again in Kretschmer's sense—rather than a true process-schizophrenia. These preliminary results suggest the possibility that the beta fraction of the 17-ketosteroids represents the metabolites of substances which may be concerned with the development of "self-confidence" in adolescence or early adult life, in a way somewhat similar to the adrenal stimulation of A.C.T.H. in raising resistance to general stress (Selye, 1950).

In the case of a drug with such positive results it is necessary to be very cautious in the matter of dosage and to vary the dose from patient to patient in accordance with constant psychiatric observation. Special prudence is demanded when aggression is present in the symptom-picture.

The results of treatment in this small group suggested that dehydroisoandrosterone might be of value in the case of constitutionally inadequate and anxious juveniles, especially those with a tendency to schizoid psychopathy. Further investigations on these lines at St. Ebba's Hospital are reported by Sands and Chamberlain (1952).

We should like to acknowledge our indebtedness to Dr. E. F. Scowen, Dr. H. Crichton-Miller, and Dr. R. E. Hemphill, to all those who rendered assistance in this preliminary communication, and especially to Organon Laboratories for supplies of dehydroisoandrosterone.

REFERENCES

- Sands, D. E., and Chamberlain, G. H. A. (1952). *British Medical Journal*, 2, 66.
Selye, H. (1950). *Ibid.*, 1, 1383.

TREATMENT OF INADEQUATE PERSONALITY IN JUVENILES BY DEHYDROISOANDROSTERONE

PRELIMINARY REPORT

BY

D. E. SANDS, F.R.C.P.Ed., D.P.M.

AND

G. H. A. CHAMBERLAIN, M.D., M.R.C.P.I., D.P.M.

(From St. Ebba's Hospital, Epsom)

Thirteen of the juvenile cases in the special unit at St. Ebba's Hospital for those aged 12 to 17 years have been distinguished by constitutional and emotional immaturity. Some were also intellectually dull. As a group they were inadequate, timid individuals, lacking confidence, and several were distinctly effeminate in attitude. They were physically small, looked younger than their years, and in two of the thirteen the genitalia were undersized and the testes incompletely descended. Eight were predominantly schizoid, three mainly anxious, one was a case of hysteria, and one an inadequate psychopath. In fact, such patients appeared to be the potential chronic schizophrenics or inadequate psychopathic personalities of early adult life. In view of the changes in mental state produced by dehydroisoandrosterone in a small group of young male adults of similar mental habitus, as reported by Strauss *et al.* (1952), it was thought possible that the drug might be worth a trial in this younger group, so lacking in development of the normal male confidence and assertiveness of youth.

By contrast, trial dosage of the drug was also given to four juveniles known to have aggressive trends. The average age of both groups was 15 years. Total 17-ketosteroid estimations were done in all but one case, though patients were selected on essentially clinical grounds. All patients had undergone the usual routine investigations and psychotherapeutic interviews for a month, and often more, before they received dehydroisoandrosterone.

The drug was given at first by injection only, the dose ranging from 0.5 ml. bi-weekly to 2 ml. daily—that is, 10–40 mg. No difference in effect was noticed when a change was made to oral administration in tablet form.

Specimen case histories are given below, but the general reaction to the drug was as follows. These patients were either schizoid, anxious, or inadequately psychopathic; and were characterized by feelings of inferiority, vagueness, timidity, apathy, and lack of social confidence. They mixed uneasily with others and at times were homosexual or effeminate. On giving dehydroisoandrosterone no immediate changes were noted, but after a period which varied from four days to four weeks, according to individual differences and the size of the dose, the following type of response was seen to a greater or lesser degree in the whole selected group of thirteen cases. First, there was an increase in activity, showing as improved performance in school or occupational department and ability to discuss their feelings and future aims. Confidence increased, and at the same time timidity and vagueness diminished. Relations with their fellows became more normal, and in some who had been prone to homo-