PSYCHOLOGICAL CONCOMITANTS OF CORTISONE AND ACTH THERAPY.

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During recent years renewed interest has been taken in the possible importance of adrenocortical function in psychiatric disorders. Psychiatric syndromes and symptoms associated with pathological functioning of the adrenal cortex found in Cushing's and Addison's diseases have been recognized for many years. The classical work of Selye (1949) and his school has elucidated the importance of the adrenal gland in the individual's reaction and adaptation to stress. Qualitative and quantitative abnormalities in adrenocortical responsivity to stresses and stimuli in various psychiatric disorders have been reported in recent years (Freeman et al., 1944; Hoagland et al., 1946; Pincus and Elmadjian, 1946; Pincus et al., 1949).

The increased availability and extended use of adrenocorticotropic hormone (ACTH) and cortisone for the treatment of a large range of diseases have provided an opportunity of studying the psychological changes occurring during the administration of these hormones.

Hench and associates (1949) in their first report on cortisone noted that increased mental capacity and activity sometimes occurred during cortisone treatment. A number of workers have subsequently reported improvement in mood with ACTH and cortisone therapy (Markson, 1949; Boland and Headly, 1950; Soffer, 1950; Goldman, 1950). Others have observed undesirable mental changes which, in some patients, were psychotic in character, e.g., schizophrenic, paranoid, depressive and manic reactions (Taylor and Morris, 1950; Du Toit and Bauer, 1950; Loeb, 1950; Mach and Barrelet, 1950; Brunsting, 1951).

Rome and Braceland (1952) have described their observations of psychological responses to cortisone and ACTH in a large series of patients. They found reactions were more likely when treatment provided for 100 mgm. or more of cortisone daily. The variations in mental activity ranged from an elevation of mood consistent with or related to improvement of the physical disease to psychotic reactions, which occurred in 10 per cent. of the patients. Reports differ widely regarding the incidence and nature of the psychological effects of ACTH and cortisone therapy. Lidz (1952) for example reports that many patients showed no significant changes during ACTH or cortisone therapy.

The present paper describes a study of the psychological changes in a series of 40 patients receiving 50 courses of treatment with ACTH or cortisone.
The patients were suffering from the following disorders:

1. Asthma.
2. Fibrinous bronchitis.
3. Rheumatoid arthritis.
4. Psoriatic arthritis.
5. Simmond's disease.
6. Anorexia nervosa.
7. Depressive states.
8. Schizophrenia.
10. Angioneurotic oedema.
11. Felty's syndrome.

METHODS.

(i) Clinical Assessment.
Each patient was observed by a team consisting of physician, allergist, paediatrician, pathologist and psychiatrist.

(ii) Clinical and Laboratory Tests.
The following tests were carried out as a routine: weight, water balance, eosinophile counts, blood electrolytes, electrocardiographs, daily blood-pressure readings.

(iii) Psychiatric Assessment.
A full psychiatric history and clinical assessment was carried out on each patient. Ratings of behaviour, mood, tension, awareness, sociability, etc., were made before, during and after treatment.

(iv) Psychological Tests.
(a) Personal tempo.—The following tests designed to measure personal tempo (Eysenck, 1947) were applied:
   1. Number of birds, flowers, etc., named in 30 seconds.
   2. Number of responses to coloured and uncoloured Rorschach cards made in seconds.

(b) Persistence.—As a measure of persistence, the length of time the patient could hold outstretched leg with heel 3" above a chair was carried out by the method of Eysenck (1947).

(v) Procedure.
For the first week the patient was given injections of saline, during which period all the tests and clinical assessments were carried out. Psychological changes occurring during ACTH or cortisone therapy may be due to the following possible causes:
(1) The effect of suggestion brought about by the therapeutic procedure.

(2) The relief or prospect of relief of distressing or incapacitating physical symptoms or disabilities.

(3) To the direct action of the hormone itself or a result of its accompanying physiological changes.

The procedure employed enabled an assessment of the effect of suggestion to be made. During the first week injections of saline were given and ACTH or cortisone administered without patients' knowledge of the change. In none of the patients in the series were there any significant changes during the period of administration of inert injections.

**Psychological Changes.**

The results are summarized in Table I.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Total</th>
<th>No significant change in mental state</th>
<th>Increased well-being</th>
<th>Marked euphoria</th>
<th>Marked excitement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma</td>
<td>10</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Fibrinous bronchitis</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>10</td>
<td>4</td>
<td>4</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Depressive states</td>
<td>6</td>
<td>4</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>6</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Angioneurotic oedema</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Felty's syndrome</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Simmond's disease</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Addison's disease</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Anorexia nervosa</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Anaphylactoid purpura</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Twenty-one patients showed no significant change in mental state or behaviour during ACTH and cortisone administration.

In 19 patients various changes in mental state and behaviour were observed. These ranged from a feeling of increased well-being to marked excitement, restlessness and irritability. The psychological reactions can be graded as follows:

1. A reaction to a new treatment or the result of suggestion.
2. Mood and behaviour changes consequent on, and attributable to improvement in the symptoms of the physical disease.
3. Improvement in mood and well-being not directly related to symptomatic improvement.
4. Undesirable mental changes.

**Suggestive Effect of the Treatment and Procedure.**

This could be assessed during the period of administration of inert injections. No patient in the series showed any significant changes during the period.
Mood and Behaviour Changes Attributable to Relief of Symptoms or Disability.

Eighteen patients showed a marked improvement in well-being, which amounted to frank euphoria in 4 patients. The increased well-being or euphoria was considered to be directly attributable to relief or disability in 6 patients, and in these patients improvement in mood and well-being occurred pari passu with improvement in physical symptoms.

Mood and Behaviour Changes Not Dependent on Relief of Physical Symptoms.

In 12 patients there was increased well-being and euphoria which was not dependent on any improvement in physical symptoms. In these patients the increased sense of well-being, which in some amount to euphoria, preceded the relief of physical symptoms, and in a number a further improvement occurred if disability or symptoms were relieved. In others marked euphoria continued even in absence of significant improvement in physical disability. Patients described an increased sense of well-being and felt physically stronger and mentally more active. In the early stages, elation free from undesirable tension was usually found. If large doses were necessary, increased irritability tended to accompany the feeling of elation. Patients reported that they felt more sociable and had more confidence. They looked forward to the future and tended to plan actively. Many reported increased clarity and facility of thinking with improvement in memory functions. Speech was often more rapid and associations quicker. These changes were similar to mild hypomania. In one patient marked irritability and excitement occurred which subsided when treatment was terminated.

Disease Groups.

Asthma patients.—No significant change in mental state occurred in 5 patients. In three of these patients the asthma cleared up with cortisone or ACTH therapy, the other two showing no improvement. In three of the five patients showing increased well-being or euphoria, the mood change was considered to be attributable to symptomatic relief. In the other two the mood change occurred independently of relief of physical disability. It was found that the tendency of cortisone or ACTH to produce euphoria was less with second courses of treatment, and was sometimes absent in repeated courses.

Rheumatoid arthritis.—The changes were similar to those found in asthma patients. Of six patients who showed increased well-being, the mood change was attributable to relief of physical symptoms in three and in the other three was independent of such relief. The tendency for euphoria was less in repeated courses.

Depressive states.—Six patients with involutional and senile depressive states were treated with ACTH therapy. Some improvement in general well-being was observed in four patients and increased appetite in three patients. A slight improvement in depression occurred in two patients which was not maintained after termination of ACTH. All patients in the group subsequently improved with electro-convulsive therapy. This suggests that
the beneficial effects of electro-convulsive therapy are not dependent on the increased endogenous release of adrenocortical hormones which may occur during its administration.

Schizophrenia.—Cortisone was given to 6 schizophrenic patients and 6 control patients were given inert injections. One patient receiving cortisone became temporarily worse and none showed any significant clinical improvement. This investigation is reported in full elsewhere (Rees and King, 1952).

Anorexia nervosa.—Some improvement in mood and appetite was produced by ACTH therapy, which was not sustained after termination of treatment. This patient subsequently recovered with psychotherapy.

Angioneurotic oedema.—Two female patients with chronic angioneurotic oedema were treated by ACTH. One patient improved, and the other showed no significant improvement. In both an increased feeling of well-being accompanied by irritability and insomnia were observed during ACTH therapy.

Simmond’s and Addison’s disease.—Both these patients were depressed and apathetic prior to treatment. Cortisone therapy resulted in marked improvement in mood and increased physical well-being.

DISCUSSION.

A striking feature of our series is the absence of severe psychiatric syndromes developing during ACTH and cortisone administration. Significant psychological changes only occurred in half the patients, and were in the nature of increased well-being, euphoria and elation and in a few patients increased irritability, tension and insomnia.

The improvement in mood would appear to be attributable to two factors: firstly, the physiological and biochemical effects of the hormones, and secondly, the result of relief of physical symptoms. The latter factor plays a large part in some patients and none in others. Other psychological reactions may occur during cortisone and ACTH therapy which may play an important role in the patient’s behaviour. The symptoms or disability may occupy a key position in the patient’s psychological defences, and the rapid disappearance of the disability may bring about conflicts or emotional tensions. On the other hand, in some patients the termination of cortisone or ACTH therapy may result in the return of the disability. If the patient is not prepared for this eventuality it may produce marked emotional reactions. Similarly, the way in which the patient is prepared for treatment can have important effects. The patient should be suitably prepared and warned that any improvement may be temporary. These psychological reactions, however, were not found to play a prominent role in the mood changes occurring in our series.

The undesirable mental symptoms of excitement, tension, irritability and insomnia, which tend to occur with high or prolonged dosage, promptly disappeared when dosage was reduced or treatment stopped.

The absence of the more severe psychiatric reactions which have been reported by some investigators could be due to a number of possible causes, e.g.,

1. That the individuals in the series were more stable, with less predisposition to the development of psychiatric disorder.
2. That the dosage was not large enough to induce severe psychiatric syndromes.
3. That the therapeutic regime prevented marked deviations in the patient’s internal environment.

The first and second possible causes can be ruled out as the material included severe depressive states, schizophrenics and serious personality disorders, and the dosage of cortisone and ACTH was, in many patients, heavy, e.g., 100–300 mgm. cortisone daily, or 20 mgm. ACTH six-hourly. The most probable reason is the third.

In every patient water and electrolytic balance was well maintained, and all patients were given potassium medication.

It is interesting to note that Torda and Wolf (1951) found a tendency in some patients to develop, towards the end of treatment with ACTH, malaise, headache and insomnia, and that these reactions were reduced by potassium chloride administration.

Both cortisone and ACTH tend to cause sodium and water retention, and Himwich (1951) believes that the alteration in electrolytic and water patterns of the body disturb enzymatic reactions, thus changing the physico-chemical constitution of the internal environment. If this is so, it might be an explanation of the absence of marked reactions in our series.

Similarly, Rome and Braceland (1951) consider that the rate as well as the magnitude of metabolic changes in the internal environment during ACTH and cortisone therapy are important in producing untoward psychiatric symptoms.

There is considerable individual variation in the capacity to adapt to changes in the internal environment. In a study of premenstrual tension, Rees (1953) found that a woman’s reactions to the hormonal, water and electrolytic changes in her internal environment during the premenstrual period was influenced by a large number of factors, including constitutional status, personality, attitudes and emotional state. Persons vary in their capacity for adjusting to changes in their internal environment, just as they differ in their capacity for adjusting to changes in their external environment. The unstable and poorly adjusted person will, other things being equal, tend to have more marked symptoms with changes in the internal environment than the stable, well adjusted person.

The type of psychological reaction produced will depend on constitutional factors as well as the patient’s psychological defences. Increased anxiety and tension, depressive reactions, schizophrenic reactions, increased paranoid trends can all occur in affected subjects with increased internal environment changes at the premenstrual period, just as they have been reported to occur with the internal environment changes brought about by cortisone and ACTH therapy.

The tendency for cortisone and ACTH to produce severe psychiatric reactions in some patients would, therefore, seem to depend on two main factors:
1. The individual’s constitution, in particular his predisposition to psychiatric breakdown, and his capacity for adjusting to internal and external environmental changes.
2. The degree of change in the internal environment, the rate at which such changes occur, and the degree to which such changes interfere with cerebral metabolic activities.

It will be seen that a multiplicity of factors is involved, and in considering the administration of cortisone and ACTH account should be taken of the patient's stability, predisposition to psychiatric disorder and his adaptive capacities. Every effort should be made to minimize undesirable changes in the internal environment, e.g., disturbances in water and electrolyte balance. This is achieved by low salt, high potassium intake and by adjustment of dosages.

**Summary and Conclusions.**

1. Published reports on psychiatric changes occurring during ACTH and cortisone therapy are briefly reviewed. A number of workers have reported severe psychiatric reactions, others minor or insignificant changes in mental state.

2. The present investigation describes the psychological changes observed in a series of patients suffering from a variety of physical and psychiatric disorders treated either with ACTH or cortisone. During the first week the patient was given injections of saline, during which period all tests and clinical assessments were carried out. No significant changes occurred during the period of inert injections, indicating that the possible suggestive effect of the procedure was not important.

3. No significant changes in mental state or behaviour occurred in 52 per cent. In the remaining patients the changes varied from an increased feeling of well-being to marked restlessness, excitement and irritability.

4. None of the changes could be attributed to suggestion. In one-third of patients showing increased well-being or euphoria the change was attributable to relief of disability or symptoms. The remaining two-thirds developed increased well-being or euphoria before or independently of any relief of symptoms.

In the early stages of treatment elation and euphoria free from undesirable tension was found. If large doses or prolonged treatment was necessary increased irritability and restlessness tended to develop. In asthmatic, rheumatoid arthritis and other patients the tendency to euphoria was less with second or subsequent courses of treatment.

5. Six patients with involutional or senile depressive states were treated with ACTH. A slight improvement in well-being and appetite occurred in some of the patients but no significant improvement occurred in the depression. All patients subsequently recovered with E.C.T. This suggests that the beneficial therapeutic effects of E.C.T. are not dependent on stimulating an increased endogenous release of ACTH.

6. The possible effects of removing psychosomatic symptoms which may occupy a key position in the patient's psychological defences and the importance of the psychological preparation of the patient for the treatment and possible relapse of disability after improvement are considered. These factors, however, did not play an important role in producing changes in our series.
7. The absence of severe psychiatric reactions is noteworthy. The possible reasons for this are discussed, and the probable explanation is that the regime employed prevented any marked deviation in the patient's internal environment during ACTH or cortisone treatment.

8. The tendency for cortisone and ACTH to produce severe psychiatric disorders appears to be dependent on two main variables. Firstly, the subject's constitution, his predisposition to psychiatric illness, his capacity for adjusting to internal and external environment changes. The second variable is the degree of change in the internal environment, the rate at which such changes occur and the degree to which such changes interfere with cerebral metabolic activities.

9. In considering the administration of cortisone or ACTH account should be taken of the patient's stability, predisposition to psychiatric disorder and his adaptive capacities. Every effort should be made to minimize undesirable changes in the internal environment, in particular disturbances in water and electrolyte balance. This is achieved by low salt diet, high potassium intake and by adjustment of dosages.

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